Modeling the effect of aneuploidy on cancer evolution

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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).

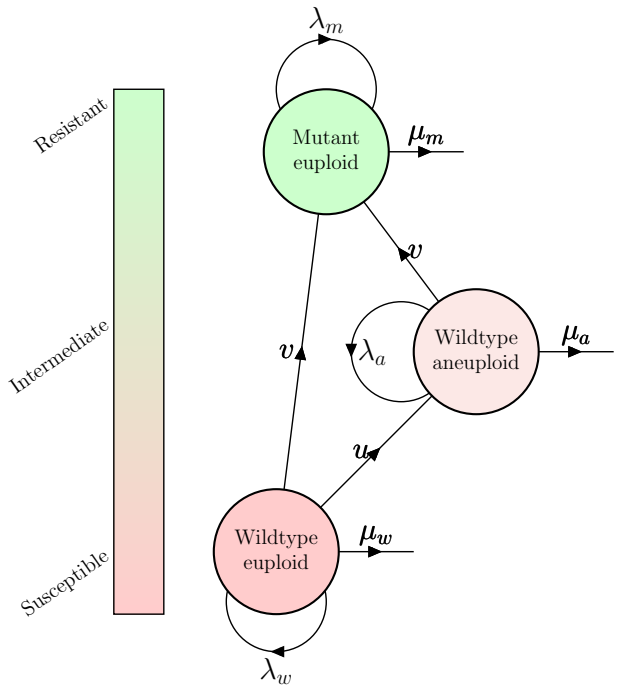

Figure 1: **Model illustration.** A population of cancer cells is composed of wildtype, aneuploid, and mutant cells, which divide with rates λ_w, λ_a, and λ_m and die at rates μ_w, μ_a, and μ_m, respectively. Wildtype cells can become aneuploid at rate u. Both aneuploid and wildtype cells can acquire a beneficial mutation with rate v. Color denotes the relative growth rates of the three genotypes such that $\lambda_w - \mu_w < \lambda_a - \mu_a < \lambda_m - \mu_m$.

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).

Evolutionary simulation

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

Evolutionary rescue occurs when mutant cells appear and fixate ($m_t >> 1$) 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. Thus, the rescue probability is given by

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

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

Now, we apply the approximations for the survival probability p_w from Equations (4), (9) and (12). Therefore, substituting $\Delta_k = \lambda_k - \mu_k$, the rescue probability is given by

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

In Figures 2 and 3 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).

Figure 4 show p_{rescue} as a function of N, including comparison of our first approximation (**??**) and simulation results.

Figures 5 and 6 show the rescue probability for initial population sizes $N = 10^4$ and $N = 10^8$, respectively.

In Figure 7, 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 We perform stochastic simulations for different values of the carrying capacity K and we plot the results in Figure 8. We observe that as K increases the simulations converge to the analytic result which is because the carrying capacity is much larger then the population size of aneuploid cells for which the probability that the population is rescued is certain.

Standing genetic variation

So far we have assumed that the initial population of cells consisted entirely of wildtype cells. We now modify this assumption so that the initial population includes a fraction f of cells with aneuploidy. 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 12 for a demonstration of F and $f*$.

Contribution of aneuploidy to the evolutionary rescue of cancer

We wish to understand the contribution of aneuploidy to evolutionary rescue of the cancer cell population. For this purpose we define the ratio of the probability of evolutionary rescue when aneuploidy can play a role in rescue ($u > 0$) to the probability where acquisition of aneuploidy is not possible ($u = 0$):

$$H = \frac{p_{rescue}\big|_{u>0}}{p_{rescue}\big|_{u=0}}. \tag{18}$$

As a result, we obtain from (14) the approximation for the ratio:

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

We plot (19) in Figure 9 for both resistent and susceptible aneuploidy as a function of the proliferation rate of the wildtype cells and in Figure 10 as a function of the initial population size of wildtype cells.

Rescue time

We calculate the mean time for the appearance of the first mutant that rescues the cancer cell population. This can occur either through the pathway *wildtype* $\rightarrow$ *aneuploid* $\rightarrow$ *mutant* or through the pathway *wildtype* $\rightarrow$ *mutant*. We start with the second pathway: let T_1 be the time at which the first mutant cell appears which rescues the population when evolutionary rescue is only possible through mutation. We are interested in the mean time $\tau_1 = \mathbb{E}[T_1]$.

The number of successful mutants generated until time t can be approximated by a inhomogeneous Poisson process with rate $R(t) = up_a w_t$ where w_t is the size of the wildtype population at time t:

$$w_t = N\mathrm{e}^{\Delta_w t}. \tag{20}$$

We are interested in the time to appearance of the first successful mutant cell conditional on population surviving:

$$\begin{aligned} P(T_1 < t) = {} & P(T_1 < t | m_{t\to\infty} \neq 0) P(m_{t\to\infty} \neq 0) \\ & + P(T_1 < t | m_{t\to\infty} = 0) P(m_{t\to\infty} = 0). \end{aligned}$$

As a result, the cumulative distribution function can be written as:

$$P(T_1 < t) = P(T_1 < t | m_{t\to\infty} \neq 0) P(m_{t\to\infty} \neq 0),$$

where we used the fact that evolutionary rescue is impossible when the mutant population is destined to be zero:

$$P(T_1 < t | m_{t\to\infty} = 0) = 0.$$

As a result, we obtain

$$P(T_1 < t | m_{t\to\infty} \neq 0) = \frac{P(\tau_1 < t)}{1 - (1-p_w)^N}, \tag{21}$$

where we have used

$$P(m_{t\to\infty} \neq 0) = 1 - (1-p_w)^N. \tag{22}$$

The probability density function of T_1 is given by:

$$f_{T_1}(t_1) = R(t_1)\,\mathrm{e}^{-\int_0^{t_1} R(t)\mathrm{d}t}. \tag{23}$$

As a result, the time T_1 conditional on evolutionary rescue is given by:

$$f_{T_1}(t_1 | m_{t\to\infty} \neq 0) = \frac{R(t_1)\,\mathrm{e}^{-\int_0^{t_1} R(t)\mathrm{d}t}}{1 - (1-p_w)^N}. \tag{24}$$

The expectation of T_1 is:

$$\tau_1 = \mathbb{E}[T_1] = \frac{\int_0^\infty \mathrm{e}^{-\int_0^\tau R(t)\mathrm{d}t}\mathrm{d}\tau}{1-(1-p_w)^N} = \frac{\int_0^\infty \mathrm{e}^{-uNp_a\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}}\mathrm{d}\tau}{1-(1-p_w)^N}. \tag{25}$$

The fration in exponential of the integrand in (25) can approximated as:

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

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

$$\tau_1 \approx \left(1+\mathrm{e}^{-Np_w}\right)\int_0^\infty \mathrm{e}^{-uNp_a\tau}\,\mathrm{d}\tau = \frac{\left(1+\mathrm{e}^{-Np_w}\right)}{uNp_a}, \tag{26}$$

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 (26) in Figure 11 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:

$$a_t = \frac{Nu\mathrm{e}^{\Delta_w t}}{\Delta_w-\Delta_a}\left[1-\mathrm{e}^{(\Delta_w-\Delta_a)t}\right]. \tag{27}$$

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:

$$\tau_2 = \frac{\int_0^\infty \mathrm{e}^{-(r_1+r_2)}\,\mathrm{d}\tau}{1-(1-p_w)^N} = \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a}\right)-vNp_m\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}\right]\mathrm{d}\tau}{1-(1-p_w)^N}, \tag{28}$$

which we plot in Figure 13 as a function of the initial population size.

