

Evolutionary rescue in a fluctuating environment

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Abstract

No environment is constant over time, and environmental fluctuations impact the outcome of evolutionary dynamics. Survival of a population not adapted to some environmental conditions is threatened unless a mutation rescues it, an eco-evolutionary process termed evolutionary rescue. We here investigate evolutionary rescue in an environment that fluctuates between a favorable state, in which the population grows, and a harsh state, in which the population declines. We develop a stochastic model that includes both population dynamics and genetics. We derive analytical predictions for the mean extinction time of a non-adapted population given that it is not rescued, the probability of rescue by a generalist mutation, and the mean appearance time of a rescue mutant, which we validate using numerical simulations. We find that evolutionary rescue is less (respectively more) likely if the environmental fluctuations are stochastic rather than deterministic and if the mean time between each environmental change is less (respectively more) than the mean survival time of the population in the harsh environment. We demonstrate that high equilibrium population sizes and *per capita* growth rates maximize the chances of evolutionary rescue. We show that an imperfectly harsh environment, which does not fully prevent births but makes the death rate to birth rate ratio much greater than unity, has almost the same rescue probability as a perfectly harsh environment, which fully prevents births. Finally, we put our results in the context of antimicrobial resistance and conservation biology.

1 Introduction

Environmental change happens all around us and impacts the populations that experience it. For example, every living organism is exposed to climate change [1, 2, 3, 4], and pathogenic microbes are treated with varying drug concentrations [5, 6], which threatens their survival. Populations too poorly adapted to changing environmental conditions may go extinct unless adaptive mutations counteract their decline, a process termed evolutionary rescue. An important question in theoretical biology is to predict whether evolutionary rescue will occur before extinction and which conditions favor adaptation [7, 8, 9].

Numerous theoretical works have shown that environmental fluctuations affect evolutionary dynamics. Specifically, analytical predictions were derived to assess the fate of a mutation in a fluctuating environment, which impacts either demography [10, 11, 12] or selection [12, 13, 14, 15]. For example, these analytical predictions showed that a cyclic change in population size or selection coefficient (resembling a fluctuating environment) results in a mutant fixation probability that is also periodic as a function of the time of appearance. However, many of

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39 these models assume that environmental fluctuations do not impact demography and selection
40 together, which is a simplification that overlooks a key aspect of evolutionary dynamics: the
41 interaction of population dynamics and population genetics (but see [16]).

42 The interaction between population dynamics and genetics is all the more important as it
43 exists everywhere in nature. For example, antimicrobial treatments are designed to decrease the
44 size of microbial populations until their eradication, which inhibits reproduction and thus the
45 appearance of mutation, but selects for antimicrobial resistant mutants that may appear during
46 drug therapy [5, 17, 18, 19, 20, 21, 22, 23, 24]. Similarly, climate change may cause extinction
47 [25, 26, 27], but some animal species adapt quickly to stressful conditions and reverse their
48 decline [28, 29, 30]. Importantly, the interaction between demography and selection can result
49 in population decline, reducing genetic diversity, which could facilitate evolutionary rescue [31].
50 To improve theoretical predictions and inference from experimental and empirical data, there
51 is a need for mathematical models that make an explicit link between ecology, evolution, and
52 demography when quantifying the fate of a population evolving in a fluctuating environment [32,
53 33]. One of the challenges to overcome is to go beyond the approximation that environmental
54 and evolutionary time scales are decoupled [34, 35]. Specifically, environmental effects are often
55 self-averaged if environmental fluctuations are rapid [36], or a constant environment is assumed
56 if environmental fluctuations are slow [37] (but see [11, 14, 38]). Another challenge is to derive
57 exact analytical predictions that do not rely on deterministic or diffusion approximations, which
58 have been shown to poorly describe extreme events such as extinction [39], yet necessary for
59 modeling evolutionary rescue.

60 In this paper, we develop a minimal model that integrates population dynamics and genetics
61 to quantify evolutionary rescue in a fluctuating environment. Specifically, we study a haploid
62 population evolving in an environment fluctuating between a favorable state, in which the pop-
63 ulation grows, and a harsh state, in which it declines. The population is initially monomorphic,
64 and mutants can appear upon reproduction. If a mutation unaffected by environmental changes
65 becomes fixed, the population is rescued from extinction. Importantly, we investigate the prob-
66 ability of evolutionary rescue using a stochastic framework with numerical and analytical tools,
67 resulting in an exact computation of the population’s fate under deterministic versus stochastic
68 environmental fluctuations. We compare a perfectly harsh (i.e., fully birth-preventing) and
69 an imperfectly harsh (i.e., not fully birth-preventing) environment and identify which growth
70 parameters promote evolutionary rescue using different growth types.

71 2 Model and methods

72 **A population model in a fluctuating environment.** We study a wild-type population
73 of size N_W , which can vary over time and is limited by a carrying capacity K . Each wild-type
74 individual has the same birth rate $b_{W,\alpha}$, which depends on the environmental state, and death
75 rate d_W . The population follows a logistic growth in which the *per capita* birth rate satisfies
76 $b_{W,\alpha}(1 - N_W/K)$, and the *per capita* death rate is equal to the intrinsic death rate. We also
77 present results for the Gompertz and Richards growths, whose *per capita* birth rates satisfy
78 $b_{W,\alpha} \log(K/N_W)$ and $b_{W,\alpha}(1 - (N_W/K)^\beta)$, respectively (see figure 1d). These growth types,
79 which are used to fit population growth data [40, 41], have different equilibrium sizes and *per*
80 *capita* growth rates that may impact the probability of evolutionary rescue. The population
81 evolves in an environment that fluctuates between two states, namely favorable F and harsh
82 H, which impacts only the birth rate. In the favorable environment, the *per capita* birth rate
83 is larger than the death rate (e.g., $b_{W,F}(1 - N_W/K) > d_W$ for the logistic growth) so that the
84 population grows towards its equilibrium size N_W^* . Conversely, in the harsh environment, the
85 *per capita* birth rate is lower than the death rate (e.g., $b_{W,H}(1 - N_W/K) < d_W$ for the logistic
86 growth), so that the population declines towards extinction. An example of a simulation run

