Modeling the effect of aneuploidy on cancer evolution

Remus Stana[1], Uri Ben-David[2], Daniel B. Weissman[3], and Yoav Ram[1,*]

[1]School of Zoology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel
[2]Department of Human Molecular Genetics and Biochemistry, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Department of Physics, Emory University, Atlanta, GA
[*]Corresponding author: yoav@yoavram.com

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Abstract

Evolutionary rescue is the process by which a population is able to survive a sudden environmental change which initially causes the population to decline towards extinction. A prime example of evolutionary rescue is the ability of cancer to survive being exposed to various treatments. We are interested in the mechanisms through which a population of cancer cells are able to adapt to chemotherapy, and in particular, the role played by chromosomal instability (aneuploidy). Cancer cells which have aneuploidy are hypothesized to have a higher fitness in an environment altered by anti-cancer drugs as they have incomplete pathways which drugs activate in order to kill the cells. Aneuploidy is highly prevalent in tumors and certain drugs which attempt to combat cancers through increasing chromosomal instability. As a result, the question we wish to answer is how aneuploidy impacts the fate of the population of cancer cells. We propose to model evolutionary rescue with the help of multi-type branching processes to obtain the probability that cancer will survive. Additionally, we will utilize large genomic datasets to asses the effects of aneuploidy on the probability of evolutionary rescue.

Introduction

Aneuploidy in cancer. Chromosomal instability (CIN) is the mitotic process in which cells suffer from chromosome mis-segregation that leads to aneuploidy, where cells are characterized by structural changes of the chromosomes and copy number alterations (Schukken and Foijer, 2018). Interestingly, aberrations in chromosome copy number have been shown to allow cancer cells to survive under stressful conditions such as drug therapy. Indeed, cancer cells are often likely to be aneuploid, and aneuploidy is associated with poor patient outcomes (Ben-David and Amon, 2020).

The role of chromosomal instability (CIN) in the emergence of cancer has been studied extensively in the past decades (Michor et al., 2005; Christine et al., 2018; Nowak et al., 2002; Pavelka et al., 2010; Komarova et al., 2003; Zhu et al., 2018). One hypothesis is that CIN facilitates tumor genesis by accelerating the removal of tumor suppression genes (TSG) and subsequent appearance of cancer. The deletion of tumor suppression genes can happen in two ways: two point mutations deleting both alleles of the TSG (assuming a diploid genotype), or one point mutation and one chromosomal loss event. Initial theoretical studies have shown that aneuploidy can have a significant role in the deletion of the the tumor suppressing genes when compared to two consecutive point mutations (Nowak et al., 2002; Komarova et al., 2003; Michor et al., 2005; Komarova et al., 2008). However, when taking into account that the appearance of aneuploidy requires a mutation to trigger CIN, the probability that CIN precedes tumor genesis is highly unlikely.

Evolutionary rescue. Populations adapted to a certain environment are vulnerable to environmental changes, which might cause extinction of the population. Examples of such environmental changes include climate change, invasive species or 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 where 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); adaptation by phenotypic plasticity without genetic modification (Carja and Plotkin, 2019, 2017; Levien et al., 2021); and adaptation through genetic modifications, e.g., mutation (Uecker et al., 2014; Uecker and Hermisson, 2016, 2011).

Models of evolutionary rescue usually assume that the fitness of the wildtype and mutant are homogeneous in time. An exception was given by Marrec and Bitbol (2020), who modeled the fitness of the wildtype and mutant as time dependent. Additionally, Uecker and Hermisson (2011) investigated the probability of fixation of a beneficial mutation in a variable environment with arbitrary time-dependent selection coefficient and population size. Most models focus on the probability that at least 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. Evolutionary rescue that requires two successive mutations has been investigated using diffusion approximation by Martin et al. (2013).

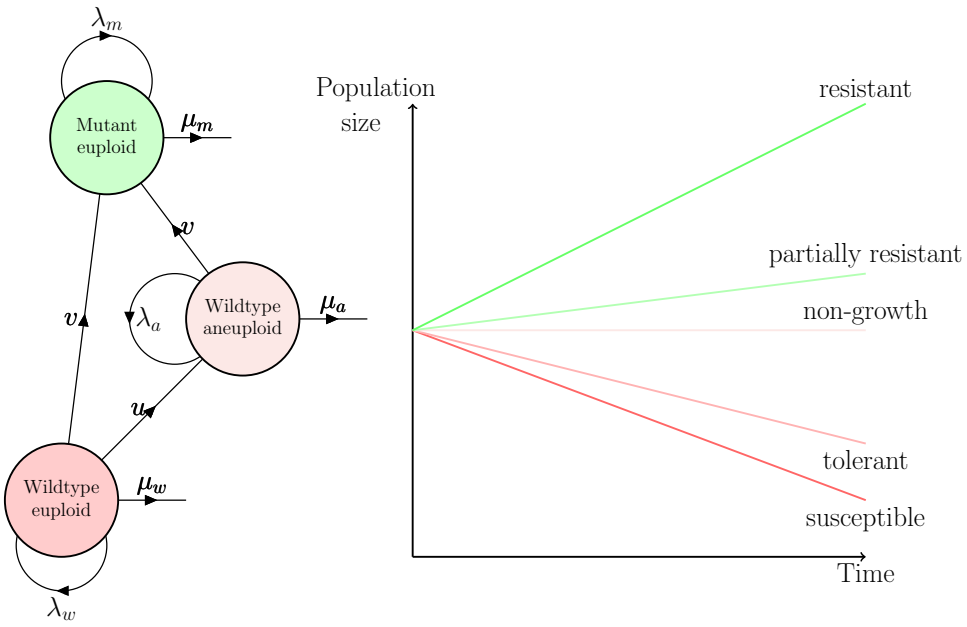

Figure 1: **Model illustration. (A)** A population of cancer cells is composed of wildtype, aneuploid, and mutant cells, which divide with rates λ_w, λ_a, and λ_m and die at rates μ_w, μ_a, and μ_m, respectively. Wildtype cells can become aneuploid at rate u. Both aneuploid and wildtype cells can acquire a beneficial mutation with rate v. Color denotes the relative growth rates of the three genotypes such that $\lambda_w - \mu_w < \lambda_a - \mu_a < \lambda_m - \mu_m$. **(B)** The wildtype and the mutant are susceptible and resistant, respectively, to the drug. The aneuploid may be tolerant, non-growing, or or partially resistant.

Methods

Evolutionary model

We follow the number of cancer cells that have one of three different genotypes at time t: wildtype, w_t; aneuploid, a_t; and mutant, m_t. These cells divide and die with rates λ_k and μ_k (for $k = w, a, m$). The difference between the division and death rate is $\Delta_k = \lambda_k - \mu_k$. We assume the population of cells is under a strong stress, such as drug therapy, to which the wildtype genotype is susceptible and therefore $\Delta_w < 0$, whereas the mutant is resistant to the stress, $\Delta_m > 0$ We analyze three scenarios: in the first, aneuploid cells are partially resistant, $\Delta_m > \Delta_a > 0$; in the second, aneuploid cells are tolerant, $0 > \Delta_a > \Delta_w$ (see Brauner et al., 2016, for the distinction between susceptible, resistant, and tolerant); in the third, aneuploid cells are non-growing or "barely growing", that is, either slightly tolerant or slightly resistant, such that $\Delta_a \approx 0$. Wildtype cells may missegregate to become aneuploids at rate u. Both aneuploid and wildtype cells may mutate to become mutants at rate v (Figure 1).

Stochastic simulations

Simulations are performed using a *Gillespie algorithm* (Gillespie, 1976, 1977) implemented in Python (Van Rossum and Others, 2007). The simulation monitors the number of cells of each type: wildtype, aneuploid, and mutant. The wildtype population initially consists of w_0 cells, whereas the other cell types are initially absent.