We wish to obtain a simpler formula for τ_2 in an analogous way to (26). 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 (28) can be written as:

$$\exp\left[-\frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}-\frac{\mathrm{e}^{\Delta_a\tau}-1}{\Delta_a}\right)-vNp_m\frac{\mathrm{e}^{\Delta_w\tau}-1}{\Delta_w}\right] \approx \exp\left(-uvNp_m\tau^2-vNp_m\tau\right)$$

$$= \exp\left(\frac{vNp_m}{2}\right) \exp\left[-\frac{uvNp_m}{2}\left(\tau + \frac{1}{u}\right)\right].$$

Consequently, the mean time τ_2 is obtained to be:

$$\tau_2 \approx [1 + \exp(-Np_w)] \exp\left(\frac{vNp_m}{2u}\right) \frac{\operatorname{erfc}\left(\sqrt{\frac{vNp_m}{2u}}\right)}{\sqrt{\frac{2uvNp_m}{\pi}}}, \tag{29}$$

where erfc is the complementary error function. We plot the expansion (29) in Figure 13 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:

$$\tau_2 \approx \left(1 + e^{-Np_w}\right) \int_0^\infty e^{-uNp_m \tau} \, d\tau = \frac{\left(1 + e^{-Np_w}\right)}{uNp_m}, \tag{30}$$

which we plot in Figure 13 and observe that it offer as a good a fit to (28) as (29). 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 10 where aneuploidy improves the probability of evolutionary rescue only for small and intermediate values of N.

Contribution of aneuploidy to mean evolutionary rescue time

$$\begin{aligned} I = \frac{\tau_2}{\tau_1} &= \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w - \Delta_a}\left(\frac{e^{\Delta_w t} - 1}{\Delta_w} - \frac{e^{\Delta_a t} - 1}{\Delta_a}\right) - vNp_m \frac{e^{\Delta_w \tau} - 1}{\Delta_w}\right] d\tau}{\int_0^\infty e^{-uNp_m \frac{e^{\Delta_w \tau} - 1}{\Delta_w}} \, d\tau} \times \frac{1 - (1 - p_w|_{u=0})^N}{1 - \left(1 - p_w|_{u>0}\right)^N} \\ &= \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w - \Delta_a}\left(\frac{e^{\Delta_w t} - 1}{\Delta_w} - \frac{e^{\Delta_a t} - 1}{\Delta_a}\right) - vNp_m \frac{e^{\Delta_w \tau} - 1}{\Delta_w}\right] d\tau}{\int_0^\infty e^{-vNp_m \frac{e^{\Delta_w \tau} - 1}{\Delta_w}} \, d\tau} \frac{1}{H}, \end{aligned} \tag{31}$$

where H, is the ratio of the probability of evolutionary rescue with and without aneuploidy, defined in (18). We plot (31) in Figure 14 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 2). 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 5) 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 9 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 8). 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 12 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 (14) 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 10). 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 13) this could explain the reappearance of cancer even after initial remission.

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Appendices

Diffusion approximation

An alternative method to obtain the probability of evolutionary rescue is to utilize a Feller diffusion approximation which is governed by two parameters: the growth rate r and the reproductive variance σ. The two parameters are obtained from the underlying demographic process as the infinitesimal relative change in mean and variance of n_t over and an infinitesimally small time interval Δt:

$$r = \lim_{\Delta t \to 0} \frac{\mathbb{E}\left(\Delta n_t | n_t\right)}{\Delta_t n_t},$$
$$\sigma = \lim_{\Delta t \to 0} \frac{\mathbb{V}ar\left(\Delta n_t | n_t\right)}{\Delta_t n_t}.$$

The rate at which mutants are generated directly from the wildtype is:

$$\theta_1 = v\bar{\pi}_f \frac{N}{|r_w|}, \tag{32}$$

where

$$\bar{\pi}_f = \int_0^\infty \int_0^\infty \left(1 - \mathrm{e}^{-\frac{2r}{\sigma}}\right) f_r\left(r, \sigma\right) \mathrm{d}r\mathrm{d}\sigma. \tag{33}$$

Letting $f_r\left(r, \sigma\right) = \delta\left(r - r_m\right)\delta\left(\sigma - \sigma_m\right)$ then:

$$\bar{\pi}_f = 1 - \mathrm{e}^{-\frac{2r_m}{\sigma_m}}, \tag{34}$$

and, as a result, we have:

$$\theta_1 = v\left(1 - \mathrm{e}^{-\frac{2r_m}{\sigma_m}}\right) \frac{N}{|\Delta_w|}. \tag{35}$$

The rate at which mutants are generated indirectly from the wildtype through aneuploidy is:

$$\begin{aligned}
\theta_2 &= \frac{uN}{|r_w|} \int_0^\infty \int_0^\infty \left(1 - \pi_f\left(r, q\right)\right) f_r\left(r, \sigma\right) p_1^*\left(r, \sigma\right) \mathrm{d}r\mathrm{d}\sigma \\
&= \frac{uN}{|\Delta_w|} p_1^*\left(r_a, \sigma_a\right) \\
&= \frac{uN}{|\Delta_w|}\left[1 - \exp\left(-\frac{|r_a|}{\sigma_a^2}\left(\sqrt{1 + \frac{2\sigma_a^2}{r_a^2}u^*} - 1\right)\right)\right] \\
&= \frac{uN}{|\Delta_w|}\left[1 - \exp\left(-\frac{|\Delta_a|}{(\lambda_a + \mu_a)^2}\left(\sqrt{1 + \frac{2(\lambda_a + \mu_a)^2}{\Delta_a^2}u^*} - 1\right)\right)\right],
\end{aligned}$$

where

$$u^* = v\left(1 - \mathrm{e}^{-\frac{2r_m}{\sigma_m}}\right). \tag{36}$$

The number of rescue mutations has a Poisson distribution with rate $\theta_1 + \theta_2$. As a result, the probability of evolutionary rescue is given by:

$$p_{rescue} = 1 - \mathrm{e}^{-(\theta_1 + \theta_2)}, \tag{37}$$

which we plot in Figure 15 as a function of Δ_w.