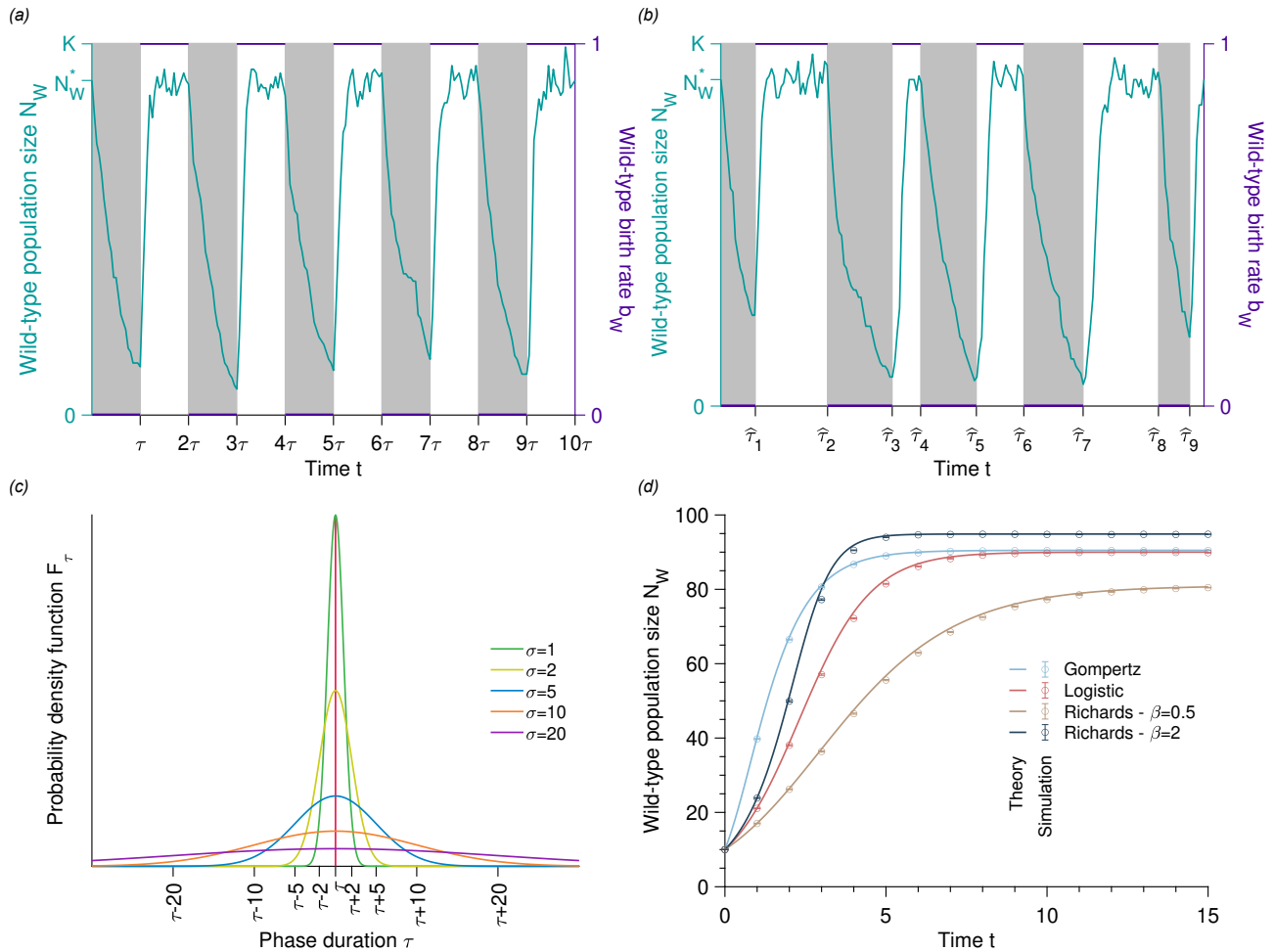


Figure 1: Illustration of the model - Population dynamics in a fluctuating environment. Wild-type population size and birth rate versus time with deterministic (a) and stochastic switches (b). In both panels, the solid line represents a realization of a simulation run under the logistic growth. The gray and white phases correspond to harsh and favorable environments, respectively. (c) Probability density function of the phase duration, which is normally distributed, positive, of mean τ and standard deviation σ . (d) Population size versus time for different population growth patterns in a constant favorable environment. Solid lines represent analytical predictions, and data points show simulated data averaged over 10^4 stochastic realizations. Error bars correspond to the 95% confidence intervals. Parameter values: wild-type birth rate in favorable environment $b_{W,F} = 1$, wild-type birth rate in harsh environment $b_{W,H} = 0$, wild-type death rate $d_W = 0.1$, carrying capacity $K = 100$, and equilibrium wild-type population size $N_W^* = 90$.

is shown in figure 1a). The environment remains in each state for a duration τ , sampled from the probability density function \mathcal{F}_τ . In the case of deterministic fluctuations, we set $\mathcal{F}_\tau(t) = \delta(t - \tau)$, in which δ is the Dirac delta. In the case of stochastic fluctuations, the phase duration is drawn from a biased normal distributions of mean τ and standard deviation σ given by $\mathcal{F}_\tau(t) = \frac{2e^{-\frac{1}{2}\left(\frac{t-\tau}{\sigma}\right)^2}}{\sigma\sqrt{2\pi}(1+\text{Erf}(t/(\sigma\sqrt{2\pi})))}$ (see figure 1b-c) that exclude negative values.

A generalist mutant appears upon reproduction with probability μ and has birth b_M and death rates d_M constant across environments. We assume that the population is initially monomorphic for the wild type and that its initial population size equals the equilibrium size N_W^* . Demographic equilibrium, obtained when births and deaths offset each other, is equal to $K(1 - d_W/b_{W,F})$ for the logistic growth. Our analytical approach uses methods from birth-

97 death processes described by master equations [42, 43]. Our simulations are based on a Gillespie
 98 algorithm and incorporate individual stochastic division, mutation, and death events [44, 45].
 99 The algorithm we used is detailed in the Supplemental Material.

100 **Timescales of environmental fluctuations.** In the fluctuating environment, either the
 101 population goes extinct at time T_0 , or a mutant appears, fixes, and thus rescues the population
 102 before T_0 . The evolutionary outcome crucially depends on how the environmental timescale τ
 103 compares to the population's lifetime $\tau_{0,H}$ in the harsh environment. In the limit of large τ , for
 104 $\tau \gg \tau_{0,H}$, very slow environmental fluctuations lead to rapid extinction (i.e., $T_0 = \tau_{0,H}$) because
 105 the harsh environment lasts much longer than the population lifetime in the harsh environment
 106 (see figure S1a). Here, the rapid extinction leaves little (if $b_{W,H} > 0$ and $d_W/b_{W,H} \gg 1$) or no
 107 opportunity (if $b_{W,H} = 0$) for rescue mutants to appear and therefore the rescue probability p_r
 108 is likely to be zero. In the limit of small τ , for $\tau \ll \tau_{0,H}$, very rapid environmental fluctuations
 109 make the population persist long enough for mutations to arise and rescue it. In the particular
 110 case of very fast environmental fluctuations, the evolutionary dynamics can be described by
 111 a constant environment with an averaged birth rate $\tilde{b}_W = (b_{W,F} + b_{W,H})/2$ and an effective
 112 equilibrium size \tilde{N}_W^* satisfying $0 < \tilde{N}_W^* < N_W^*$ (see figure S1b). Although rapid environmental
 113 fluctuations maintain the population in an equilibrium state, its extinction time \tilde{T}_0 is reduced
 114 compared to if it remained indefinitely in the favorable environment. In the case of an effective
 115 constant environment, the mean appearance time of a beneficial mutant of selection coefficient
 116 \tilde{s} (i.e., $\tilde{s} = (b_M \times \tilde{d}_W)/(\tilde{b}_W \times d_M) - 1 > 0$) that becomes fixed is given by $\tilde{\tau}_{\text{af}} = 1/(\mu \tilde{N}_W^* \tilde{d}_W \tilde{s})$
 117 (see figure S2). If this time is much shorter than the mean extinction time \tilde{T}_0 , the rescue
 118 probability p_r is likely to be one.

