The role of aneuploidy in the evolution of cancer drug resistance

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Abstract

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).

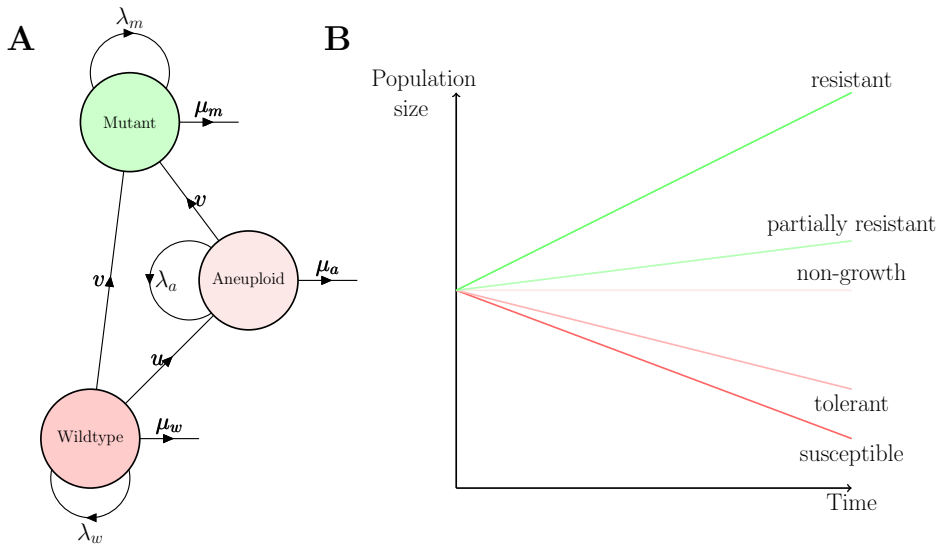

Figure 1: **Model illustration. (A)** A population of cancer cells is composed of wildtype, aneuploid, and mutant cells, which divide with rates λ_w, λ_a, and λ_m and die at rates μ_w, μ_a, and μ_m, respectively. Wildtype cells can become aneuploid at rate u. Both aneuploid and wildtype cells can acquire 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.

where H, is the ratio of the probability of evolutionary rescue with and without aneuploidy, defined in (**??**). We plot (29) in Figure 8 as a function of the initial wildtype population for varying values of the Malthusian fitness of aneuploid cells Δ_a.

Discussion

Evolutionary rescue is the process where the population acquires a trait that increases fitness in the new environment such that extinction is averted. Here, we have modeled a tumor–a population of cancer cells–exposed to drug therapy that causes the cell population to decline towards extinction. The cancer cell population can escape extinction either by a mutation that confers resistance, or by first generating aneuploid cells in which the effect of the drug is diminished, and then producing a mutation that confers full resistance (Figure 1).

Using multitype branching processes, we derived the probability of evolutionary rescue of the population of cancer cells under various scenarios for the effect of aneuploidy, including both tolerance and partial resistance to the drug. We obtained both exact and approximate expressions for the probability of evolutionary rescue. As expected, our analytic results in **??** show that the probability of evolutionary rescue increases with the initial tumor size N, the wildtype growth rate $\Delta_w = \lambda_w - \mu_w$, and the mutation v and aneuploidy u rates.

When aneuploid cells are partially resistant to the drug ($\Delta_w \ll 0 \ll \Delta_a \ll \Delta_m$), evolutionary rescue can be approximated by a one-step evolutionary rescue process where aneuploidy itself rescues the population (Figure 2). When aneuploidy only provides tolerance to the drug ($\Delta_w \ll \Delta_a \ll 0 \ll \Delta_m$), it cannot rescue the population. Instead, aneuploidy acts as a *stepping stone* through which the resistant mutant can appear in a more expedient fashion, given that the aneuploid cell population declines slower then the wildtype cell population. In this case, aneuploidy provides two benefits. First, it delays the extinction of the population–providing more time for appearance of the resistance mutations. Second, it increases the population size relative to a wildtype population–providing more cells for generating mutations, i.e., it increases the mutation supply.