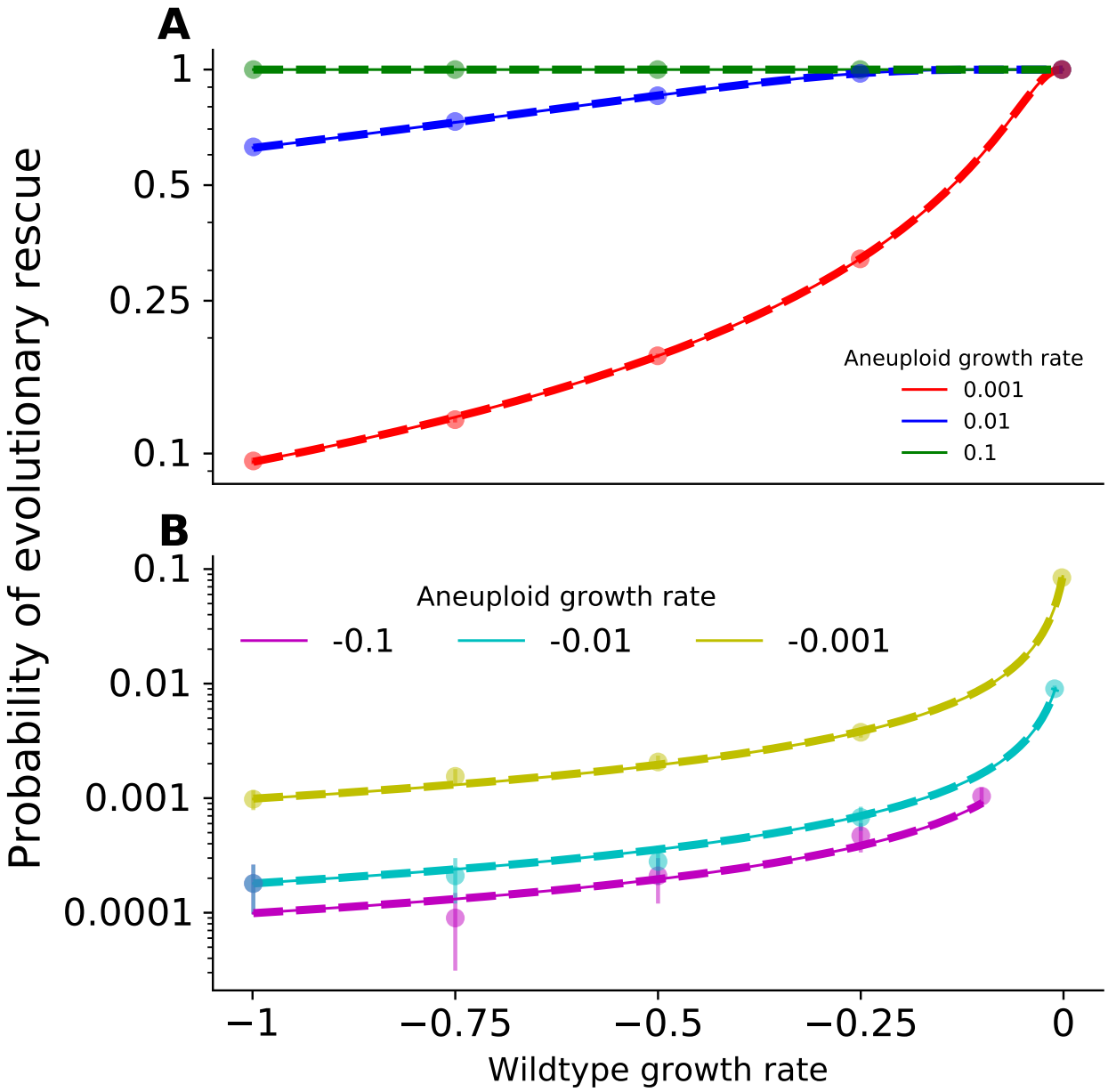

Figure 2: Plot of the probability of evolutionary rescue of a population, consisting initially of N wildtype cells, as a function of the proliferation rate of the wildtype cells for various values of the proliferation rate of the aneuploid cells. The continuous lines represent the exact result (**??**) while the dashed lines represent the approximation (**??**) for the upper plot and (**??**) for the lower plot. The 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: $N = 10^4, \lambda_a = 1 + 10^{-2}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

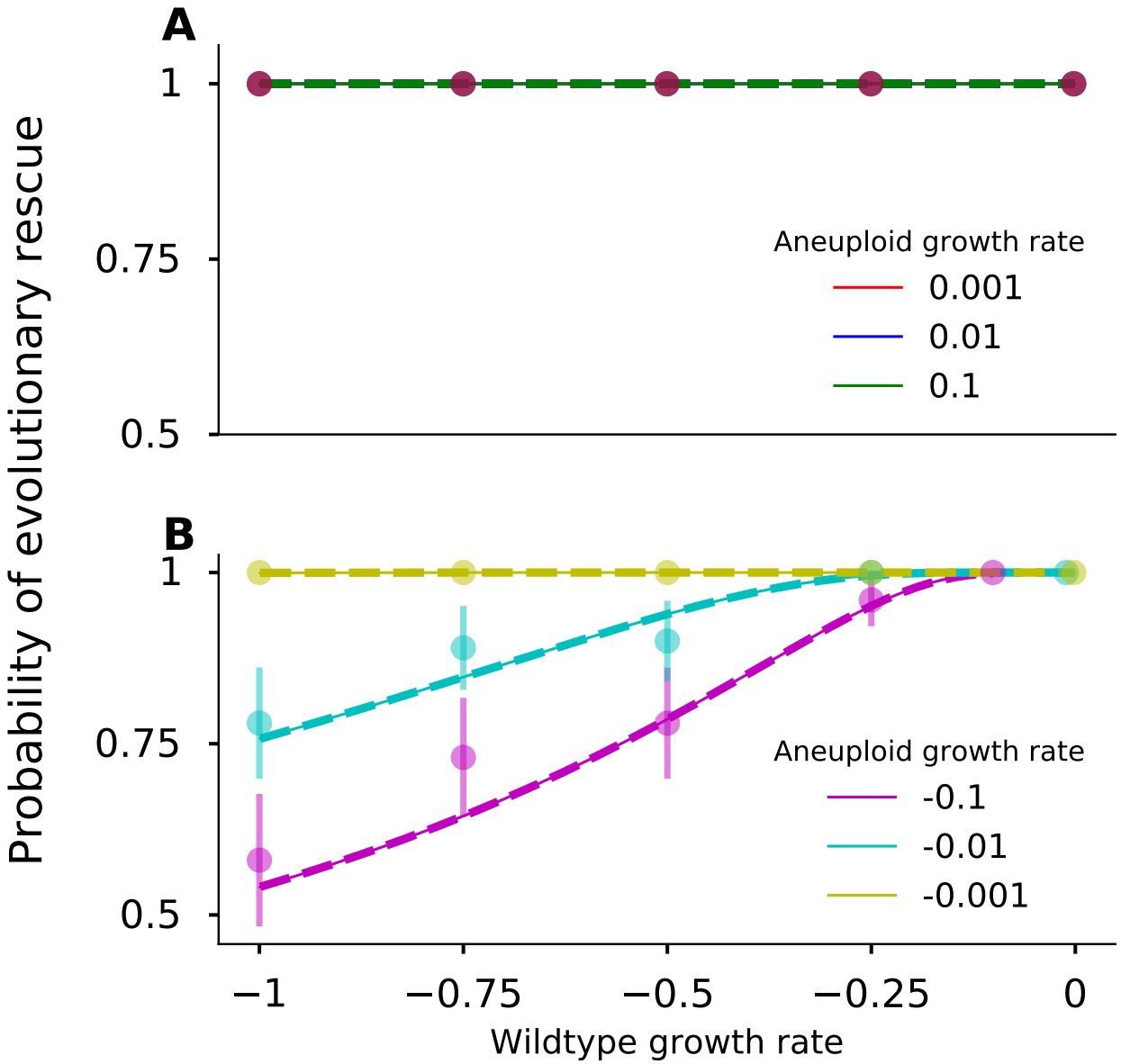

Figure 3: Plot of the probability of evolutionary rescue of a population, consisting initially of N wildtype cells, as a function of the proliferation rate of the wildtype cells for various values of the proliferation rate of the aneuploid cells. The continuous lines represent the exact result (**??**) while the dashed lines represent the approximation (**??**) for the upper plot and (**??**) for the lower plot. The 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: $N = 10^8, \lambda_w = 0.14, \lambda_a = 0.14, \lambda_m = 0.14, \mu_m = 0.13, u = 10^{-2}, v = 10^{-7}$.