119 In the following, we focus on nontrivial cases in which the environmental timescale is of the
 120 same order of magnitude as the population lifetime in the harsh phase (i.e., $\tau \sim \tau_{0,H}$) and the
 121 rescue probability is likely to satisfy $0 < p_r < 1$.

122 **Stochastic dynamics of the wild-type population.** We describe the population dynamics
 123 as a Markovian birth-death process that includes stochasticity inherent to demographic noise
 124 [42, 43]. More specifically, the probability that a population has a given size between 0 and K
 125 at a given time t is described by a system of $K + 1$ differential equations. This system is coupled
 126 since a population jumps from one to another size with a rate depending on its current size.
 127 The system of differential equations, called the master equation, governs the time-evolution of
 128 the probability $P_\alpha(N_W, t|N_{W,0})$ of having N_W individuals at time t in the environmental state
 129 α given that $N_{W,0}$ were initially present, and reads for the logistic growth

$$\begin{aligned} \frac{dP_\alpha(N_W, t|N_{W,0})}{dt} = & b_{W,\alpha} \left(1 - \frac{N_W - 1}{K}\right) (N_W - 1) P_\alpha(N_W - 1, t|N_{W,0}) \\ & + d_W (N_W + 1) P_\alpha(N_W + 1, t|N_{W,0}) \\ & - \left(b_{W,\alpha} \left(1 - \frac{N_W}{K}\right) + d_W\right) N_W P_\alpha(N_W, t|N_{W,0}). \end{aligned} \quad (1)$$

130 We write equation (1) in a matrix form, $d\vec{P}_\alpha/dt = \mathbf{R}\vec{P}_\alpha$, where \vec{P}_α is the probability column
 131 vector and \mathbf{R} the $K + 1 \times K + 1$ transition rate matrix. The solution of equation (1) reads
 132 $\vec{P}_\alpha(t) = e^{\mathbf{R}t}\vec{P}_\alpha(0)$, where $\vec{P}_\alpha(0)$ is the initial condition column vector, whose $N_{W,0}^{\text{th}}$ row is equal
 133 to 1 whereas the others are zero. We assume that each favorable phase is long enough for the
 134 population to reach its equilibrium size, that is $\tau \gg 1/(b_{W,F} - d_W)$, given that the population is
 135 not extinct. Then, each harsh phase starts from a population size $N_{W,0} = N_W^*$. When the harsh
 136 environment fully prevents the birth of individuals (i.e., $b_{W,H} = 0$), equation (1) is analytically

137 solvable, and we obtain

$$P_H(N_W, t|N_W^*) = \begin{cases} \binom{N_W^*}{N_W} (e^{-d_W t})^{N_W} (1 - e^{-d_W t})^{N_W^* - N_W} & \text{if } 0 \leq N_W \leq N_W^*, \\ 0 & \text{otherwise.} \end{cases} \quad (2)$$

138 The previous equation shows that the population size N_W is sampled according to a normal
 139 distribution $N_W(t) \sim \mathcal{B}(N_W^*, e^{-d_W t})$ when $b_{W,H} = 0$ in the harsh environment. When the harsh
 140 environment does not fully prevent the birth of individuals (i.e., $b_{W,H} \neq 0$), equation (1) is
 141 solved numerically. To obtain the wild-type population size at any time t given that it has not
 142 gone extinct, we need to modify the master equation since equation (1) includes the stochastic
 143 trajectories leading to rapid extinction [39]. To exclude these trajectories, we consider a biased
 144 master equation giving the probability $Q_\alpha(N_W, t|N_{W,0}) = P_\alpha(N_W, t|N_{W,\alpha}) / (1 - P_\alpha(0, t|N_{W,0}))$
 145 of having N_W individuals at time t in the environmental state α , given that $N_{W,0}$ were initially
 146 present and that the population is not extinct [12, 46]. This master equation is similar to
 147 equation (1) with an additional term $Q_\alpha(N_W, t|N_{W,0})(dP_\alpha(0, t|N_{W,0})/dt) / (1 - P_\alpha(0, t|N_{W,0}))$.
 148 Note that $P_F(0, t|N_{W,0})$ can be analytically obtained by linearizing the master equation, whereas
 149 $P_H(0, t|N_{W,0})$ is computed numerically if $b_{W,H} > 0$, or using equation (2) if $b_{W,H} = 0$. The
 150 mean population size in the environmental phase α starting from $N_{W,0}$ individuals is given by
 151 $d\langle N_W|N_{W,0}\rangle_\alpha/dt = \sum_{N_W} N_W dP_\alpha(N_W, t|N_{W,0})/dt$, which for the logistic growth leads to

$$\begin{aligned} \frac{d\langle N_W|N_{W,0}\rangle_\alpha}{dt} &= (b_{W,\alpha} - d_W) \langle N_W|N_{W,0}\rangle \\ &\quad - \frac{b_{W,\alpha}}{K} \langle N_W^2|N_{W,0}\rangle \\ &\quad + \frac{dP_\alpha(0, t|N_{W,0})}{dt} \frac{\langle N_W|N_{W,0}\rangle_\alpha}{1 - P_\alpha(0, t|N_{W,0})}. \end{aligned} \quad (3)$$

152 The initial condition $N_{W,0}$ is equal to N_W^* in the harsh environment, whereas it is more difficult
 153 to obtain it in the favorable environment. That is because the initial size in the favorable phase
 154 is random and depends on the previous harsh phase. Thus, we calculate the mean population
 155 size in the favorable phase by summing the trajectories with all possible initial conditions $N_{W,0}$
 156 weighted by their respective probability

$$P_F(N_{W,0}) = \left(\int_0^\infty \mathcal{F}_\tau(t) P_F(N_{W,0}, t|N_W^*) dt \right) / \left(\int_0^\infty \mathcal{F}_\tau(t) (1 - P_F(N_{W,0}, t|N_W^*)) dt \right). \quad (4)$$