The state of the stochastic system at time t is represented by the triplet (w_t, a_t, m_t). The following describes the events that may occur (right column), the rates at which they occur

	Name	Value	Units	References
N	Initial tumor size	$10^7 - 10^9$	cells	Del Monte (2009)
λ_w	Wildtype division rate	0.14	1/days	(Bozic et al., 2013)
μ_w	Wildtype death rate	0.17	1/days	Bozic et al. (2013)
λ_a	Aneuploid division rate*	0.14	1/days	-
μ_a	Aneuploid death rate*	$0.13 - 0.17$	1/days	-
λ_m	Mutant division rate	0.14	1/days	Bozic et al. (2013)
μ_m	Mutant death rate	0.13	1/days	Bozic et al. (2013)
u	Missegregation rate	$10^{-3} - 10^{-2}$	1/cell division	Nowak et al. (2004); Bakker et al. (2023)
v	Mutation rate	$10^{-7} - 10^{-9}$	1/gene/cell division	Nowak et al. (2004)

Table 1: **Model parameters.** Aneuploid birth rate λ_a is set to the same value as the wildtype and mutant birth rates, λ_w and λ_m. Aneuploid death rate μ_a is set to an intermediate value between the wildtype and mutant death rates, μ_w and μ_m.

(middle column), and the effect these events have on the state (Figure 1):

$$\begin{aligned}
(+1,0,0): &\quad \lambda_w w_t \quad \text{(birth of wildtype cell)}\,,\\
(-1,0,0): &\quad \mu_w w_t \quad \text{(death of wildtype cell)}\,,\\
(-1,+1,0): &\quad u w_t \quad \text{(wildtype cell becomes aneuploid)}\,,\\
(-1,0,+1): &\quad v w_t \quad \text{(wildtype cell becomes mutant)}\,,\\
(0,+1,0): &\quad \lambda_a a_t \quad \text{(birth of aneuploid cell)}\,,\\
(0,-1,0): &\quad \mu_a a_t \quad \text{(death of aneuploid cell)}\,,\\
(0,-1,+1): &\quad v a_t \quad \text{(aneuploid cell becomes mutant)}\,,\\
(0,0,+1): &\quad \lambda_a m_t \quad \text{(birth of mutant cell)}\,,\\
(0,0,-1): &\quad \mu_a m_t \quad \text{(death of mutant cell)}\,.
\end{aligned}$$

Each iteration of the simulation loop starts with computing the rates ν_j of each event j. 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 $\Delta t \sim Exp(\sum_j \nu_j)$. Then, we randomly determine which event occurred, where the probability for event j is $p_j = \nu_j / \sum_i \nu_i$. Finally, we update the number of cells of each type 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 types is zero) or the number of mutant cells is high enough so that its extinction probability is $< 0.1\%$, that is until

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

τ-leaping. When the size of the initial population is large we utilize τ-leaping (Gillespie, 2001), where change in number of cells of genotype i in a fixed time interval Δt is Poisson distributed

with mean $\nu_i \Delta t$. If the increment is negative and larger then the subpopulation size then updated to be zero.

Density-dependent growth. In our analysis we assume that lineages produced by cells from the initial population divide and die independently of each other, which may be unrealistic, as cells usually compete for resources. A more realistic model includes competition for limited resources and spatial structure, which may play an important role in the development of cancer (e.g., Martens et al., 2011). To simulate birth and death rates that depend on the number of cells in the population, we transform the rates of division and death to the following:

$$\begin{aligned}
\lambda'_w &= \lambda_w, \\
\mu'_w &= \mu_w, \\
\lambda'_a &= C_1 + (\lambda_a - \mu_a)\left(1 - \frac{w+a+m}{K}\right), \\
\mu'_a &= C_1, \\
\lambda'_m &= C_2 + (\lambda_m - \mu_m)\left(1 - \frac{w+a+m}{K}\right), \\
\mu'_m &= C_2,
\end{aligned}$$

where $C_1, C_2 > 0$ are constants.

Code and data availability.

All source code is available online at `https://github.com/yoavram-lab/EvolutionaryRescue`.

Results

Survival probability

To analyze evolutionary rescue in this model, we use the framework of *multitype branching processes* (Rybnikov et al., 2021; Harris et al., 1963). 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_w, p_a, and p_m be the survival probabilities of a population consisting initially of single wildtype cell, aneuploid cell, or mutant cell, respectively. The complements $1-p_w$, $1-p_a$, and $1-p_m$ are the extinction probabilities, which satisfy each its respective equation,

$$\begin{aligned}
1 - p_w =& \frac{\mu_w}{\lambda_w + \mu_w + u + v} + \frac{u}{\lambda_w + \mu_w + u + v}(1 - p_a) + \\
& \frac{\lambda_w}{\lambda_w + \mu_w + u + v}(1 - p_w)^2 + \frac{v}{\lambda_w + \mu_w + u + v}(1 - p_m), \\
1 - p_a =& \frac{\mu_a}{\lambda_a + \mu_a + v} + \frac{v}{\lambda_a + \mu_a + v}(1 - p_m) + \frac{\lambda_a}{\lambda_a + \mu_a + v}(1 - p_a)^2, \\
1 - p_m =& \frac{\mu_m}{\lambda_m + \mu_m} + \frac{\lambda_m}{\lambda_m + \mu_m}(1 - p_m)^2.
\end{aligned} \tag{2}$$

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

$$\begin{aligned} p_w &= \frac{\lambda_w - \mu_w - u - v + \sqrt{(\lambda_w - \mu_w - u - v)^2 + 4\lambda_w (up_a + vp_m)}}{2\lambda_w}, \\ p_a &= \frac{\lambda_a - \mu_a - v + \sqrt{(\lambda_a - \mu_a - v)^2 + 4\lambda_a v p_m}}{2\lambda_a}, \\ p_m &= \frac{\lambda_m - \mu_m}{\lambda_m}. \end{aligned} \tag{3}$$

Note that the equation for p_w 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_w. 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, $(\lambda_a - \mu_a - v)^2 > 4\lambda_a v p_m$. We thus rewrite eq. (3) as

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

Using the quadratic 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 wildtype cell,

$$p_w \approx -\frac{vp_m + up_a}{\lambda_w - \mu_w - u - v} \tag{4}$$

$$\approx -\frac{1}{\lambda_w - \mu_w} \left[\frac{u(\lambda_a - \mu_a)}{\lambda_a} + \frac{uv(\lambda_m - \mu_m)}{\lambda_m(\lambda_a - \mu_a)} + \frac{v(\lambda_m - \mu_m)}{\lambda_m}\right] \tag{5}$$

Second-order approximation. To improve our approximation, we can consider the second term of the Taylor series expansion,

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

which gives us the following approximation,

$$p_a \approx \frac{\lambda_a - \mu_a - v}{\lambda_a} + \frac{vp_m}{\lambda_a - \mu_a - v} - \frac{\lambda_a (vp_m)^2}{8(\lambda_a - \mu_a - v)^3}. \tag{6}$$

We therefore have

$$p_w \approx -\frac{1}{\lambda_w - \mu_w - u - v} \left[\frac{u(\lambda_a - \mu_a - v)}{\lambda_a} + \frac{uv(\lambda_m - \mu_m)}{\lambda_m(\lambda_a - \mu_a - v)} + \frac{v(\lambda_m - \mu_m)}{\lambda_m} - \frac{uv^2\lambda_a(\lambda_m - \mu_m)^2}{8\lambda_m^2(\lambda_a - \mu_a - v)^3}\right]$$

$$\approx -\frac{1}{\lambda_w - \mu_w}\left[\frac{u\left(\lambda_a - \mu_a\right)}{\lambda_a} + \frac{uv\left(\lambda_m - \mu_m\right)}{\lambda_m\left(\lambda_a - \mu_a\right)} + \frac{v\left(\lambda_m - \mu_m\right)}{\lambda_m} - \frac{uv^2\lambda_a\left(\lambda_m - \mu_m\right)^2}{8\lambda_m^2\left(\lambda_a - \mu_a\right)^3}\right], \tag{7}$$

and using $\Delta_k = \lambda_k - \mu_k$, we can write the above equation as

$$p_w \approx -\frac{1}{\Delta_w}\left(\frac{u\Delta_a}{\lambda_a} + \frac{uv\Delta_m}{\lambda_m\Delta_a} + \frac{v\Delta_m}{\lambda_m} - \frac{uv^2\lambda_a\Delta_m^2}{8\lambda_m^2\Delta_a^3}\right). \tag{8}$$

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 wildtype cells, $\lambda_w - \mu_w < \lambda_a - \mu_a < 0$. We also assume that the decline are significant, $\left(\lambda_a - \mu_a - v\right)^2 > 4\lambda_a v p_m$. We rewrite eq. (3) as

$$p_w = \frac{\lambda_w - \mu_w - u - v}{2\lambda_w}\left(1 - \sqrt{1 + \frac{4\lambda_w\left(vp_m + up_a\right)}{\left(\lambda_w - \mu_w - u - v\right)^2}}\right), \text{and}$$
$$p_a = \frac{\lambda_a - \mu_a - v}{2\lambda_a}\left(1 - \sqrt{1 + \frac{4\lambda_a v p_m}{\left(\lambda_a - \mu_a - v\right)^2}}\right).$$