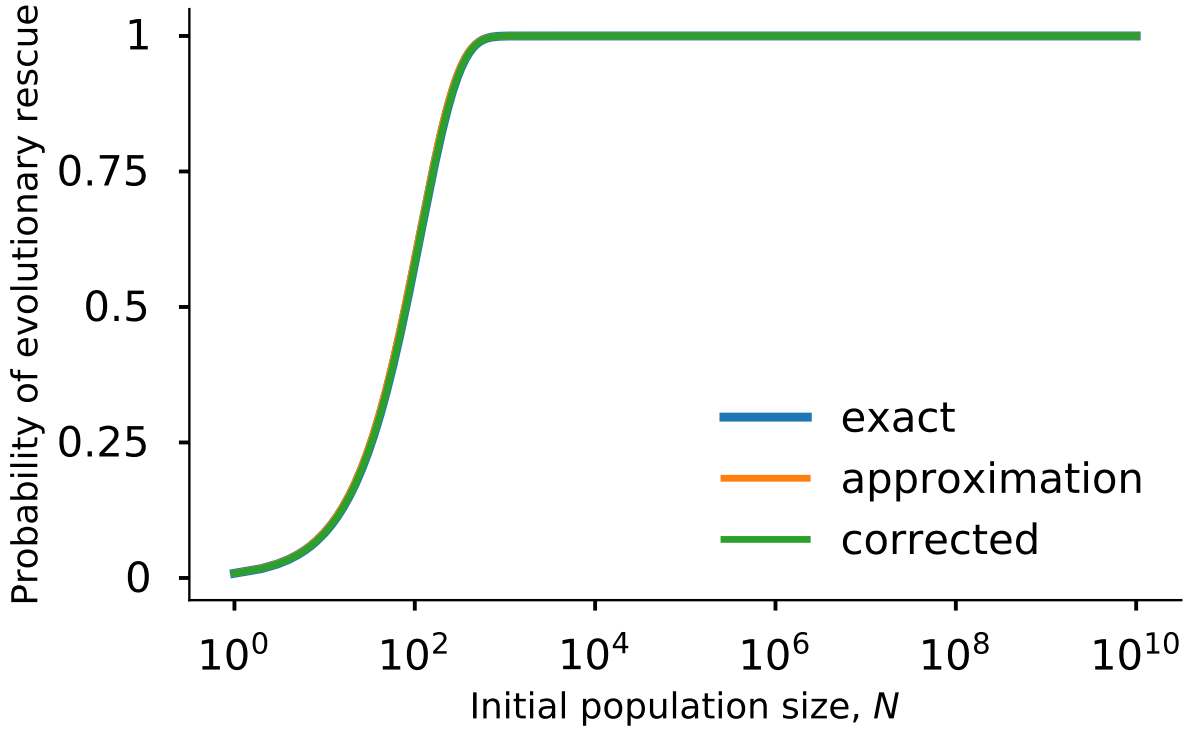

Figure 4: Plot of the probability of survival of a population as a function of the initial population size of wildtype cells. The blue line represents the exact solution (**??**), the orange line line represents the approximation (**??**), the green line represents the first order correction (8) and the red dots represents stochastic simulations. For the simulations we have chosen the following parameters: $\lambda_w = 0.14, \lambda_a = 0.14, \lambda_m = 0.14, \mu_w = 0.17, \mu_a = 0.135, \mu_m = 0.13$. The error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the mean probability of evolutionary rescue and $n = 100$ is the number of simulations.

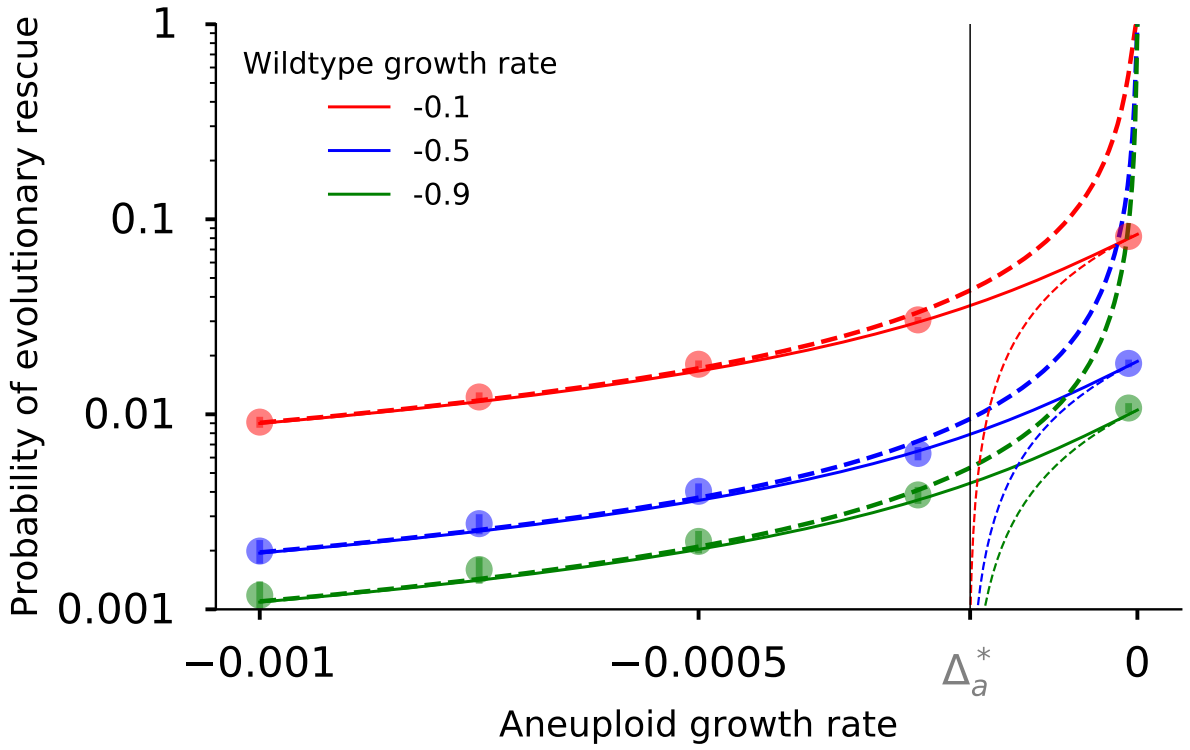

Figure 5: Plot of the probability of evolutionary rescue, of an initial population, consisting of N wildtype cells, as a function of proliferation rate of the wildtype cells $\Delta_w = \lambda_w - \mu_w$ for various values of the proliferation rate of the aneuploid cells $\Delta_a = \lambda_a - \mu_a$. The continuous lines represent the exact result (**??**) while the dashed lines represent the approximations (**??**) and (**??**). The dots represent numerical simulations where the error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the mean probability of evolutionary rescue and n is the number of simulations. The value highlighted in grey is the threshold Δ_a^* from (15) which marks the transition between the regime dictated by (**??**) to the one dictated by (**??**). Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $N = 10^4, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

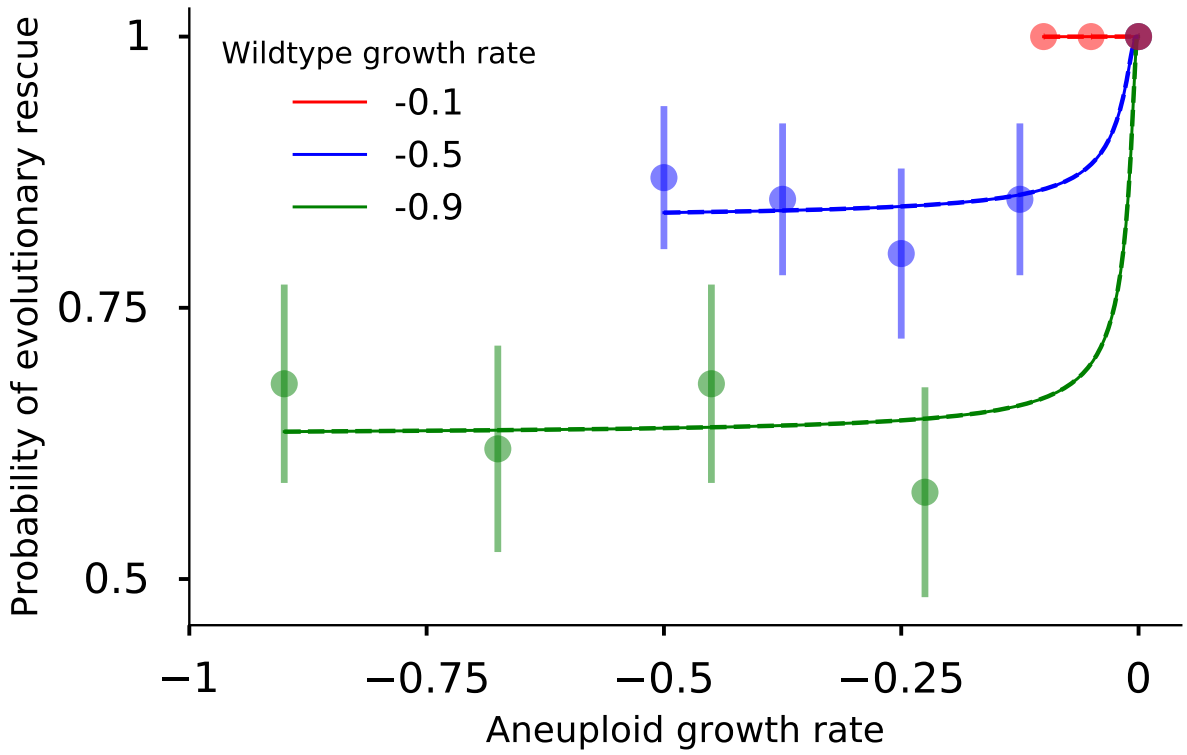

Figure 6: Plot of the probability of evolutionary rescue, of an initial population, consisting of N wildtype cells, as a function of proliferation rate of the wildtype cells $\Delta_w = \lambda_w - \mu_w$ for various values of the proliferation rate of the aneuploid cells $\Delta_a = \lambda_a - \mu_a$. The continuous lines represent the exact result (**??**) while the dashed lines represent the approximations (**??**). The dots represent numerical simulations where the error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/n}$ 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: $N = 10^8, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