We find that aneuploidy can have a significant effect on evolutionary rescue (Figure 6). For example, when aneuploidy cells are "barely-resistant" (they grow at a very low rate, $\Delta_a = 10^{-3}$)

	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.

$$= \frac{\int_0^\infty \exp\left[-\frac{uvNp_m}{\Delta_w-\Delta_a}\left(\frac{e^{\Delta_w t}-1}{\Delta_w}-\frac{e^{\Delta_a t}-1}{\Delta_a}\right)-vNp_m\frac{e^{\Delta_w \tau}-1}{\Delta_w}\right]\mathrm{d}\tau}{\int_0^\infty e^{-vNp_m\frac{e^{\Delta_w\tau}-1}{\Delta_w}}\mathrm{d}\tau}\frac{1}{H}, \tag{29}$$

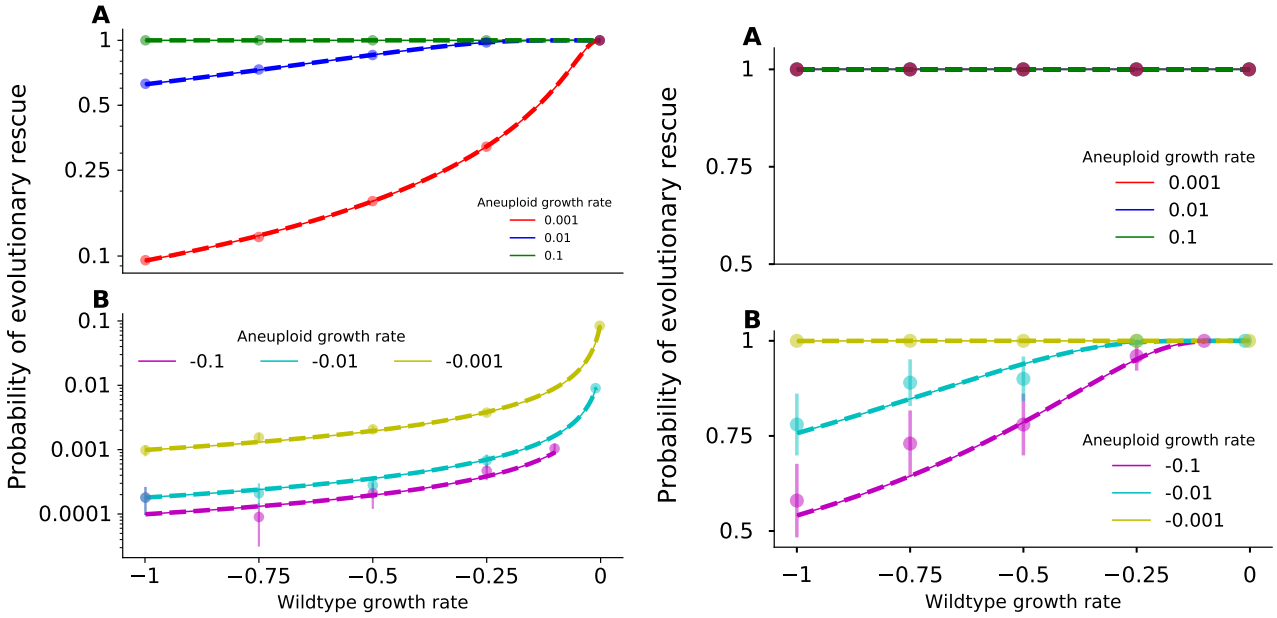

Figure 2: **Evolutionary rescue probability with partially resistant or tolerant aneuploid cells.** Rescue probability is very high when aneuploidy provides partial resistance ($\lambda_a = 0.01$), in an initially small tumor (**Aleft**, $N = 10^4$) and even more so in an initially large tumor (**Aright**, $N = 10^8$). 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 (**??** in **??**); dashed lines for the approximate formula (**??**), demonstrating that they all agree. Here, aneuploidy rate is $u = 10^{-2}$ and mutation rate is $v = 10^{-7}$.