Since $u, v \ll 1$, this can be approximated by

$$\begin{aligned} p_w &\approx -\frac{vp_m + up_a}{\lambda_w - \mu_w - u - v} \\ &\approx \frac{1}{\lambda_w - \mu_w - u - v}\left[\frac{uv\left(\lambda_m - \mu_m\right)}{\lambda_m\left(\lambda_a - \mu_a - v\right)} - \frac{v\left(\lambda_m - \mu_m\right)}{\lambda_m}\right] \\ &\approx \frac{v\left(\lambda_m - \mu_m\right)}{\lambda_m\left(\lambda_w - \mu_w\right)}\left[\frac{u}{\left(\lambda_a - \mu_a\right)} - 1\right] \end{aligned} \tag{9}$$

Scenario 3: Aneuploid cells are non-growing

We now assume that the growth rate of aneuploid cells is close to zero (either positive or negative), such that $\left(\lambda_a - \mu_a - v\right)^2 < 4\lambda_a v p_m$. We rewrite eq. (3) as

$$p_a = \frac{\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m}\left(1 + \frac{\left(\lambda_a - \mu_a - v\right)^2}{4\lambda_a v p_m}\right)^{\frac{1}{2}}}{2\lambda_a}. \tag{10}$$

Using a following Taylor series expansion

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

we obtain the approximation

$$\begin{aligned} p_a &\approx \frac{\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m}\left[1 + \frac{(\lambda_a-\mu_a-v)^2}{8\lambda_a v p_m}\right]}{2\lambda_a} \\ &= \frac{\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m} + \frac{(\lambda_a-\mu_a-v)^2}{4\sqrt{\lambda_a v p_m}}}{2\lambda_a} \\ &= \frac{\left(\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m}\right)^2 + 4\lambda_a v p_m}{8\lambda_a\sqrt{\lambda_a v p_m}} \\ &= \frac{4\lambda_a v p_m + 4\lambda_a v p_m\left(1 + \frac{\lambda_a-\mu_a-v}{2\sqrt{\lambda_a v p_m}}\right)^2}{8\lambda_a\sqrt{\lambda_a v p_m}} \\ &= \frac{1}{2\lambda_a}\left(\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m}\right). \end{aligned} \tag{11}$$

From Equation (9), the survival probability of a population starting from one wildtype individual is

$$\begin{aligned} p_w &\approx -\frac{1}{\lambda_w - \mu_w - u - v}\left[v\frac{\lambda_m - \mu_m}{\lambda_m} + \frac{u}{2\lambda_a}\left(\lambda_a - \mu_a - v + 2\sqrt{\lambda_a v p_m}\right)\right] \\ &= -\frac{1}{\lambda_w - \mu_w - u - v}\left[v\frac{\lambda_m - \mu_m}{\lambda_m} + \frac{u}{2\lambda_a}\left(\lambda_a - \mu_a - v\right) + u\sqrt{\frac{v\left(\lambda_m - \mu_m\right)}{\lambda_a\lambda_m}}\right]. \end{aligned} \tag{12}$$

Evolutionary rescue probability

In our model, *evolutionary rescue* occurs when resistant cells appear and fixate ($m_t \gg 1$) in the population 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 $0 > \Delta_a > \Delta_w$) the extinction of the population before mutant cells appear and fixate.

To estimate the rescue probability p_{rescue}, we assume independence between clonal lineages starting from an initial population of N wildtype cells (we check the effect of density-dependent growth on our results below). Thus, the rescue probability is given by

$$p_{rescue} = 1 - (1 - p_w)^N \approx 1 - \mathrm{e}^{-Np_w}, \tag{13}$$

where the approximation $(1 - p_w) \approx e^{-p_w}$ assumes that p_w (but not Np_w) is small.

Applying the approximations for the survival probability p_w from eqs. (4), (9) and (12) and substituting $\Delta_k = \lambda_k - \mu_k$, we find that the rescue probability can be approximated by

$$p_{rescue} \approx \begin{cases} 1 - \exp\left[\frac{N}{\Delta_w - u - v}\left(v\frac{\Delta_m}{\lambda_m} + \frac{u(\Delta_a - v)}{2\lambda_a} + u\sqrt{\frac{v\Delta_m}{\lambda_a\lambda_m}}\right)\right], & 4\lambda_a v p_m > \left(\Delta_a - v\right)^2, \\ 1 - \exp\left[\frac{v\Delta_m N}{\lambda_m\Delta_w}\left(1 - \frac{u}{\Delta_a}\right)\right], & \Delta_a < 0 \quad \text{and} \quad 4\lambda_a v p_m < \left(\Delta_a - v\right)^2, \\ 1 - \exp\left[\frac{N}{\Delta_w}\left(\frac{u\Delta_a}{\lambda_a} + \frac{uv\Delta_m}{\lambda_m\Delta_a} + \frac{v\Delta_m}{\lambda_m}\right)\right], & \Delta_a > 0 \quad \text{and} \quad 4\lambda_a v p_m < \left(\Delta_a - v\right)^2. \end{cases} \tag{14}$$

We validate these approximations by comparing them to results of stochastic evolutionary simulations. We find that the approximations work very well (Figures 2 to 5).

In **????** we explore the effects of the wildtype and aneuploid growth rates on the rescue probability for small and large population sizes ($N = 10^4$ and $N = 10^8$, respectively).

?? show p_{rescue} as a function of N, including comparison of our first approximation (**??**) and simulation results.

???? show the rescue probability for initial population sizes $N = 10^4$ and $N = 10^8$, respectively.

In **??**, we compare the exact result (eq. (3)) with numerical simulations. The transition between the regimes defined by **??** and **??** respectively occurs at:

$$\Delta_a^* = 2vp_m + v + 2\sqrt{vp_m\left(vp_m + \mu_a + v\right)}. \tag{15}$$

Density-dependent growth. In our analysis we used branching processes, which assume that growth (division and death) are density-independent. However, in some cases growth may be limited by resources (oxygen, nutrients, etc.) and therefore depend on cell density. We therefore performed stochastic simulations of a logistic growth model with carrying capacity K (Methods). We find that ... (Figure 5).

Standing genetic variation In the above we assumed that upon beginning of drug therapy, the initial tumor consisted entirely of wildtype cells. However, aneuploid cells are likely generated even before onset of treatment at some rate $\tilde{u} \leq u$ (because the treatment itself may promote generation of aneuploid cells REF), which are likely to have a deleterious effect (REF). But if the number of cells in the tumor N is large, as expected if drug treatment is applied, there may already be a fraction $f = \tilde{u}/s$ of aneuploid cells in the population, where s is the cost of aneuploidy (REF).

In this scenario, The probability of evolutionary rescue by cells with aneuploidy from the initial population is

$$p_{old} = 1 - (1 - p_a)^{fN} \approx 1 - \mathrm{e}^{-fNp_a}.$$

The total probability of evolutionary rescue is given by

$$\begin{aligned} p_{total} &= p_{new} + (1 - p_{new})\, p_{old} \\ &= 1 - \exp\left(-\left[(1-f)\, p_w + f p_a\right] N\right). \end{aligned} \tag{16}$$

The fraction of cases in which the population is rescued by the standing genetic variation is given by $F(f) = \frac{p_{old}}{p_{total}}$. Setting $F = \frac{1}{2}$, we use the expansion $\mathrm{e}^x \approx 1 + x$ to obtain

$$f^* \approx \frac{p_w}{p_w + p_a}. \tag{17}$$

See Figure 6 for a demonstration of F and $f*$.