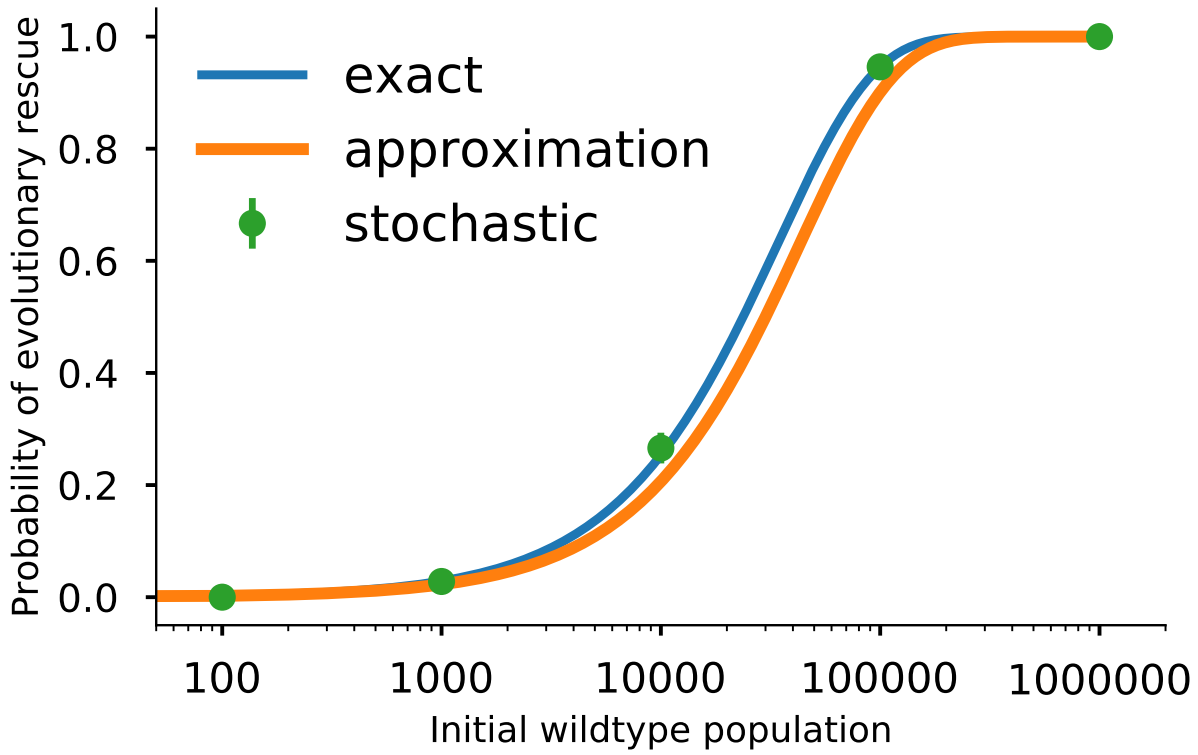

Figure 7: Plot of the probability of evolutionary rescue of a population, consisting of N wildtype cells, as a function of the initial population size of wildtype cells. The blue line represent the exact result (**??**) while the orange lines represent the approximation (**??**). The green dots represent 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: $\lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

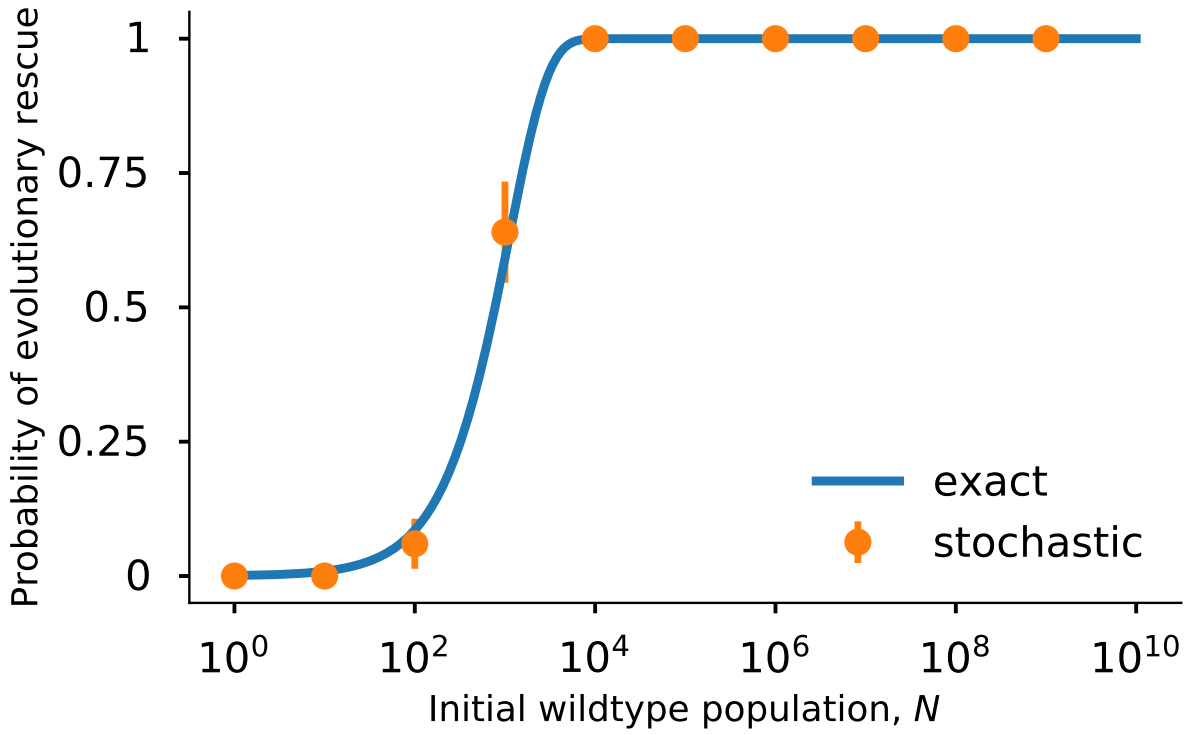

Figure 8: Plot of the probability of evolutionary rescue of a population, consisting of N wildtype cells, as a function of the initial population size of wildtype cells where maximum population size is constrained by the carrying capacity K. The blue line represent the exact result (**??**) while the 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: $\lambda_w = 1 - 10^{-1}, \lambda_a = 1 + 10^{-4}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_m = 1, u = 10^{-2}, v = 10^{-7}, C_1 = C_2 = 1, K = 10^9$.