157 In other words, $P_F(N_{W,0})$ is the probability of having $N_{W,0}$ individuals at the end of each harsh
 158 phase, given that the population is not extinct. The denominator of equation (4) ensures that
 159 only trajectories in which the population did not go extinct in the previous harsh phase are
 160 considered. This yields

$$\langle N_W \rangle_F = \sum_{N_{W,0}=1}^{N_W^*} \langle N_W|N_{W,0} \rangle_F P_F(N_{W,0}). \quad (5)$$

161 Now that we have quantified the dynamics in both environments, namely favorable and harsh,
 162 we can write the complete dynamics as

$$\langle N_W \rangle(t) = \begin{cases} \langle N_W \rangle_H(t \bmod \tau) & \text{if } t \bmod 2\tau < \tau \\ \langle N_W \rangle_F(t \bmod \tau) & \text{otherwise,} \end{cases} \quad (6)$$

163 where $m \bmod n$ is the modulo operation that yields the remainder of the division of m by n .
 164 An example in which equation (6) is tested against simulated data is shown in figure S3. A

165 technical point should be made clear. Since our birth rates are nonlinear, unless $b_{W,H} = 0$, the
166 mean population size given by equation (3) depends on higher-order moments. In other words,
167 the system of equations for the moment dynamics is not closed. Because the system of moment
168 equations is not closed, we apply a binomial moment closure approximation as it proves to be
169 the best for the logistic growth. In contrast, we use a mean field approximation (equivalent to
170 a deterministic equation) for the Gompertz and Richards growths (citation to come).

171 **Appearance and fixation of a mutant.** A beneficial mutant rescues a population from ex-
172 tinction only if it survives the initial drift phase at low frequencies and becomes fixed. Following
173 [12, 47], the fixation probability reads

$$p_{\text{fix}}(t_0) = \frac{1}{1 + d_M \int_{t_0}^{\infty} e^{\rho(t)} dt}, \quad (7)$$

174 where t_0 is the appearance time and

$$\rho(t) = \int_{t_0}^{\infty} \left[d_M - b_M \left(1 - \frac{\langle N_W \rangle(u)}{K} \right) \right] du. \quad (8)$$

175 The previous equation applies to the logistic growth. To obtain the fixation probability for the
176 Gompertz and Richards growths, b_M must be multiplied by $\log(K/\langle N_W \rangle)$ and $(1 - (\langle N_W \rangle/K)^\beta)$,
177 respectively. Equation (7) shows that the fixation probability of the mutant in our eco-
178 evolutionary model depends on its appearance time (see figure S4). In contrast, the fixation
179 probability is constant for fixed and infinite population sizes in a constant environment.

180 In our model with fluctuating selection coefficients, a mutant is more likely to fix in the
181 harsh phase than in the favorable phase since $d_W/b_{W,F} > d_W/b_{W,H}$. If the harsh environment
182 fully prevents the reproduction of wild-type individuals, the fixation probability of a mutant is
183 maximal just before the beginning of the harsh phase [47, 48, 49].

184 Since environmental fluctuations lead to varying birth rates, the number of mutants that
185 appear per unit of time is not constant. We calculate the probability that a mutant appears
186 and fixes between 0 and t given that none has done so before as $p_{\text{af}}(t) = 1 - e^{-\Sigma(t)}$ [47], where

$$\Sigma(t) = \mu \int_0^t p_{\text{fix}}(s) b_W(s) \left(1 - \frac{\langle N_W \rangle(s)}{K} \right) \langle N_W \rangle(s) ds. \quad (9)$$

187 Here, the wild-type birth rate depends on time because of the assumed environmental fluctua-
188 tions. Taking the limit $t \rightarrow \infty$ of $p_{\text{af}}(t)$ yields the rescue probability p_r . Note that equation (9)
189 applies to the logistic growth model. To adjust equation (9) for the Gompertz and Richards
190 growths, $b_W(s)$ must be multiplied by $\log(K/\langle N_W \rangle)$ and $(1 - (\langle N_W \rangle/K)^\beta)$, respectively.

191 **Data availability.** Simulations were performed with C (version gcc-9) and Matlab (ver-
192 sion R2021a). All annotated code to repeat the simulations and visualizations is available at
193 <https://github.com/LcMrc> and will be deposited on Zenodo upon acceptance of the paper.

194 3 Heuristic analysis

195 **Two different extinction mechanisms contribute to failed evolutionary rescue.** En-
196 vironmental fluctuations decrease the persistence time of a population if they induce paths to
197 extinction. In the harsh environment, the population declines because the death rate exceeds

198 the birth rate. If the harsh phase duration τ is longer than the survival time $\tau_{0,H}$, the pop-
199 ulation goes extinct. The survival time in the harsh environment is stochastic and extinction
200 occurs with probability $p_{0,H} = \int_0^\infty \mathcal{F}_\tau(t) P_H(0, t | N_W^*) dt$ (see equation (2)).

201 A second path to extinction exists in the favorable environment. If the population survives
202 the previous harsh phase, it possibly starts the new favorable phase with few individuals. Small
203 initial population sizes lead to strong demographic noise that may drive the population to ex-
204 tinction with probability $p_{0,F} = \sum_{N_W=1}^{N_W^*} (\int_0^\infty \mathcal{F}_\tau(t) P_H(N_W, t | N_W^*) dt) P_F^\infty(0 | N_W) / (\int_0^\infty \mathcal{F}_\tau(t) P_H(0, t | N_W^*) dt)$
205 [39]. An example of each extinction mechanism is shown in Fig S5. The proportion of extinc-
206 tions occurring in the favorable phase, which is given by $\omega_F \approx p_{0,F} / (p_{0,F} + p_{0,H})$, is expected to
207 decrease with increasing phase duration. The longer the harsh phase, the more certain it drives
208 the population to extinction. Conversely, short harsh phases do not drive the population to
209 extinction but, in some cases, decrease the population size enough to lead to rapid extinction
210 in the next favorable phase.

211 **Stochastic environmental switches can increase or decrease the rescue probabil-**
212 **ity.** As explained before, the fate of the population depends on how the survival time of the

213 wild-type in the harsh environment compares to the phase duration. If the environmental fluc-
214 tuations are deterministic and the mean phase duration is shorter than the mean survival time
215 in the harsh environment (i.e., $\tau < \tau_{0,H}$), the harsh phase is too short to drive the population
216 to extinction. However, if the environmental fluctuations are stochastic, some harsh phases
217 are longer than average, which favors extinction and decreases the total extinction time and
218 the rescue probability. If the environmental fluctuations are deterministic and the mean phase
219 duration is longer than the mean survival time in the harsh environment (i.e., $\tau_{0,H} < \tau$), the
220 harsh phase is long enough to drive the population to extinction. However, if the environmental
221 fluctuations are stochastic, some harsh phases are shorter than average, which favors popula-
222 tion survival and increases the total extinction time and the rescue probability. In summary,
223 no matter whether the environmental fluctuations are deterministic or stochastic, the total
224 extinction time and the probability of rescue decrease as the phase duration increases. How-
225 ever, for a mean phase duration shorter than the mean survival time in the harsh environment
226 (i.e., $\tau < \tau_{0,H}$), the stronger the environmental stochasticity, the lower the total extinction and
227 the rescue probability. The opposite is valid for a mean phase duration longer than the mean
228 survival time in the harsh environment (i.e., $\tau_{0,H} < \tau$).