Effect of aneuploidy on evolutionary rescue

To determine the extent to which aneuploidy may affect evolutionary rescue, we define H to be the ratio of the rescue probability with aneuploidy ($u > 0$) and the rescue probability without aneuploidy ($u = 0$),

$$H = \frac{p_{rescue}(u > 0)}{p_{rescue}(u = 0)}. \tag{18}$$

Plugging in our approximations from eq. (13), we have

$$H = \begin{cases} \frac{1-\exp\left[\frac{N}{\Delta_w-u-v}\left(v\frac{\Delta_m}{\lambda_m}+\frac{u(\Delta_a-v)}{2\lambda_a}+u\sqrt{\frac{v\Delta_m}{\lambda_a\lambda_m}}\right)\right]}{1-\exp\left[\frac{vN\Delta_m}{(\Delta_w-v)\lambda_m}\right]}, & 4\lambda_a v p_m > (\Delta_a - v)^2, \\ \frac{1-\exp\left[\frac{v\Delta_m N}{\lambda_m\Delta_w}\left(1-\frac{u}{\Delta_a}\right)\right]}{1-\exp\left(\frac{v\Delta_m N}{\lambda_m\Delta_w}\right)}, , & \Delta_a < 0 \quad \text{and} \quad 4\lambda_a v p_m < (\Delta_a - v)^2, \\ \frac{1-\exp\left[\frac{N}{\Delta_w}\left(\frac{u\Delta_a}{\lambda_a}+\frac{uv\Delta_m}{\lambda_m\Delta_a}+\frac{v\Delta_m}{\lambda_m}\right)\right]}{1-\exp\left[\frac{v\Delta_m N}{\lambda_m\Delta_w}\right]}, & \Delta_a > 0 \quad \text{and} \quad 4\lambda_a v p_m < (\Delta_a - v)^2. \end{cases} \tag{19}$$

We find that the rescue ratio increase with the aneuploidy growth rate Δ_a, because the better aneuploid cells are in growth, the better they are at rescuing the population (when they provide partial resistance) or delaying the extinction of the population (when they provide tolerance). However, the rescue decreases with the wildtype growth rate Δ_w, because the better the wildtype is at growth, the less is depends on aneuploidy for rescue or delay, and the more likely it is to directly produce mutant cells, rather than relying on aneuploid cells for producing mutant cells (Figure 7). The effect of the initial tumor size N is mostly the same as the wildtype growth rate, except when aneuploidy provides tolerance and the population size is very large, in which case the ratio ...

Evolutionary rescue time

Even evolutionary rescue occurs, it may take a long time; therefore, it is crucial to estimate the mean waiting time for rescue and the effect aneuploidy may have on it. We therefore calculate the mean time for the appearance of the first mutant that rescues the cell population. This can occur either through the evolutionary trajectory *wildtype* $\rightarrow$ *mutant* or through the trajectory *wildtype* $\rightarrow$ *aneuploid* $\rightarrow$ *mutant*. We start with the former.

Assuming no aneuploidy ($u = 0$), we define T_1 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 $m_{t\to\infty} = 0$, then it is implied that $T_1 = \infty$, and vice versa if $T_1 < \infty$ then $m_{t\to\infty} \neq 0$.

The number of successful mutants generated until time t can be approximated by an inhomogeneous Poisson process with rate $R(t) = up_a w_t$ where w_t is the number of wildtype cells at time t, $w_t = N\mathrm{e}^{\Delta_w t}$. The probability density function of T_1 is thus $R(t)\,\mathrm{e}^{-\int_0^t R(z)\mathrm{d}z}$. Therefore, the probability density function of $(T_1 \mid T_1 < \infty)$ is $f_1(t) = \frac{R(t)\mathrm{e}^{-\int_0^t R(z)\mathrm{d}z}}{p_{rescue}}$.

We are interested in the mean conditional time, $\tau_1 = \mathbb{E}[T_1 \mid T_1 < \infty]$, which is given by

$$\tau_1 = \int_0^\infty t f_1(t)\mathrm{d}t = \frac{\int_0^\infty tup_a N\mathrm{e}^{\Delta_w t}\mathrm{e}^{-\int_0^t up_a N\mathrm{e}^{\Delta_w z}\mathrm{d}z}\mathrm{d}t}{p_{rescue}}. \tag{20}$$

$$\frac{\int_0^\infty \mathrm{e}^{-\int_0^t R(z)\mathrm{d}z}\mathrm{d}t}{1-(1-p_w)^N} = \frac{\int_0^\infty \mathrm{e}^{-uNp_a\frac{\mathrm{e}^{\Delta_w t}-1}{\Delta_w}}\,\mathrm{d}t}{1-(1-p_w)^N} \tag{21}$$

The fraction in exponential of the integrand in (20) can approximated as:

$$\frac{\mathrm{e}^{\Delta_w t}-1}{\Delta_w} = \frac{1+\Delta_w t + O(t^2) - 1}{\Delta_w} = t + O(t^2).$$

As a result, the mean time τ_1 can be simplified:

$$\tau_1 \approx \left(1+\mathrm{e}^{-Np_w}\right)\int_0^\infty \mathrm{e}^{-uNp_a\tau}\,\mathrm{d}\tau = \frac{\left(1+\mathrm{e}^{-Np_w}\right)}{uNp_a}, \tag{22}$$

where in the previous line we have used the approximation:

$$\frac{1}{1-\mathrm{e}^{-Np_w}} \approx 1+\mathrm{e}^{-Np_w}.$$

We plot the expansion (22) in Figure 8 and observe that it is a very good fit for intermediate and large values of the initial wildtype population size.

When $Nu \gg 1$ the aneuploid population can be assumed to be deterministic and approximated by the solution to the system of ODEs:

$$a_t = \frac{Nu\mathrm{e}^{\Delta_w t}}{\Delta_w-\Delta_a}\left[1-\mathrm{e}^{(\Delta_w-\Delta_a)t}\right]. \tag{23}$$

As a result, when $N \gg 1$ the number of successful mutants created by direct mutation or though aneuploidy are an inhomogeneous Poisson processes with the rates:

$$\begin{aligned} r_1(t) &= vp_m\int_0^t a_\tau\,\mathrm{d}\tau = \frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{\mathrm{e}^{\Delta_w t}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a t}-1}{\Delta_a}\right),\\ r_2(t) &= vp_m\int_0^t w_\tau\,\mathrm{d}\tau = vNp_m\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}. \end{aligned}$$

For large initial population sizes we can assume that both rescue mutations produced through direct mutation and aneuploidy are independent and, as a result, they can be merged into a single Poisson process with rate $(r_1+r_2)(t)$. Consequently, the mean time to the appearance of the first rescue mutant is:

$$\tau_2 = \frac{\int_0^\infty \mathrm{e}^{-(r_1+r_2)}\,\mathrm{d}\tau}{1-(1-p_w)^N} = \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a}\right)-vNp_m\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}\right]\mathrm{d}\tau}{1-(1-p_w)^N}, \tag{24}$$

which we plot in Figure 9 as a function of the initial population size.

We wish to obtain a simpler formula for τ_2 in an analogous way to (22). For this, we make use of the following expansions:

$$\begin{aligned} \frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w} &= \frac{1+\Delta_w\tau+\frac{\Delta_w^2\tau^2}{2}+O(\tau^3)-1}{\Delta_w} = \tau+\frac{\Delta_w}{2}\tau^2+O(\tau^3).\\ \frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a} &= \frac{1+\Delta_a\tau+\frac{\Delta_a^2\tau^2}{2}+O(\tau^3)-1}{\Delta_a} = \tau+\frac{\Delta_w}{2}\tau^2+O(\tau^3), \end{aligned}$$

which allow us to write:

$$\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a} \approx \frac{(\Delta_w-\Delta_a)\tau^2}{2}.$$

As a result, the integrand in (24) can be written as:

$$\begin{aligned} &\exp\left[-\frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a}\right)-vNp_m\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}\right] \approx \exp\left(-uvNp_m\tau^2-vNp_m\tau\right)\\ &= \exp\left(\frac{vNp_m}{2}\right)\exp\left[-\frac{uvNp_m}{2}\left(\tau+\frac{1}{u}\right)\right]. \end{aligned}$$

Consequently, the mean time τ_2 is obtained to be:

$$\tau_2 \approx [1 + \exp(-Np_w)] \exp\left(\frac{vNp_m}{2u}\right) \frac{\operatorname{erfc}\left(\sqrt{\frac{vNp_m}{2u}}\right)}{\sqrt{\frac{2uvNp_m}{\pi}}}, \tag{25}$$

where erfc is the complementary error function. We plot the expansion (25) in Figure 9 and observe that it is a very good fit for large values of the initial wildtype population size.