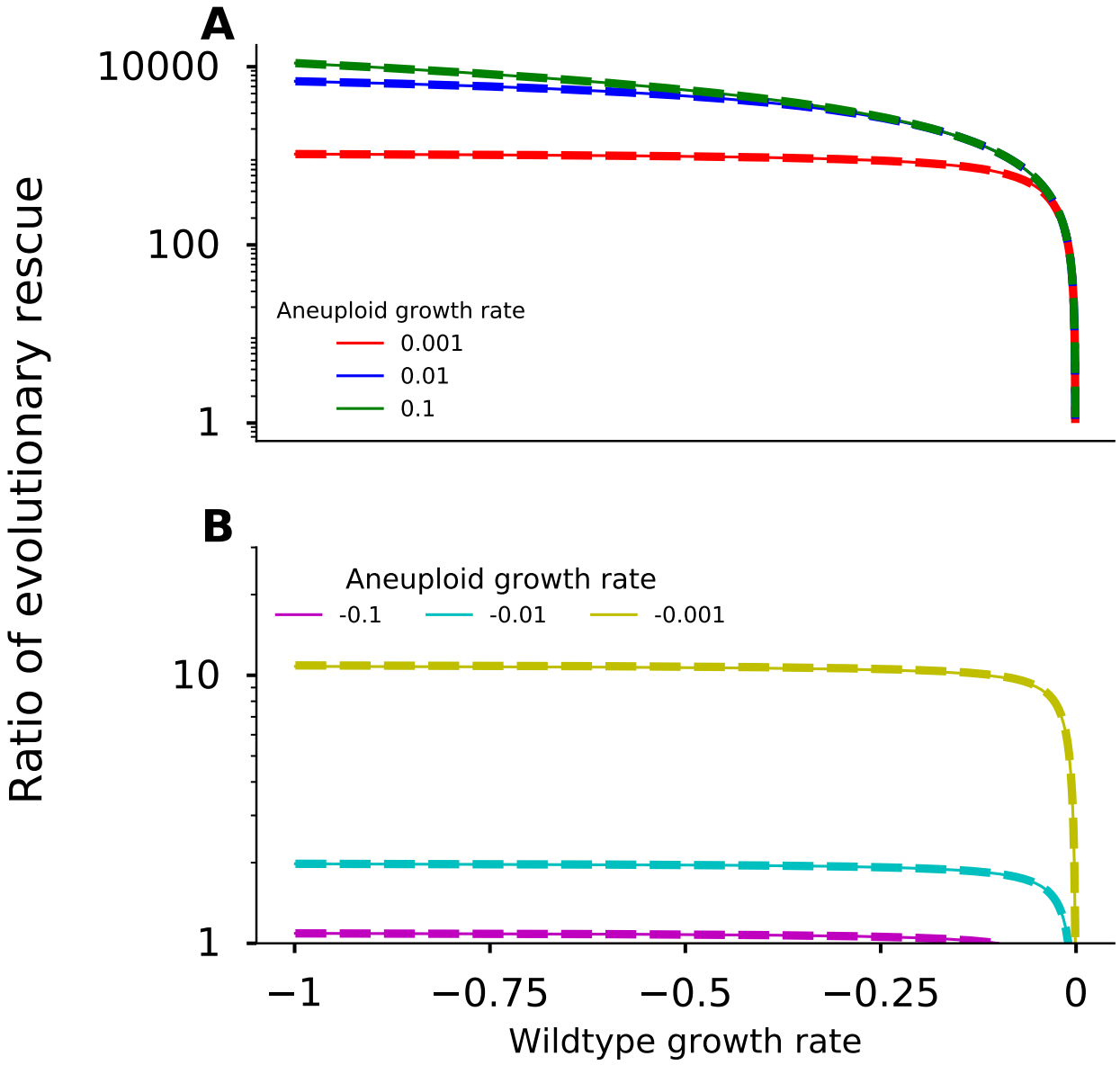

Figure 9: Plot of the ratio of the probability of evolutionary rescue when aneuploidy can play a role in rescue ($u > 0$) to the probability where acquisition of aneuploidy is not possible ($u = 0$) as a function of the proliferation rate of the wildtype cells. The continuous lines represent the exact result (18) while the dashed lines represent the approximation (19). The upper plot show the case when aneuploidy is resistant while the lower plot shows the case when it is susceptible. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

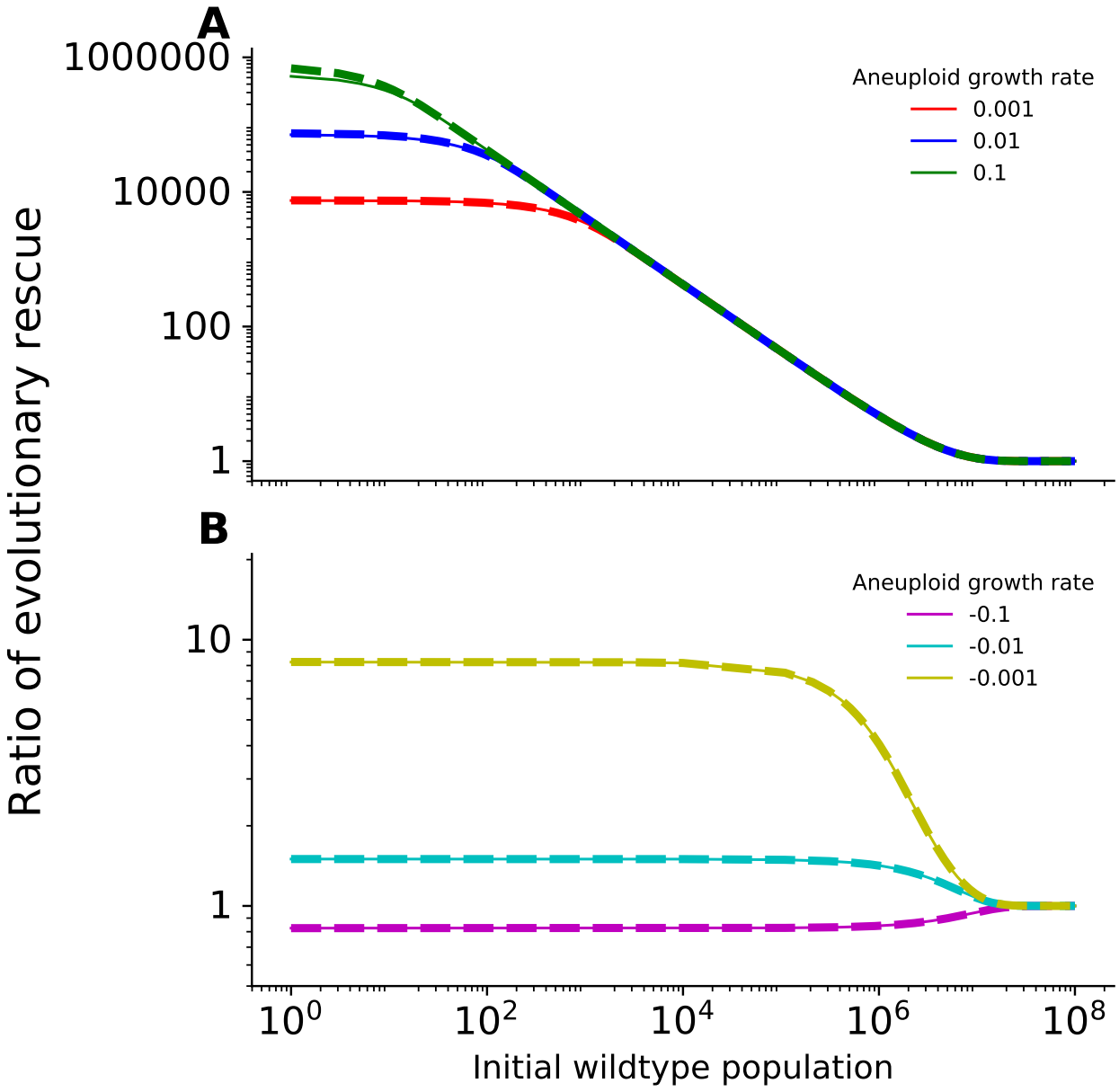

Figure 10: Plot of the ratio of the probability of evolutionary rescue when aneuploidy can play a role in rescue ($u > 0$) to the probability where acquisition of aneuploidy is not possible ($u = 0$) as a function of the initial population size of wildtype cells. The continuous lines represent the exact result (18) while the dashed lines represent the approximation (19). The upper plot show the case when aneuploidy is resistant while the lower plot shows the case when it is susceptible. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 0.14, \lambda_a = 0.14, \lambda_m = 0.14, \mu_w = 0.17, \mu_m = 0.13, u = 10^{-2}, v = 10^{-7}$.