229 **Small birth rates in the harsh environment leave rescue probabilities almost un-**
230 **changed.** The harsh environment induces a wild-type birth rate lower than the death rate.

231 Specifically, a perfectly harsh environment fully prevents births, whereas an imperfectly harsh
232 environment allows for a small number of births during the harsh phase. As long as the
233 birth rate in the harsh environment is much lower than the death rate (i.e., $d_W/b_{W,H} \gg 1$;
234 e.g., $d_W/b_{W,H} = 10$), the population is driven to extinction on a time scale equal to $\tau_{0,H} \approx$
235 $\log(N_W^*)/d_W$ (see figure S6). Thus, the mean total extinction time should not significantly dif-
236 fer between perfectly and imperfectly harsh environments that satisfy $d_W/b_{W,H} \gg 1$. However,
237 $b_{W,H}$ may impact the rescue probability as it determines how many births occur and how many
238 mutants appear. Specifically, there are $N_{\text{birth}} \approx b_{W,H} N_W^* (2K - N_W^*) / (2d_W K)$ births in each
239 harsh phase, and the probability that at least one mutant appears is given by $1 - (1 - \mu)^{N_{\text{birth}}}$
240 (see figure S7). Thus, the larger the birth rate $b_{W,H}$ and the mutation probability μ , the more
241 mutants appear in the harsh environment. However, if the death rate to birth rate ratio satisfies
242 $d_W/b_{W,H} \gg 1$, the number of births in the harsh environment is expected to be very small, and
243 the number of mutants that appear is much smaller. Therefore, the rescue probability in an
244 imperfectly harsh environment is likely similar to that in a perfectly harsh environment.

245 **Rescue probability depends on population growth types.** In addition to studying
 246 evolutionary rescue under the logistic growth, we also present results for the Gompertz and
 247 Richards growths. Each of these growth types has a different equilibrium size N_W^* and growth
 248 rate, which affect the total extinction time and the rescue probability. First, the larger the
 249 equilibrium size, the longer it takes for the population to go extinct in the harsh environment
 250 since $\tau_{0,H} \approx \log(N_W^*)/d_W$. Thus, the probability $p_{0,H}$ of extinction in a harsh environment
 251 at a given phase duration τ decreases as the equilibrium size increases. Second, the faster
 252 the growth, the lower the demographic stochasticity. The probability of rapid extinction $p_{0,F}$
 253 of a population with initial size $N_{W,0}$ is very small compared to its equilibrium size, which
 254 is given by $(d_W/b_{W,F})^{N_{W,0}}$ for the logistic and Richards growths and $(d_W/(b_{W,F} \log(K)))^{N_{W,0}}$
 255 for the Gompertz growth. Thus, the probability of extinction $p_{0,F}$ for a given phase duration
 256 decreases for populations with a higher growth rate. An increased total extinction time leaves
 257 more opportunities for mutants to appear and become fixed. Moreover, a larger growth rate
 258 results in more births, resulting in more mutants and, therefore, a higher rescue probability.
 259 As a result, growth according to the Gompertz and Richards growths with $\beta > 1$ is likely to
 260 favor evolutionary rescue over the logistic and Richards growths with $\beta < 1$ (see figure 1a).

261 4 Formal analysis

262 **Extinction time.** From the extinction probabilities, namely $p_{0,F}$ and $p_{0,H}$ (see Model and
 263 methods), we compute the probability P_{q_F} that the population undergoes q_F favorable phases
 264 before it goes extinct as

$$P_{q_F}(k) = (1 - p_{0,H})^k (1 - p_{0,F})^k (p_{0,H} + (1 - p_{0,H})p_{0,F}). \quad (10)$$

265 The favorable phases in which a rapid extinction occurs are excluded from this count because
 266 we focus on the favorable phases in which a mutant is most likely to appear. We obtain the
 267 mean number of favorable phases before extinction by calculating $\langle q_F \rangle = \sum_{k=0}^{\infty} k \times P_{q_F}(k)$,
 268 which yields

$$\langle q_F \rangle = \frac{-1 + p_{0,H} + p_{0,F} - p_{0,H} \times p_{0,F}}{-p_{0,H} - p_{0,F} + p_{0,H} \times p_{0,F}}. \quad (11)$$

269 Equation (11) shows that both extinction mechanisms (extinction in the harsh phase vs. ex-
 270 tinction due to low numbers at the beginning of the favorable phase) are important in assessing
 271 population persistence. The probabilities $p_{0,F}$ and $p_{0,H}$ increase as the phase duration increases
 272 (see figure S8a-b), reducing $\langle q_F \rangle$. Specifically, the probability of extinction in the harsh envi-
 273 ronment ranges from 0 to 1 (i.e., $0 < p_{0,H} < 1$) since short phases do not leave enough time for
 274 the population to go extinct. In contrast, long phases surely drive it to extinction before the
 275 next environmental change. The probability of extinction in the favorable environment ranges
 276 from 0 to $d_W/b_{W,H}$ (i.e., $0 < p_{0,F} < d_W/b_{W,H}$), where $d_W/b_{W,H}$ is equal to the probability that
 277 a population starting with one individual rapidly goes to extinction. Using equation (11) and
 278 the proportion ω_F of extinction in the favorable environment (i.e., $\omega_F \approx p_{0,F}/(p_{0,F} + p_{0,H})$), we
 279 derive the mean total extinction time as

$$T_0 = 2\langle q_F \rangle \tau + (1 - \omega_F)\tau_{0,H} + \omega_F\tau_{0,F}. \quad (12)$$

280 Independent of whether extinction occurs in the favorable or harsh environment, the population
 281 persists during $\langle q_F \rangle$ epochs of a mean duration τ plus the mean survival time in the favorable
 282 (respectively harsh) environment, given that the population goes extinct, weighted by the
 283 probability that extinction occurs in the favorable (respectively harsh) environment. The mean
 284 total extinction time ranges from $\tau_{0,H}$ to \tilde{T}_0 (i.e., $\tau_{0,H} \leq T_0 \leq \tilde{T}_0$), where the mean survival
 285 time $\tau_{0,H}$ in the harsh environment is obtained for very long phase durations. In contrast,