If we select only linear terms in the following expansions:

$$\frac{e^{\Delta_w \tau} - 1}{\Delta_w} = \frac{1 + \Delta_w \tau + O(\tau^2) - 1}{\Delta_w} = \tau + O(\tau^2).$$
$$\frac{e^{\Delta_a \tau} - 1}{\Delta_a} = \frac{1 + \Delta_a \tau + O(\tau^2) - 1}{\Delta_a} = \tau + O(\tau^2),$$

we obtain the first order approximation for τ_2:

$$\tau_2 \approx \left(1 + e^{-Np_w}\right) \int_0^\infty e^{-uNp_m \tau} \, d\tau = \frac{\left(1 + e^{-Np_w}\right)}{uNp_m}, \tag{26}$$

which we plot in Figure 9 and observe that it offer as a good a fit to (24) as (25). Additionally, we observe that for large initial wildtype populations sizes direct mutation drives evolutionary rescue while aneuploidy plays a role for intermediate sized tumors. This is consistent with the information obtained from Figure **??** where aneuploidy improves the probability of evolutionary rescue only for small and intermediate values of N.

Contribution of aneuploidy to mean evolutionary rescue time

$$\begin{aligned} I = \frac{\tau_2}{\tau_1} &= \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w - \Delta_a}\left(\frac{e^{\Delta_w t}-1}{\Delta_w} - \frac{e^{\Delta_a t}-1}{\Delta_a}\right) - vNp_m \frac{e^{\Delta_w \tau}-1}{\Delta_w}\right] d\tau}{\int_0^\infty e^{-uNp_m \frac{e^{\Delta_w \tau}-1}{\Delta_w}} \, d\tau} \times \frac{1 - (1 - p_w|_{u=0})^N}{1 - \left(1 - p_w|_{u>0}\right)^N} \\ &= \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w - \Delta_a}\left(\frac{e^{\Delta_w t}-1}{\Delta_w} - \frac{e^{\Delta_a t}-1}{\Delta_a}\right) - vNp_m \frac{e^{\Delta_w \tau}-1}{\Delta_w}\right] d\tau}{\int_0^\infty e^{-vNp_m \frac{e^{\Delta_w \tau}-1}{\Delta_w}} \, d\tau} \frac{1}{H}, \end{aligned} \tag{27}$$

where H, is the ratio of the probability of evolutionary rescue with and without aneuploidy, defined in (18). We plot (27) in Figure 10 as a function of the initial wildtype population for varying values of the Malthusian fitness of aneuploid cells Δ_a.

Discussion

In this paper, we have modelled a population of cancer cells which are exposed to chemotherapeutic drugs and decline towards extinction. Evolutionary rescue is the process where the population acquires a trait that increases fitness in the new environment such that extinction is averted. We have derived the probability of evolutionary rescue of the population of cancer cells under various demographic scenarious. The cancer cell population can escape extinction either through direct mutation or through mutation from aneuploidy. We have used multitype branching processes to study our model (Figure 1) which allows us to obtain exact solutions for the probability of evolutionary rescue.

The case when the aneuploid cells are resistant can be approximated by the one step evolutionary rescue process where the aneuploidy rescues the population (Figure **??**). However, when the growth rate of the aneuploid cells is negative then they cannot rescue the population and they can only act as a stepping stone (Figure **??**) through which the mutant can be obtain in a more expedient fashion, given that the aneuploid population declines slower then the wildtype population, compared to the case of direct mutation from the wildtype.

We observe from Figure **??** that aneuploidy has a significant contribution towards evolutionary rescue. When aneuploidy is slightly increasing ($\Delta_a = 10^{-3}$) the probability of evolutionary rescue is three orders of magnitude larger when aneuploidy is present compared to the case when aneuploidy is not present under the parameters previously described for tumors (see Table 1).

For our model we have assumed that cancer cell lineages are independent of each other. However this is not always true as cancer cells compete for resources which can have an effect on the probability of evolutionary rescue. We observe that this is not the case when the carrying capacity if sufficiently large the probability of evolutionary rescue is not impacted by the logistic model (see Figure **??**). Future work should include using density dependent branching process in order to better model the conditions under cancer cells proliferate.

The presence of aneuploid cancer cells at the onset of chemotherapy can facillitate evolutionary rescue by acting as a stepping stone for the appearance of resistant mutant cells. From Figure 6 we observe that, for even a relative small fraction of the initial population being composed of aneuploid cells, evolutionary rescue is more likely to occour through the initial aneuploidy.

We propose experiments similar to the ones highlighted in (Martin et al., 2013) in order to test the predictions of our model. For example, in order to study the effects of initial population size on the probability of evolutionary rescue we propose to derive a large culture mass from a single cancer cell in permissive conditions and then dilute to a wide range of stating population sizes ($10^7 - 10^9$). Afterwards, we expose the population to anti-cancer drug which induces aneuploidy or to saline solution for control. Final density, in both cases, would be measured by optical density and the results compared to predictions from out model.

We observe from equations (**??**) and (13) that the probability of evolutionary rescue increases when the initial population size increases, the wildtype population does not decline too quickly, the mutation and aneuploidy rates are high and the probabilities p_a and p_m are elevated.

The probability of evolutionary rescue is enhanced by aneuploidy for small and intermediate sized tumors (see Figure **??**). As a result, aneuploidy is unlikely to to contribute to primary tumors overcoming chemotherapy but it can contribute to the evolutionary rescue of secondary tumors whose size might be below the detection threshold of $\sim 10^7$ (Bozic et al., 2013). Given the fact that the mean time for small and intermediate tumors to overcome chemotherapy can be of the order of 100 days (see Figure 9) this could explain the reappearance of cancer even after initial remission.

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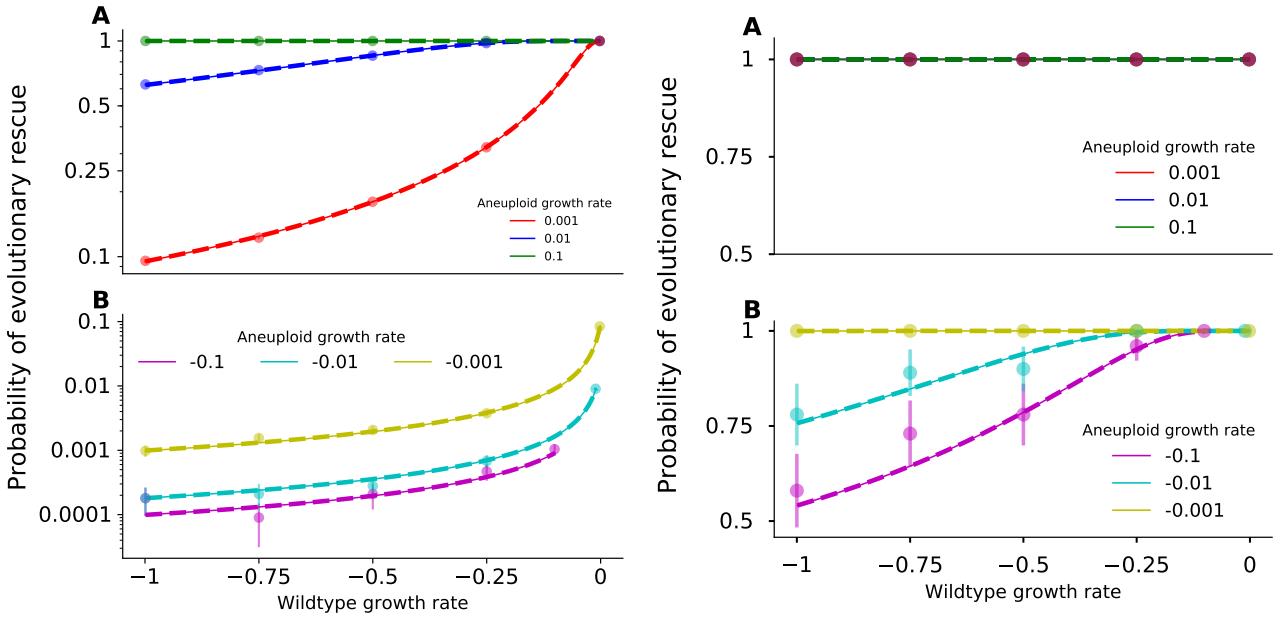

Figure 2: **Evolutionary rescue probability with partially resistant or tolerant aneuploid cells.** Rescue probability is very high when aneuploidy provides partial resistance, in an initially small tumor (**Aleft**, $N = 10^4$) and even more so in an initially large tumor (**Aright**, $N = 10^8$). When aneuploidy provides tolerance (**Bleft**, $N = 10^4$; (**Bright**, $N = 10^8$), the rescue probability is much lower. In both scenarios, rescue probability increase with both the wildtype growth rate (x-axis) and the aneuploidy growth rate (colors). Markers represent simulation results with 95% CI; solid and dashed lines for the exact formula (eq. (3) in eq. (13)); dashed lines for the approximate formula (eq. (14)), demonstrating that they all agree.