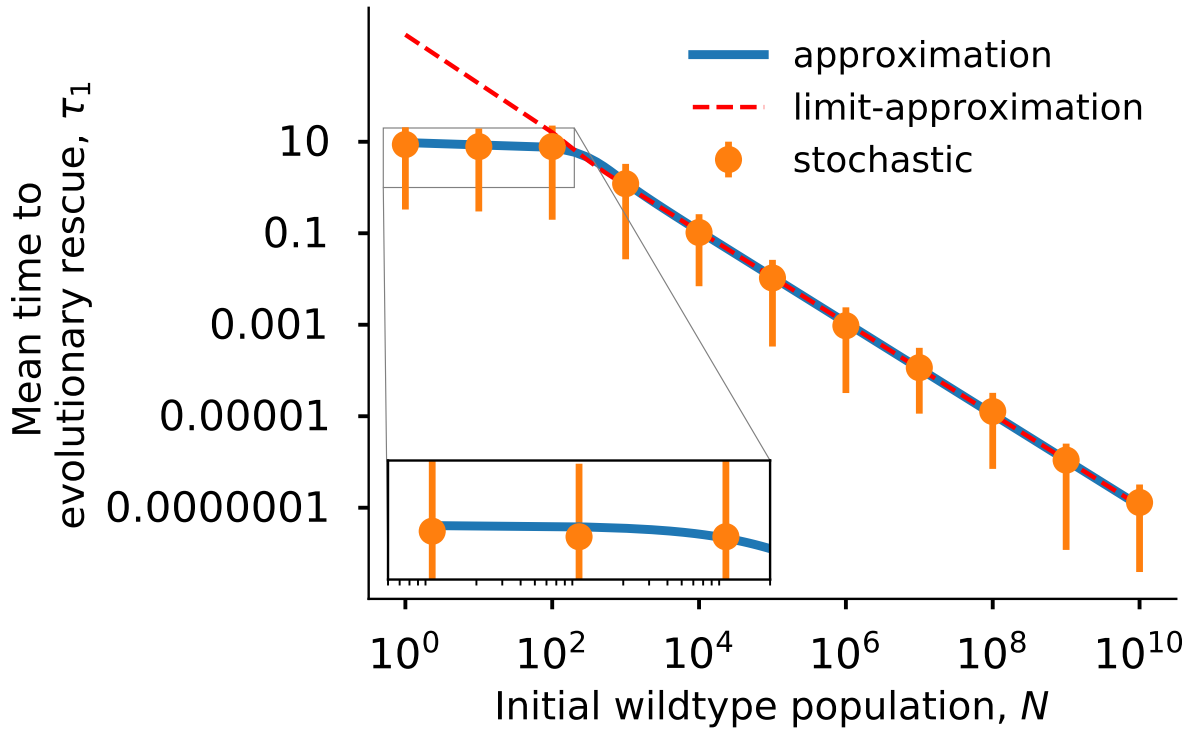

Figure 11: Plot of the mean time until the appearance of a resistance mutation which rescues the population in the case when evolutionary rescue is possible only through mutation but not aneuploidy and mutation. The blue line represents the approximation (25) and the dashed red line represents the first 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. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_m = 1, u = 10^{-2}, v = 10^{-7}$.

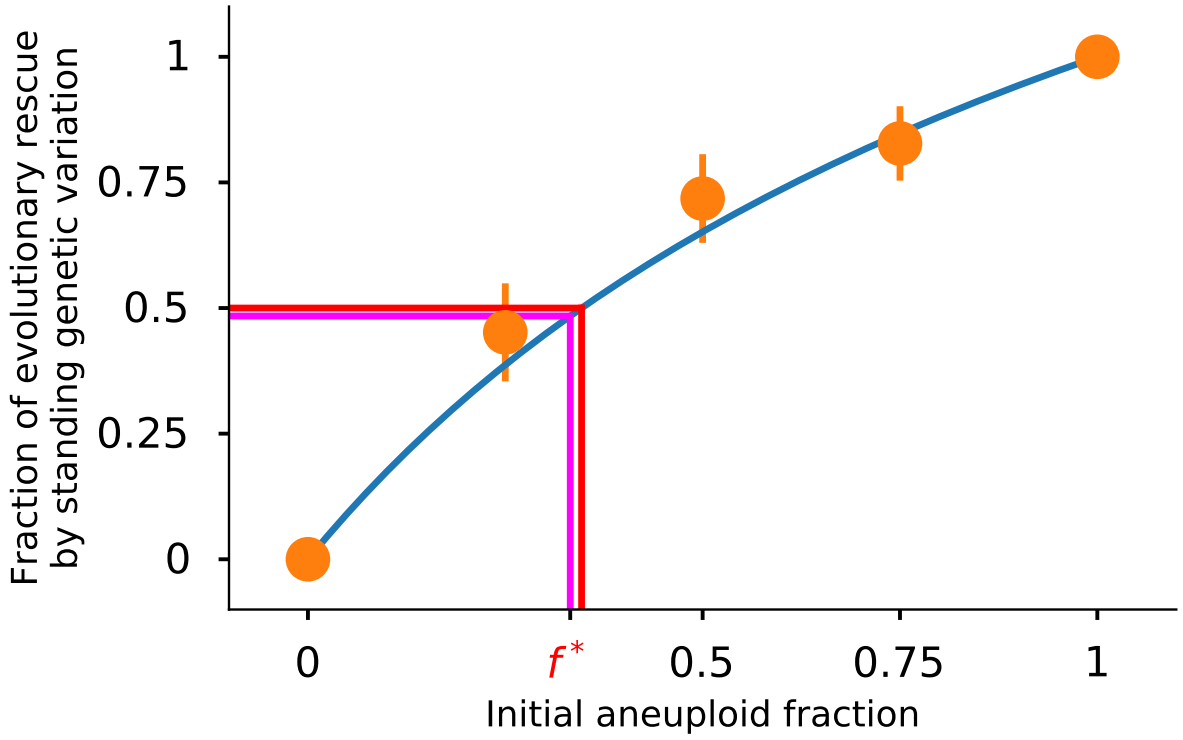

Figure 12: Plot of the fraction of the cases the population is rescue by standing genetic variation as a function of the fraction of initial cells which are aneuploid. The red vertical line highlights the the value of f for which half the times the population is rescues by aneuploid cells while the pink line is our approximation (17). For this plot we have chosen the following parameters: $N = 10^3, \lambda_w = 1 - 10^{-2}, \lambda_a = 1 - 10^{-4}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$. The error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the mean probability of evolutionary rescue and n is the number of simulations. The value of 0.332 highlighted in red is the value of the initial fraction of the population which in aneuploid for which half of the cases of evolutionary rescue are due to the initial aneuploid cell population.