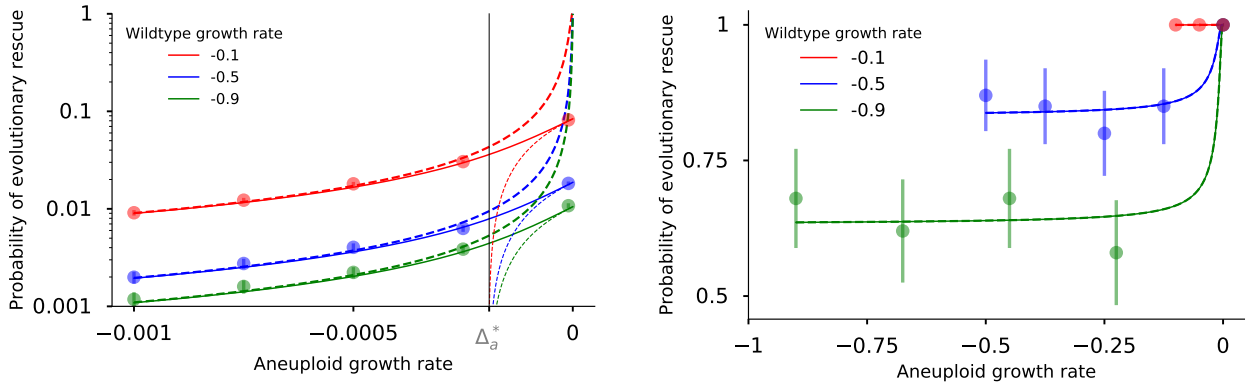

Figure 3: **Evolutionary rescue probability with tolerant or non-growing aneuploid cells.** Rescue probability grows with the aneuploid growth rate Δ_a (x-axis), and is much higher in an initially large tumor than in a small one ((A) $N = 10^4$; **(B)** $N = 10^8$). Markers for simulation results with 95% CI; solid lines for the exact formula (**??** in **??**); dashed lines for the approximate formula (**??**). 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 $\Delta_a^* = 2vp_m + v + 2\sqrt{vp_m\,(vp_m + \mu_a + v)}$.

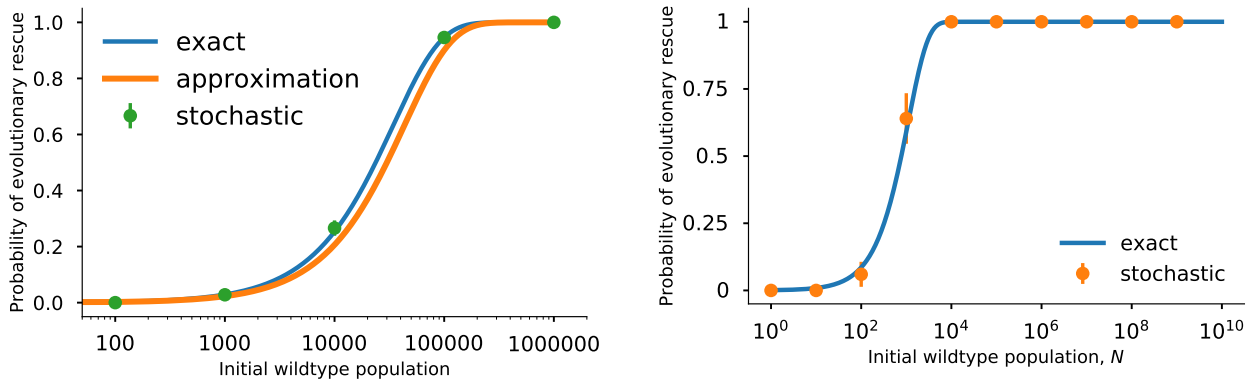

Figure 4: **Evolutionary rescue probability for variable initial tumor size. (A)** Comparison of simulation results (markers with 95% CI, too small to appear with 10^5 simulations per marker), the exact formula (blue line, **??** in **??**) and the approximate formula (orange line, **??**). **(B)** Comparison of results of simulations with density-dependent growth (markers with with 95% CI) and the exact formula (blue line, **??** in **??**). Here, $K = 10^9$.