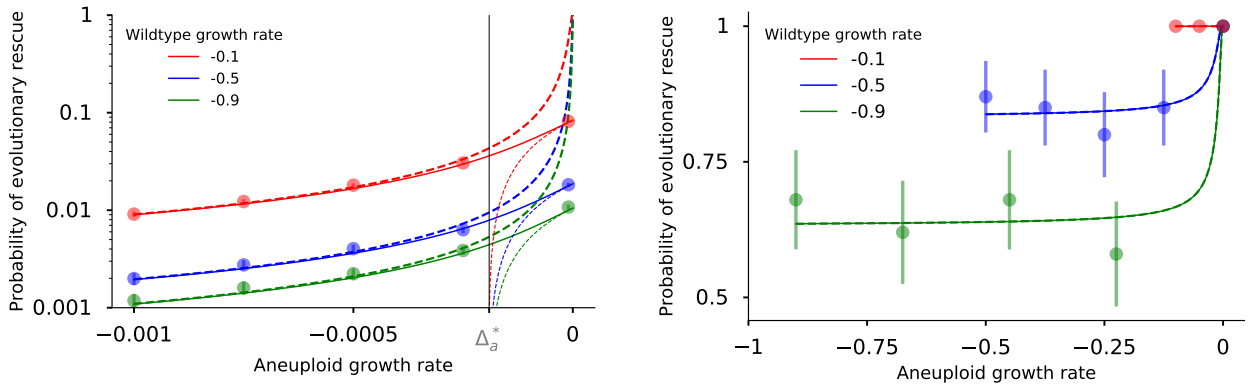

Figure 3: **Evolutionary rescue probability with tolerant or non-growing aneuploid cells.** Rescue probability grows with the aneuploid growth rate Δ_a (x-axis), and is much higher in an initially large tumor than in a small one ((A) $N = 10^4$; **(B)** $N = 10^8$). Markers represent simulation results with 95% CI; solid and dashed lines for the exact formula (eq. (3) in eq. (13)); dashed lines for the approximate formula (eq. (14)). The approximation agrees with the simulation and exact solution when the initial tumor size is large (panel B). When the tumor size is small (panel A), we switch between the approximation for tolerant and for non-growing aneuploid cells; the switch occurs at $\Delta_a^* = 2vp_m + v + 2\sqrt{vp_m\left(vp_m + \mu_a + v\right)}$.

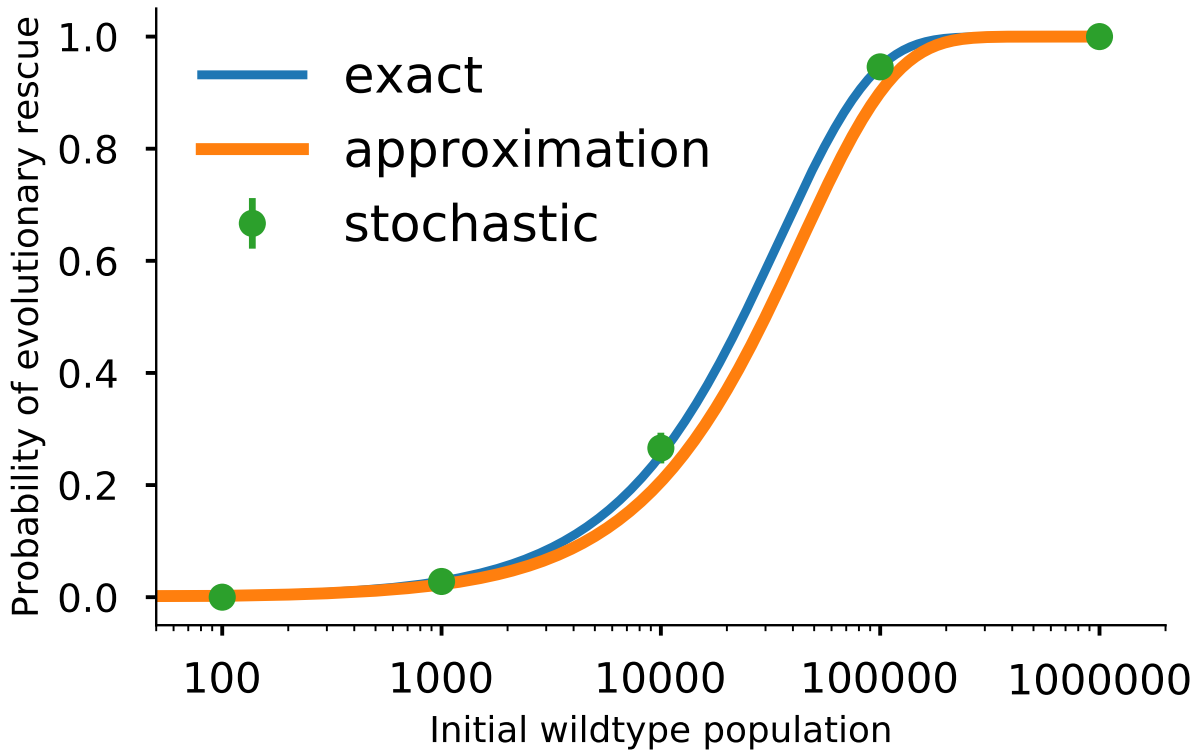

Figure 4: Plot of the probability of evolutionary rescue of a population, consisting of N wildtype cells, as a function of the initial population size of wildtype cells. The blue line represent the exact result (**??**) while the orange lines represent the approximation (**??**). The green dots represent numerical simulations where the error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\left(1-p\right)/n}$ where p is the mean probability of evolutionary rescue and n is the number of simulations. The error bars are present but are not visible given the fact that we have used $n = 10^5$ simulations for each combination of parameters. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

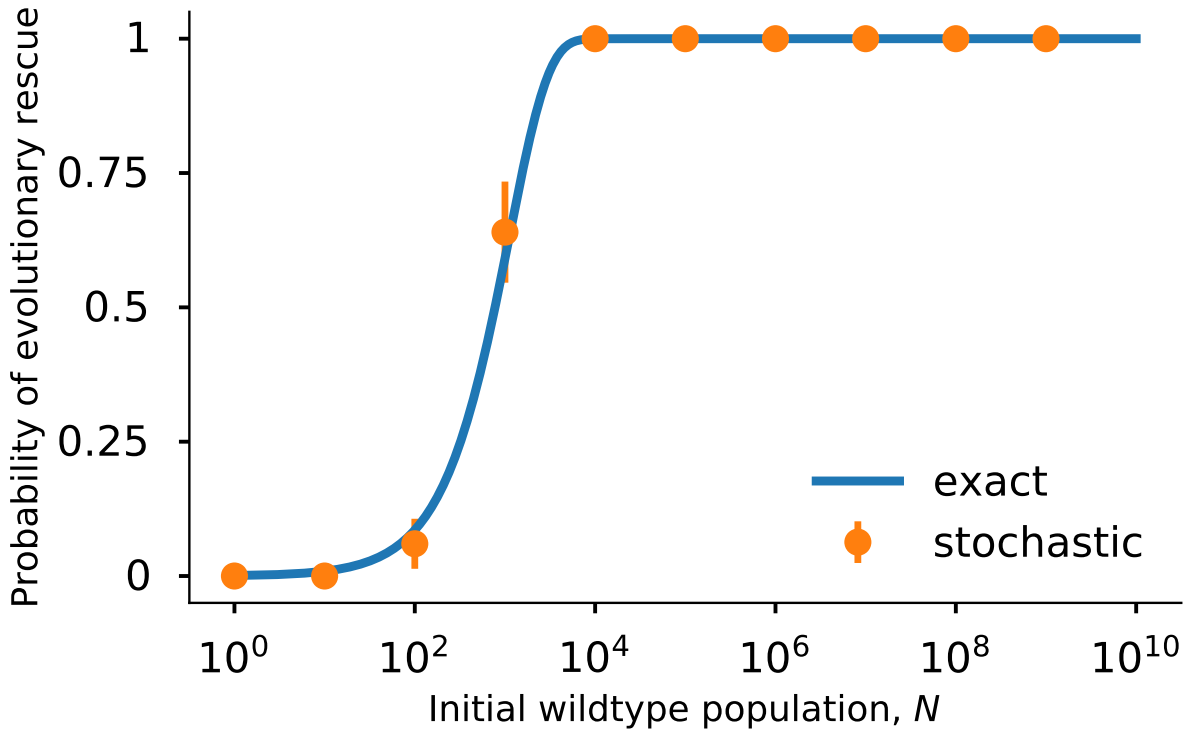

Figure 5: Plot of the probability of evolutionary rescue of a population, consisting of N wildtype cells, as a function of the initial population size of wildtype cells where maximum population size is constrained by the carrying capacity K. The blue line represent the exact result (**??**) while the orange dots represent numerical simulations where the error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\left(1-p\right)/n}$ where p is the mean probability of evolutionary rescue and n is the number of simulations. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_a = 1 + 10^{-4}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_m = 1, u = 10^{-2}, v = 10^{-7}, C_1 = C_2 = 1, K = 10^9$.