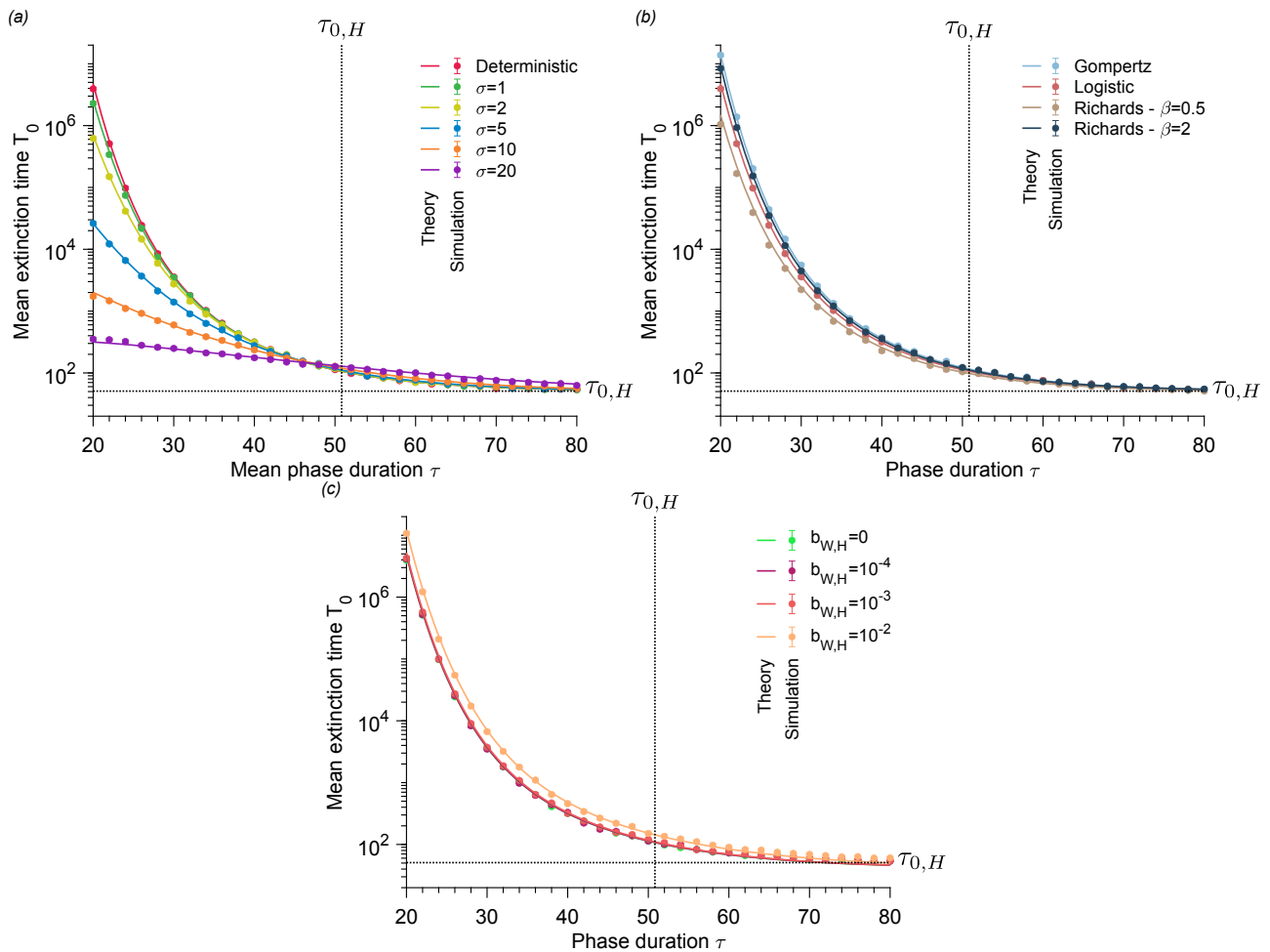


Figure 2: Extinction time decreases as phase duration increases. Mean extinction time versus phase duration. Panel (a) compares deterministic and stochastic switches for the logistic model, panel (b) compares different population growth models, and panel (c) compares a perfectly harsh environment to imperfectly harsh environments for the logistic model. The solid lines represent analytical predictions, and the points simulated data averaged over 10^4 stochastic realizations. The error bars correspond to the 95% confidence intervals. Vertical dotted lines represent the mean survival time in the harsh environment. Parameter values: wild-type birth rate in favorable environment $b_{W,F} = 1$, wild-type birth rate in harsh environment $b_{W,H} = 0$ (in a and b), wild-type death rate $d_W = 0.1$, carrying capacity $K = 100$, and equilibrium wild-type population size $N_W^* = 90$.

286 the mean extinction time \tilde{T}_0 in an effectively constant environment is obtained for very short
 287 phase durations. The proportion ω_F of extinction in the favorable environment decreases as
 288 the phase duration increases (see figure S8c), reducing T_0 . If the ratio of death rate to birth
 289 rate in the favorable environment is much smaller than unity (i.e., $d_W \ll b_{W,F}$), we can assume
 290 that rapid extinction in the favorable environment occurs only if the population starts with
 291 a single individual, hence $\tau_{0,F} \approx 1/d_W$. The extinction time $\tau_{0,H}$ in the harsh environment
 292 is then approximately equal to $\log(N_W^*)/d_W$ if $\tau > \tau_{0,H}$, or to τ otherwise. Our analytical
 293 predictions accurately predict the simulated data (see figure 2; see also figure S9 for $\langle q_F \rangle$). As
 294 reported in figure 2a), the greater the environmental stochasticity (i.e., the larger the standard
 295 deviation σ), the smaller the mean total extinction time T_0 . Even small values of the standard
 296 deviation of environmental stochasticity σ dramatically affect population persistence. The mean
 297 total extinction time for deterministic and stochastic fluctuations intersect around the mean
 298 survival time in the harsh environment. Beyond this time, the population persists longer in an

environment with highly stochastic fluctuations, but the difference to the result for deterministic fluctuations becomes much smaller. As described by Jensen’s theorem [50], as soon as the mean total extinction time with deterministic fluctuations resembles a convex function, addition of stochasticity reduces this convexity. As reported in figure 2b), populations growing under a growth type with a larger equilibrium size and growth rate have an increased extinction time. This difference fades as the phase duration increases since extinction occurs mainly in the harsh environment, where the extinction probability is independent of the growth type. Finally, figure 2c) shows that for any ratio $d_W/b_{W,H}$ much greater than unity, the mean total extinction time is equal because the probability of extinction in the harsh environment is the same as if $b_{W,H} = 0$. Note that the maximum population size scales the window of phase durations that lead to non-trivial rescue probabilities (i.e., $\tau \sim \tau_{0,H}$ so that $0 < p_r < 1$). Specifically, the mean survival time in the harsh environment is given by $\tau_{0,H} \approx \log(N_W^*)/d_W$. In contrast, its variance is approximately equal to $1/d_w^2$ (both quantities can be derived from equation 2). We present additional results for different maximum population sizes as a function of $\tau/\tau_{0,H}$ in figure S10.