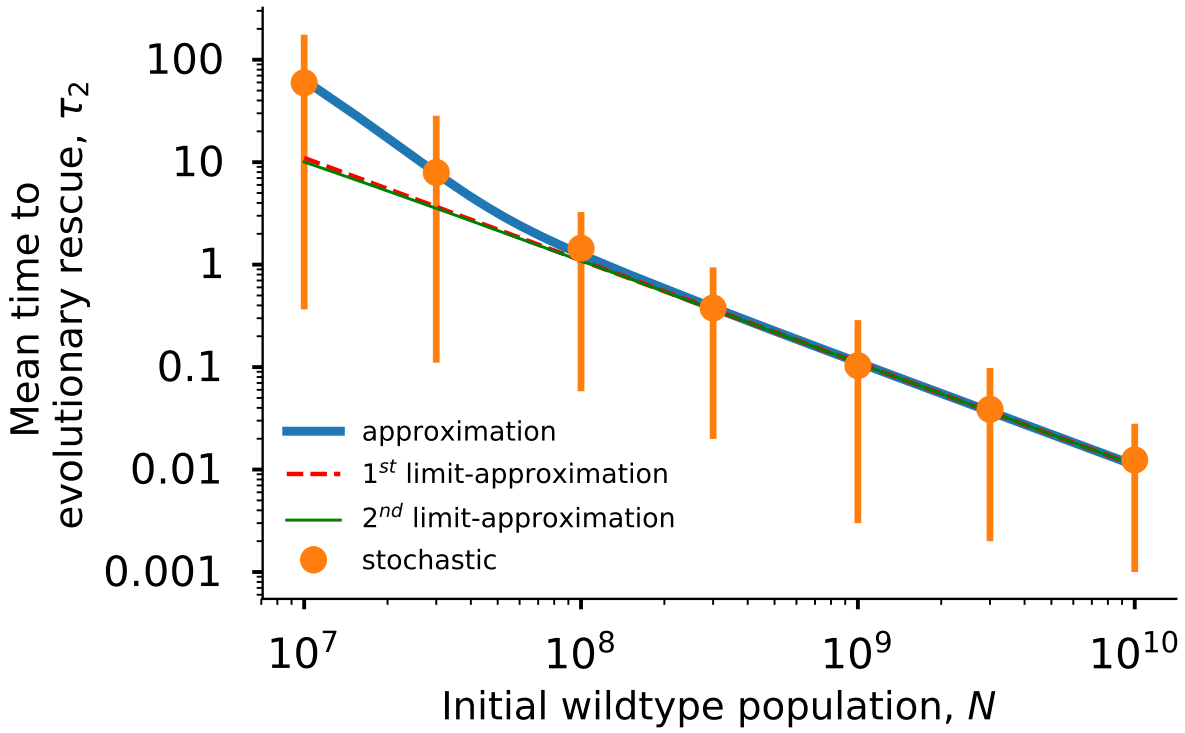

Figure 13: Plot of the mean time until the appearance of a resistance mutation which rescues the population in the case when evolutionary rescue is possible through mutation and aneuploidy. Here the population initially consists of N wildtype cells and for the simulations we have chosen the following 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 (28), the dashed red line represents the second order approximation (29) and the green line is first order approximation (30). 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.

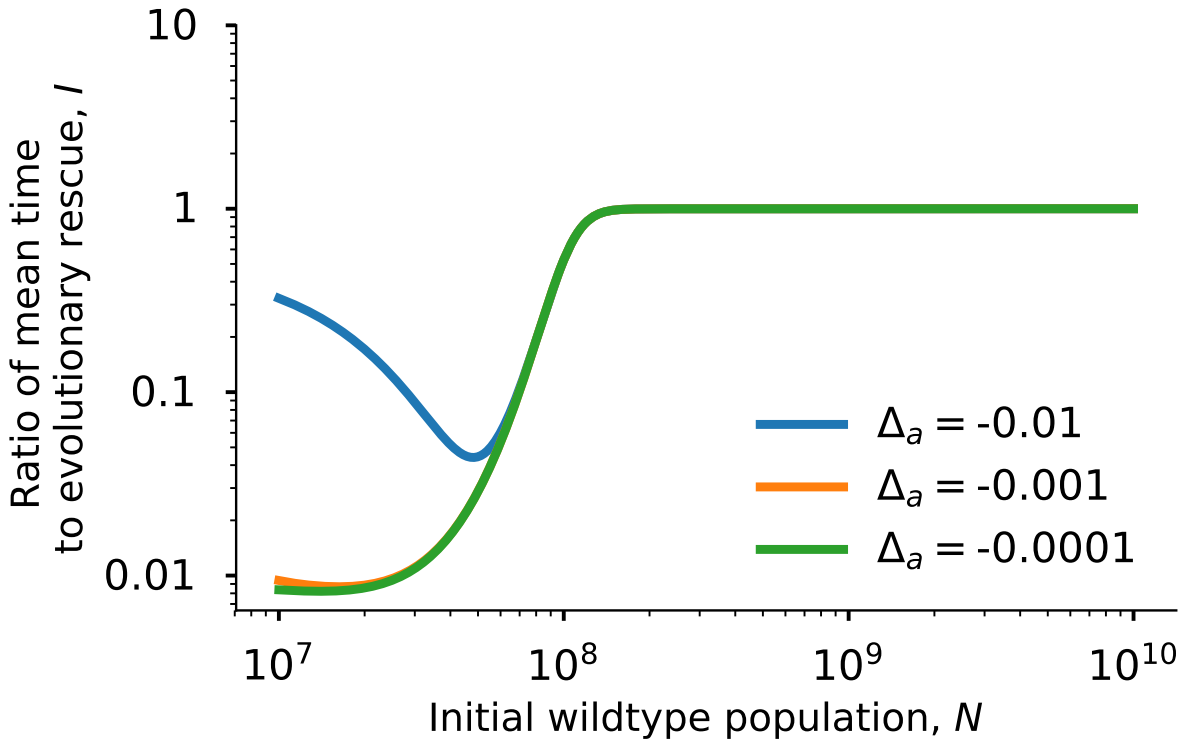

Figure 14: Plot of the ratio of the mean time to evolutionary rescue when aneuploidy can play a role in rescue ($u > 0$) to the mean time where acquisition of aneuploidy is not possible ($u = 0$) as a function of the initial population size of wildtype cells. The continuous lines represent the approximation (31). Here the population initially consists of N wildtype cells and for the simulations we have chosen the following parameters: $\lambda_w = 1 - 10^{-1}, \lambda_m = 1 + 10^{-1}, \mu_w = 1, \mu_a = 1, \mu_m = 1$.

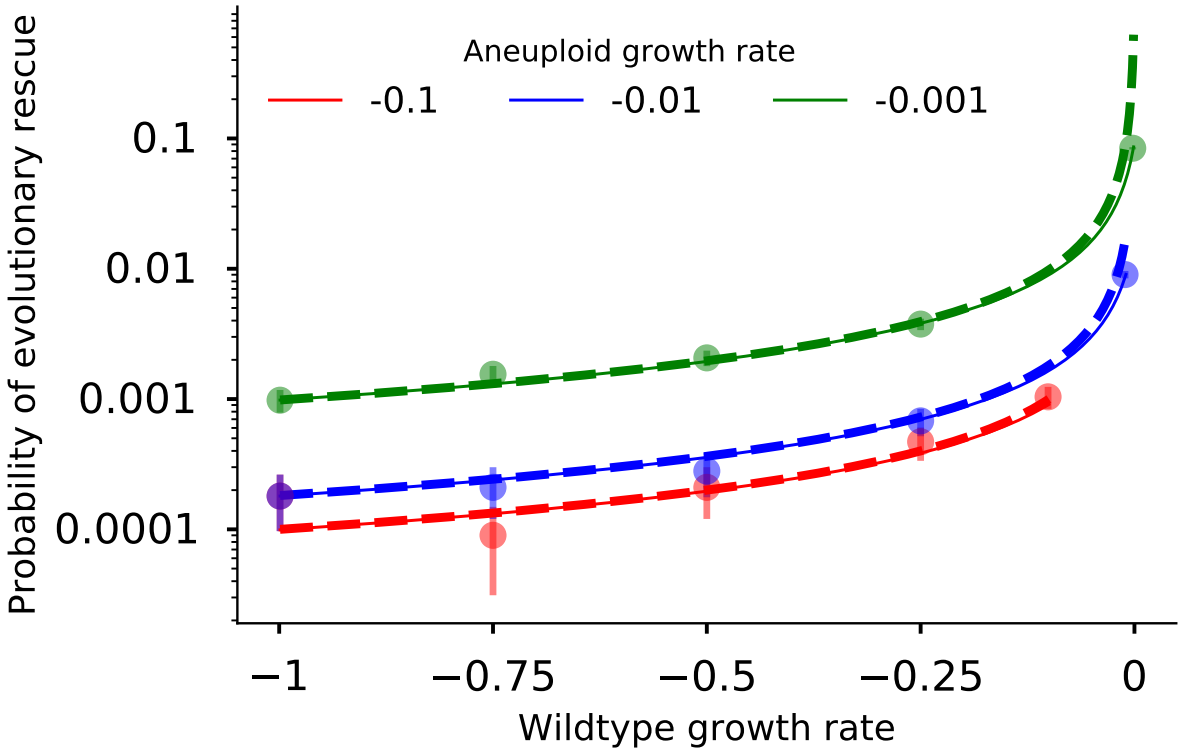

Figure 15: Plot of the survival probability of an initial population consisting of $w_0 = 10^4$ wild-type cells as a function of $\Delta_a = \lambda_a - \mu_a$ for various values of $\Delta_w = \lambda_a - \mu_a$. The continuous lines represent the exact result (**??**) while the dashed lines represent the Feller diffusion approximation (37). The error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/w_0}$ where p is the mean probability of evolutionary rescue.