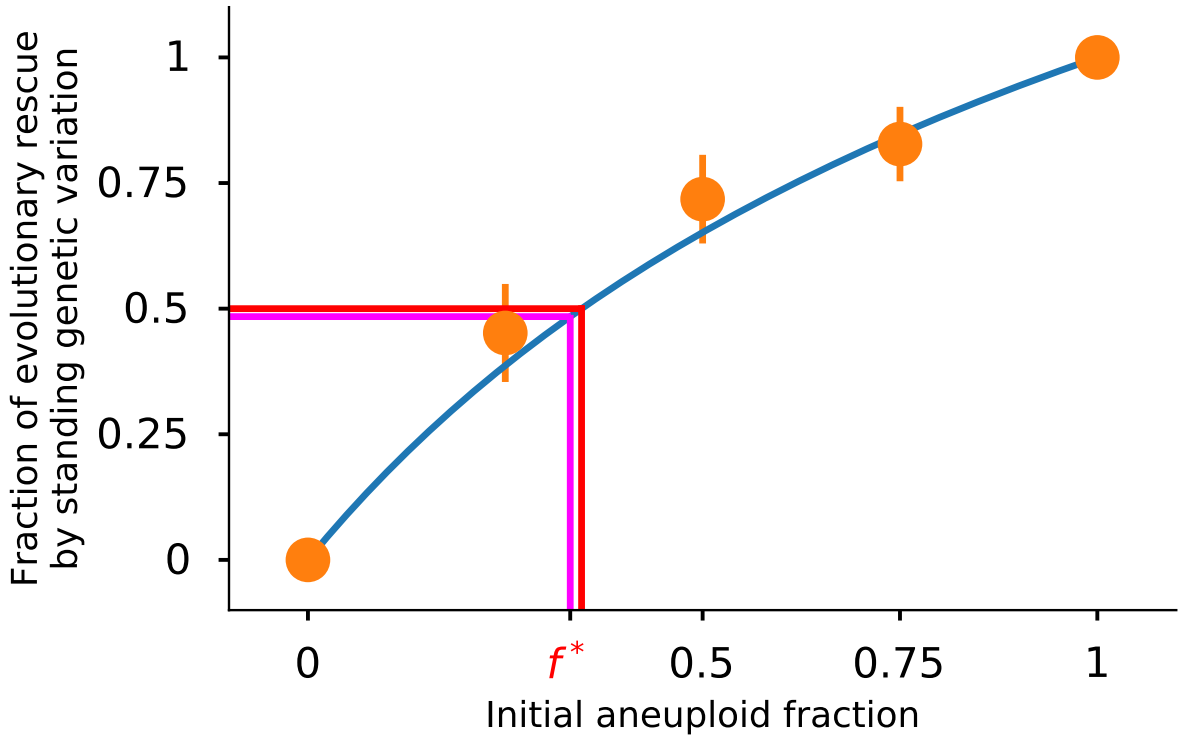

Figure 6: **Effect of standing variation on evolutionary rescue.** In aneuploid cells already exist in the population at the onset of drug therapy as standing genetic variation, then evolutionary rescue is more likely...

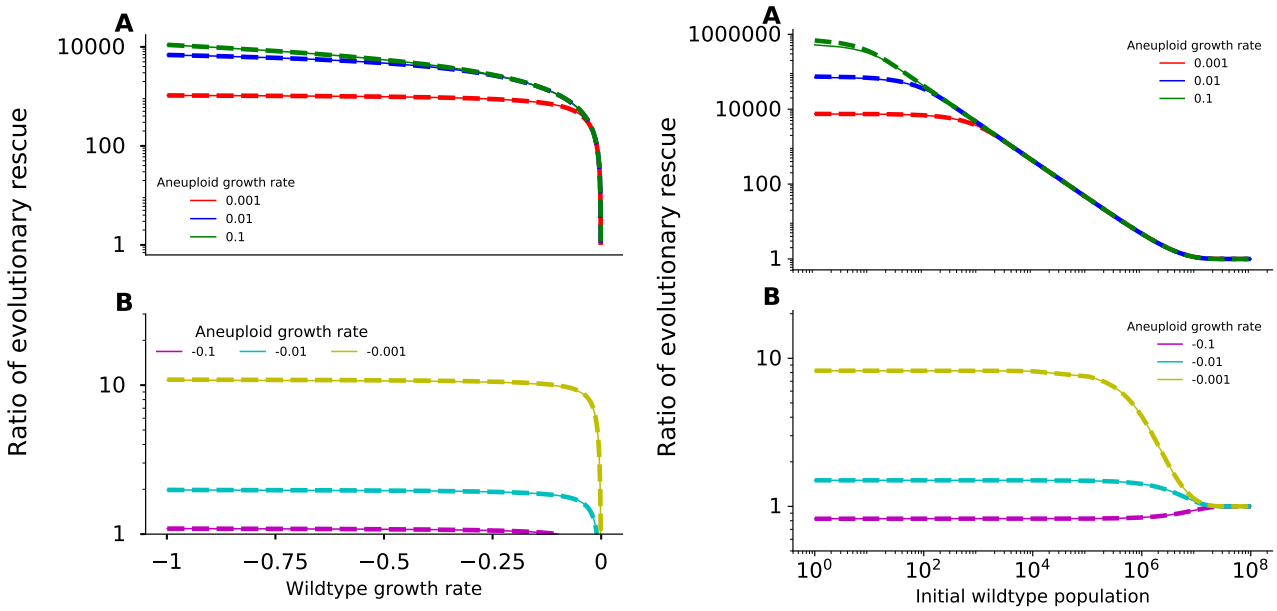

Figure 7: **Effect of aneuploidy on evolutionary rescue.** The ratio of rescue probability with and without aneuploid (H, eq. (19)) increases with the aneuploid growth rate (colors) and decreases with the wildtype growth rates and initial tumor size (x-axis), except for large tumors where aneuploid cells are tolerant (see right side of panel B-right). **(A-left,A-right)** Aneuploidy provides partial resistance. **(B-left, B-right)** Aneuploidy provides tolerance. Solid and dashed lines apply p_{rescue} from the exact formula of (eq. (3) in eq. (13)); dashed lines apply p_{rescue} from the approximate formula (eq. (14)), with good agreement.