Rescue probability. Using the mean number $\langle q_F \rangle$ of favorable phases that the population undergoes, we calculate the probability that a generalist mutant (i.e., one not affected by environmental fluctuations) appears and takes over the population before extinction occurs. We obtain

$$p_r = \int_0^\infty \mathcal{F}_{T_0}(t) p_{\text{af}}(t) dt, \quad (13)$$

where \mathcal{F}_{T_0} is the probability density function of the total extinction time. Equation (13) is simplified by separating the contribution of the favorable and harsh environments. Either the mutant appears in the favorable environment while the population is growing or in the harsh environment if the division is not fully hindered. Thus, the rescue probability p_r reads

$$p_r = \sum_{k=0}^\infty P_{q_F}(k) (1 - e^{-(k+1)\Sigma_H - k\Sigma_F}), \quad (14)$$

where

$$\Sigma_H = \mu b_{W,H} \int_0^\tau \langle N_W \rangle_H(t) (1 - \langle N_W \rangle_H(t)/K) p_{\text{fix}}(t) dt, \quad (15)$$

and

$$\Sigma_F = \mu b_{W,F} \int_0^\tau \langle N_W \rangle_F(t) (1 - \langle N_W \rangle_F(t)/K) p_{\text{fix}}(t + \tau) dt. \quad (16)$$

Our analytical predictions match the simulated data very well (see figure 3). In particular, figure 3a) shows that equation (14) is valid from the rare to the frequent mutation regime. All panels highlight the transition from the regime of fast fluctuations, in which $p_r \approx 1$, to slow fluctuations, in which $p_r \approx 0$. This transition is more abrupt for rare mutations than for frequent mutations. The more mutants there are, the more likely one mutant becomes fixed and rescues the population before extinction, hence the higher rescue probability at a given phase duration. As reported in figure 3b), environmental stochasticity decreases the chances of evolutionary rescue because it also decreases the mean total extinction time. Population growth types with the highest growth rates and equilibrium sizes have the highest rescue probabilities at a given phase duration because they lead to more mutant appearances per unit of time (see figure 3c). As shown in figure 3d), a harsh environment that does not fully prevent the reproduction of individuals leaves more opportunities for mutants to appear, resulting in a higher rescue probability.

The rescue probability is independent of the carrying capacity K at a given normalized phase duration $\tau/\tau_{0,H}$ if the mutational influx $K\mu$ is constant (see figure S11). The carrying capacity value determines the phase duration window in which the rescue probability transitions from 1 to 0 through the mean survival time in harsh environment. The product $K\mu$ determines the number of mutants that appear per unit of time.

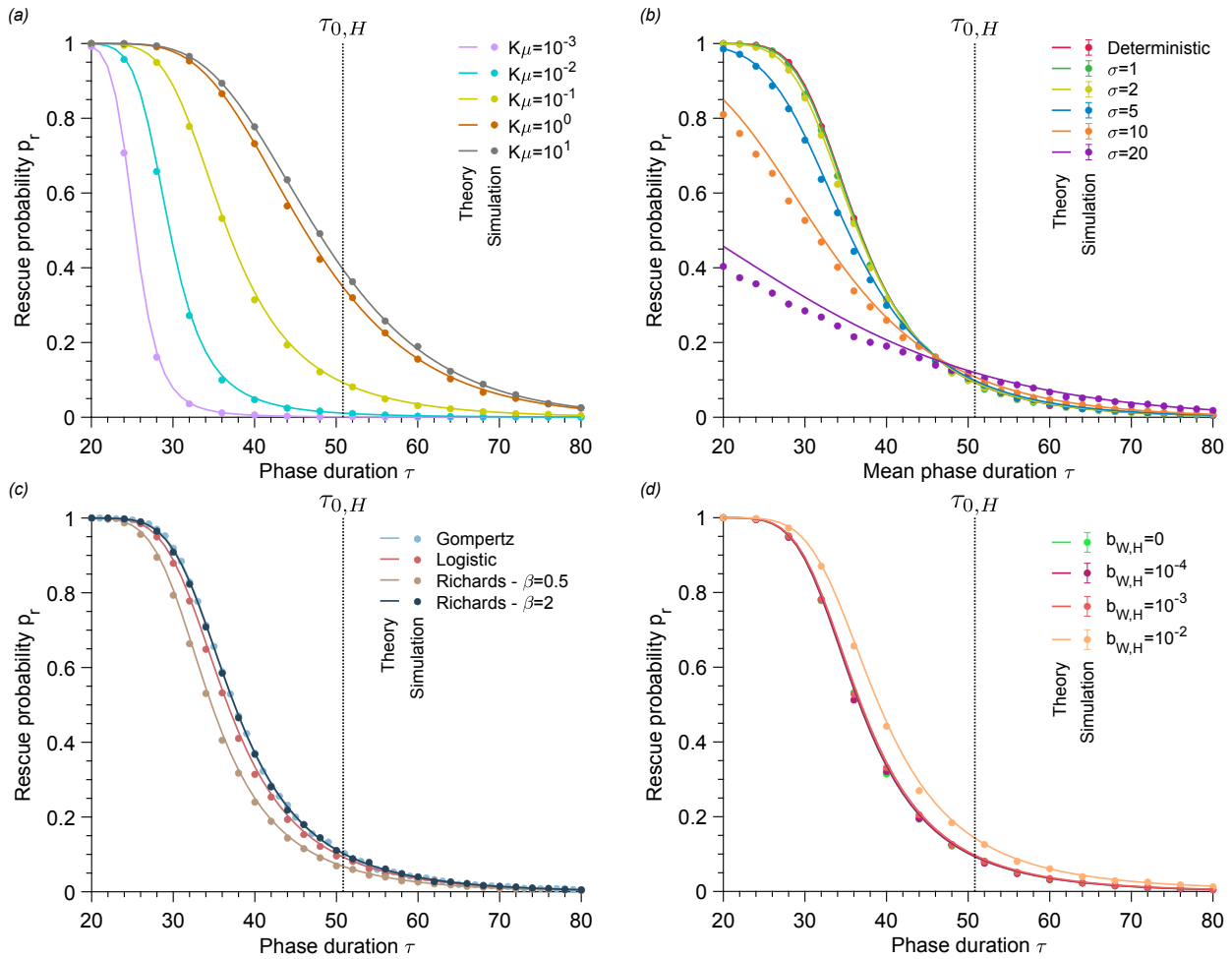


Figure 3: Rescue probability decreases as phase duration increases. Rescue probability versus phase duration. Panel (a) compares different mutation rates, panel (b) deterministic and stochastic switches for the logistic growth, panel (c) different population growth types, and panel (d) a perfectly vs. imperfectly harsh environment for the logistic growth. The solid lines represent analytical predictions, and the points simulated data averaged over 10^4 stochastic realizations. The error bars correspond to the 95% confidence intervals. Vertical dotted lines represent the mean survival time in the harsh environment. Parameter values: wild-type birth rate in favorable environment $b_{W,F} = 1$, wild-type birth rate in harsh environment $b_{W,H} = 0$ (in a, b and c), wild-type death rate $d_W = 0.1$, mutant birth rate $b_M = 1$, mutant death rate $d_M = 0.1$, carrying capacity $K = 100$, mutation rate $\mu = 10^{-3}$ (in b, c, and d) and equilibrium wild-type population size $N_W^* = 90$.