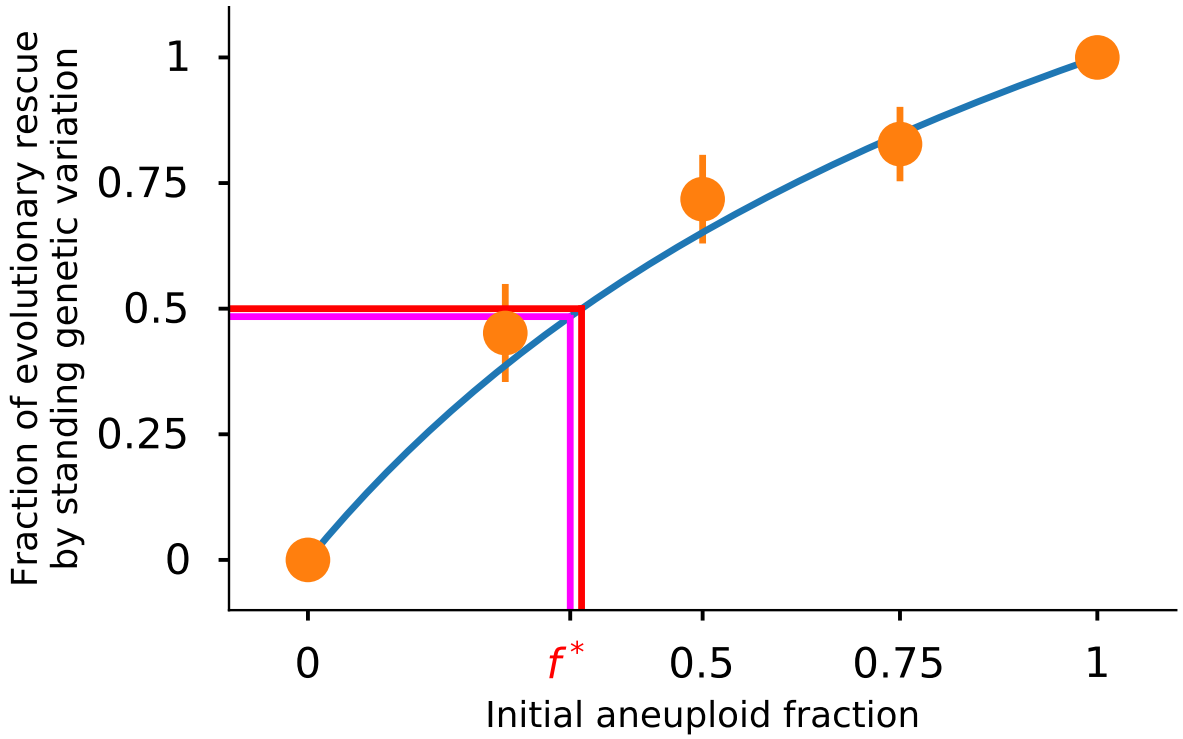

Figure 5: **Effect of standing variation on evolutionary rescue.** In aneuploid cells already exist in the population at the onset of drug therapy as standing genetic variation, then evolutionary rescue is more likely...