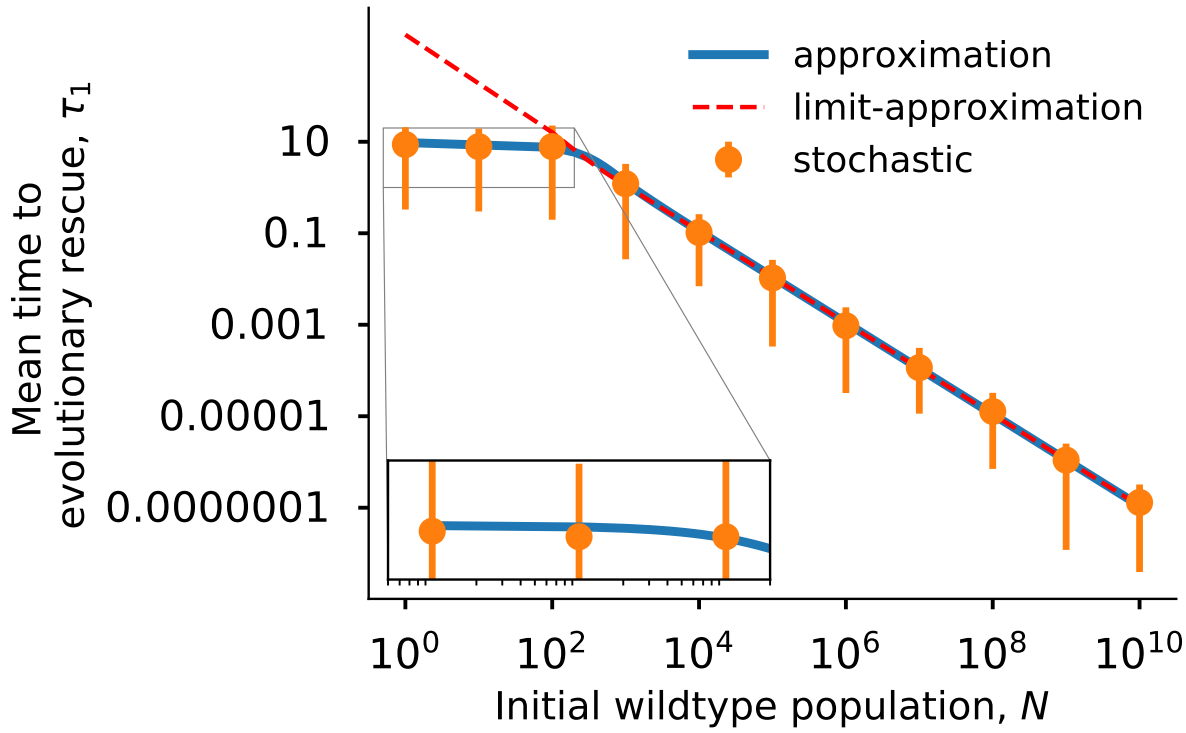

Figure 8: Plot of the mean time until the appearance of a resistance mutation which rescues the population in the case when evolutionary rescue is possible only through mutation but not aneuploidy and mutation. The blue line represents the approximation (20) and the dashed red line represents the first order approximation (22). The orange dots represent the numerical simulations while the error bars represent the interval centered at the mean which containing 95% of the simulated values. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_m = 1, u = 10^{-2}, v = 10^{-7}$.

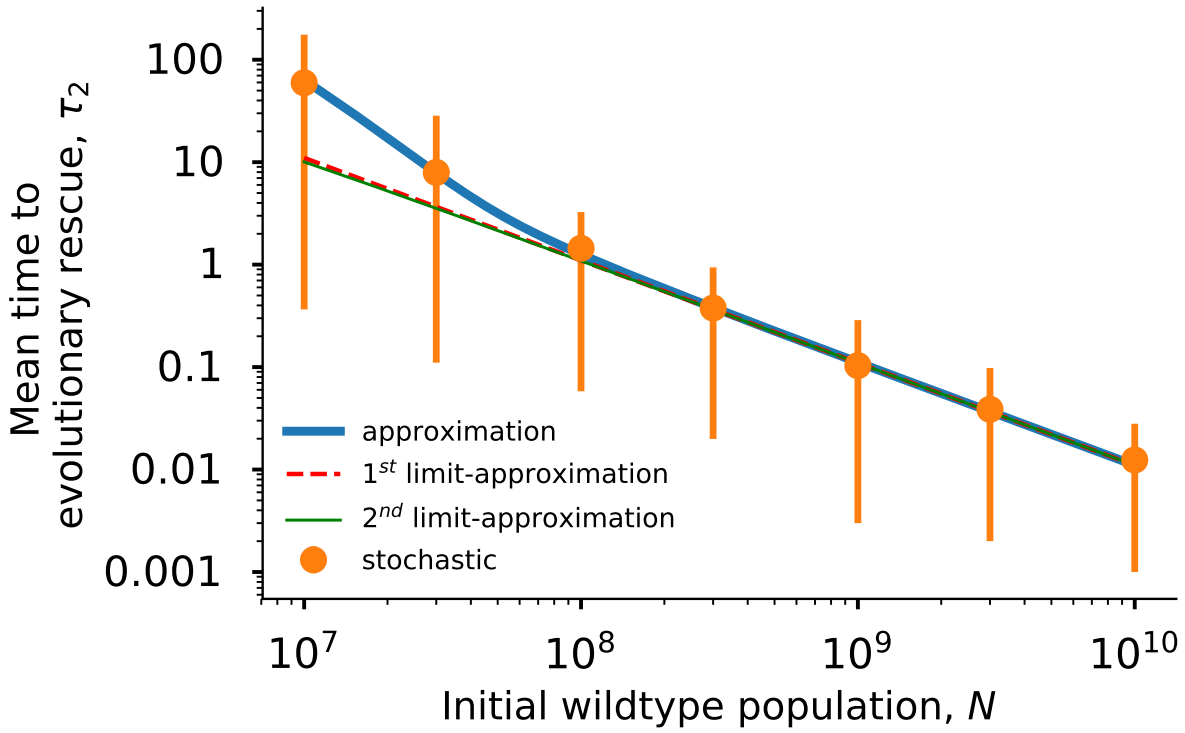

Figure 9: Plot of the mean time until the appearance of a resistance mutation which rescues the population in the case when evolutionary rescue is possible through mutation and aneuploidy. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_a = 1 - 10^{-2}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1, u = 10^{-2}, v = 10^{-7}$. The blue line represents the approximation (24), the dashed red line represents the second order approximation (25) and the green line is first order approximation (26). The orange dots represent the numerical simulations while the error bars represent the interval centered at the mean which containing 95% of the simulated values.

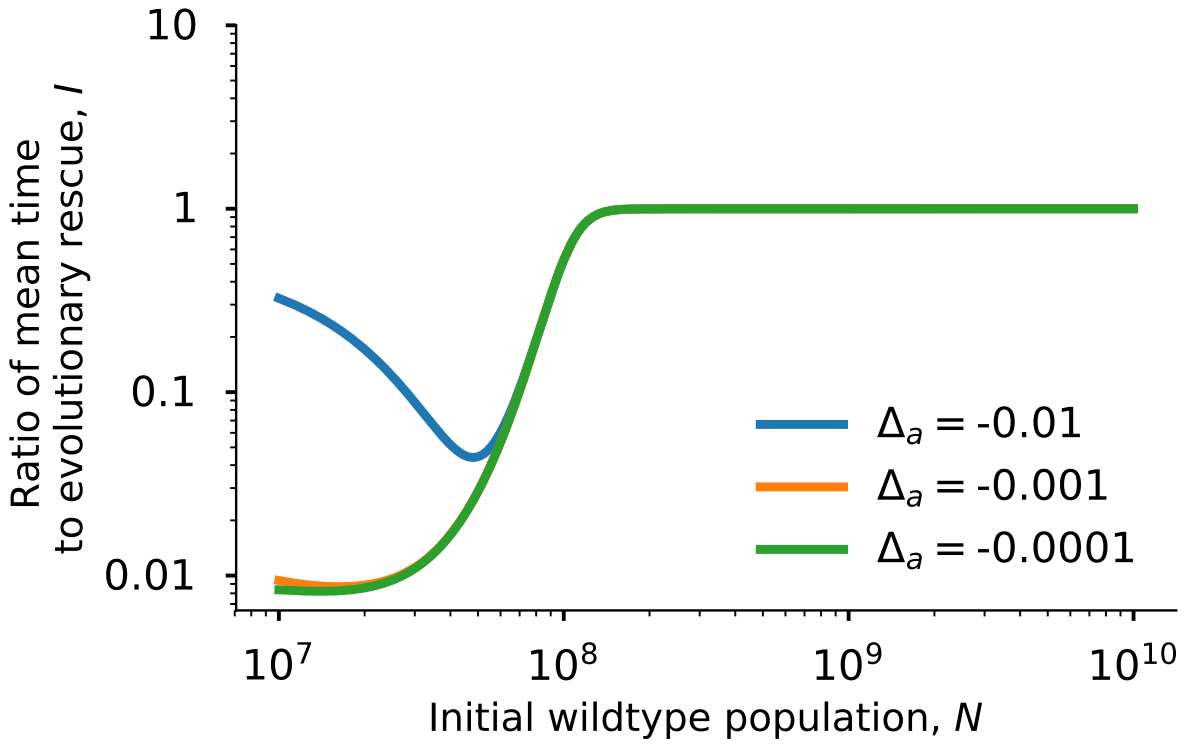

Figure 10: Plot of the ratio of the mean time to evolutionary rescue when aneuploidy can play a role in rescue ($u > 0$) to the mean time where acquisition of aneuploidy is not possible ($u = 0$) as a function of the initial population size of wildtype cells. The continuous lines represent the approximation (27). Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.