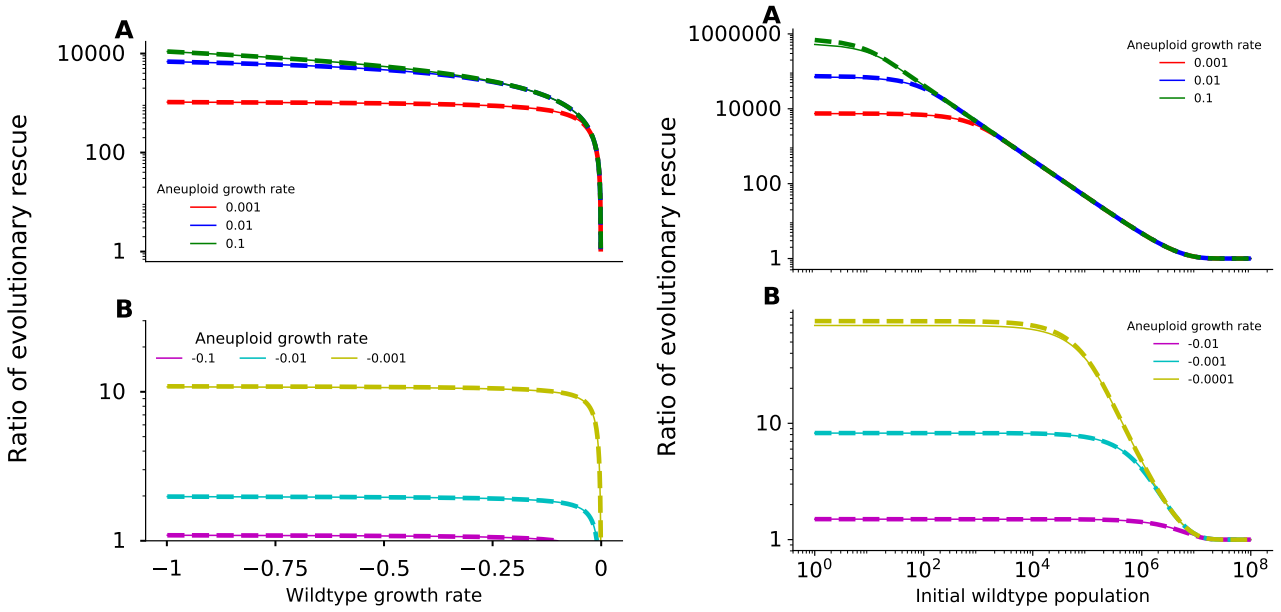

Figure 6: **Effect of aneuploidy on evolutionary rescue.** The ratio of rescue probability with and without aneuploid (H, **??**) increases with the aneuploid growth rate (colors) and decreases with the wildtype growth rates and initial tumor size (x-axes), except for large tumors where where the ratio converges to unity. **(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 (**??** in **??**); dashed lines apply p_{rescue} from the approximate formula (**??**), with good agreement.

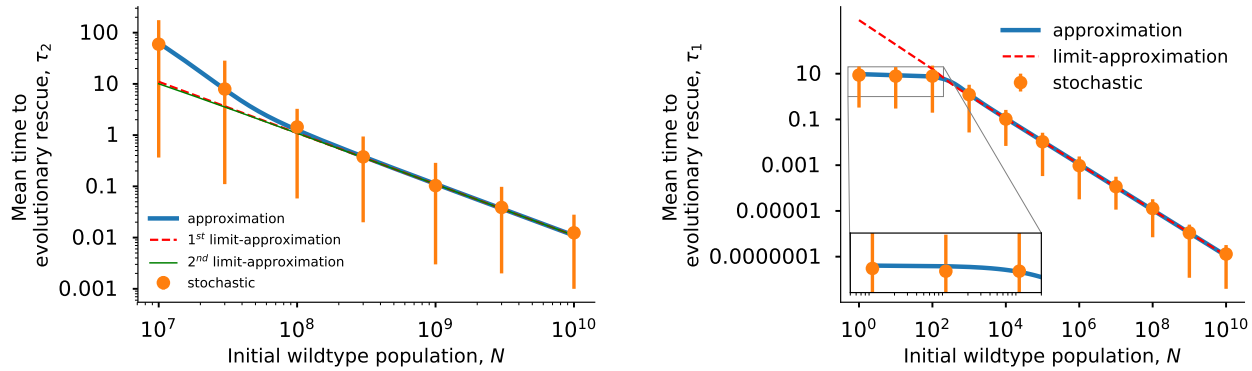

Figure 7: **Evolutionary rescue time.** Shown is the mean time for appearance of a resistance mutation the leads to evolutionary rescue **(left)** with ($u > 0$) and **(right)** without ($u = 0$ aneuploidy. Our inhomogeneous Poisson-process approximations (solid blue lines, right: **??**, left: **??**) is in agreement with simulation results (orange markers with 95% CI). Our 1st-order (dashed red lines, right: **??**, left: **??**) and 2nd-order (green line, left: **??**) approximations work well when the initial tumor size is large (here $> 10^8$ cells).

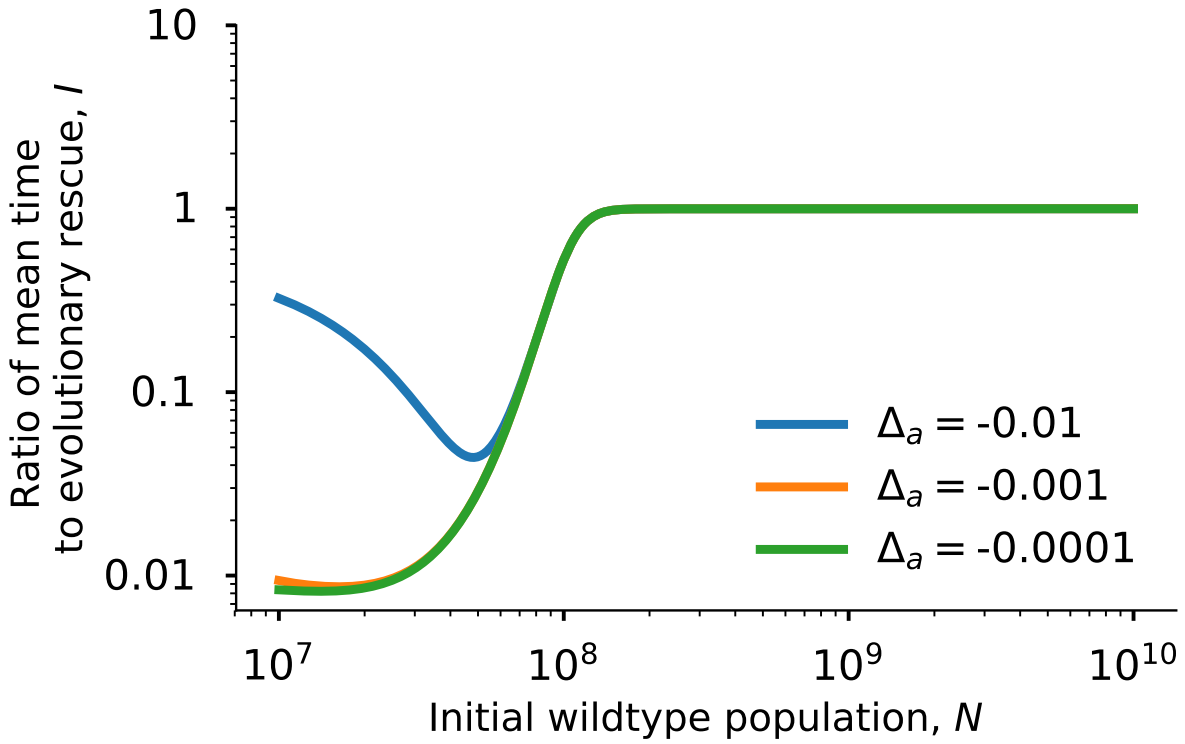

Figure 8: **Ratio of evolutionary rescue time with and without aneuploidy.** The ratio of the mean time to appearance of a resistance mutation that leads to evolutionary rescue with ($u > 0$) and without ($u = 0$) aneuploidy for variable initial tumor sizes (eq. (29)) when aneuploidy provides tolerance to the drug ($\Delta_a \ll 0$). When the initial tumor size is not large ($< 10^8$), aneuploidy can decrease the rescue time by 10-100-fold. *I THINK THERE IS A MISTAKE IN THE BLUE LINE*