341 **Appearance time.** We derive the average appearance time τ_{af} of a mutant that fixes, given
 342 that the population is rescued, as

$$\tau_{af} = (2\langle q_{af,F} \rangle - 1)\tau + t_{af}. \quad (17)$$

343 The mean number $\langle q_{af,F} \rangle$ of favorable phases that occur before a mutant appears and fixes,
 344 given that the population is rescued, is given by

$$\langle q_{af,F} \rangle = \sum_{k=0}^{+\infty} P_{q_F}(k) \sum_{q=0}^k q e^{-(q-1)\Sigma_F} (1 - e^{-\Sigma_F}) / p_r, \quad (18)$$

345 and t_{af} is the mean appearance time of a mutant that becomes fixed in the favorable environ-
 346 ment. Since the mean total extinction time and rescue probability are similar for $d_W/b_{W,H} \gg 1$

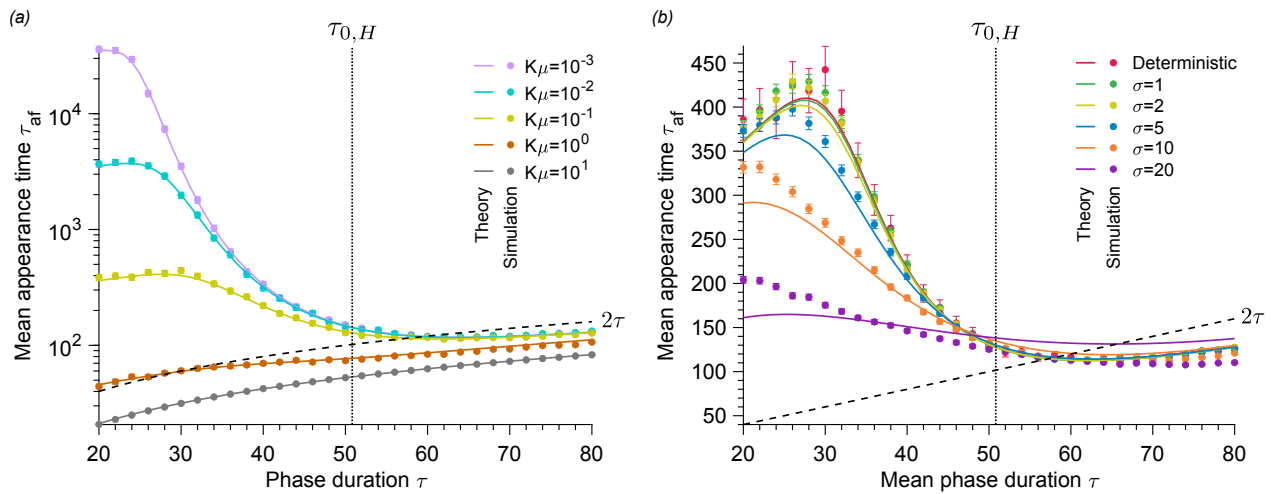


Figure 4: **The higher the mutation rate and phase duration, the earlier the rescue mutant appears.** Mean appearance time of a mutant that rescues the population versus phase duration. Panel (a) compares different mutation rates and panel (b) deterministic and stochastic fluctuations for the logistic growth. The solid lines represent analytical predictions, and the points simulated data averaged over 10^4 stochastic realizations. The error bars correspond to the 95% confidence intervals. Vertical dotted lines represent the mean survival time in the harsh environment. Parameter values: wild-type birth rate in favorable environment $b_{W,F} = 1$, wild-type birth rate in harsh environment $b_{W,H} = 0$, wild-type death rate $d_W = 0.1$, mutant birth rate $b_M = 1$, mutant death rate $d_M = 0.1$, carrying capacity $K = 100$, mutation rate $\mu = 10^{-3}$ (in b) and equilibrium wild-type population size $N_W^* = 90$.

(see figures 2 and 3), we assume that a mutant is unlikely to emerge in the harsh environment. In the moderate to frequent mutation regime and regardless of phase duration, the mutant that rescues the population appears during the first favorable phase (see figures 4 and S12). Then τ_{af} increases as τ increases. If mutations are rare, the number of favorable phases before a rescue mutant appears decreases as the phase duration increases. More precisely, $\langle q_{af,F} \rangle$ converges to unity when the phase duration is longer than the survival time in the harsh phase. The population goes extinct quickly for such a phase duration, so the mutant must appear in the first favorable phases. Our results confirm previous observations that the mutant rescue the population from extinction tends to appear just before an environmental change from the favorable to the harsh state [47, 48, 49].

5 Discussion

Whether it is microbes subjected to varying antimicrobial concentrations or animal species caught up in climate change, populations experience environmental changes threatening their survival. Determining whether populations adapt or perish is a fundamental question in many fields, from antimicrobial resistance to conservation biology. In this paper, we develop a minimal model to address evolutionary rescue in a fluctuating environment. We fully analyze our model using analytical and numerical tools from stochastic processes. Specifically, we derive equations for the extinction time, the rescue probability, and the appearance time of a rescue mutant and validate them with numerical simulations.

Stochastic environmental fluctuations accelerate extinction and hinder evolutionary rescue compared to deterministic fluctuations. Our study quantifies the probability of evolutionary rescue of a population evolving in an environment that fluctuates, either de-

369 terministically or stochastically, between a harsh state (i.e., causing a population decline) and
370 a favorable state (i.e., allowing population growth). We show that environmental and survival
371 time scales determine whether stochastic environmental fluctuations favor evolutionary rescue
372 compared to deterministic ones. Specifically, we prove that stochastic environmental fluctu-
373 ations with a mean phase duration shorter than the survival time in the harsh environment
374 dramatically decrease the mean total extinction time, the rescue probability, and the mean
375 appearance time of a rescue mutant. Although the mean phase duration is shorter than the
376 mean survival time, environmental stochasticity leads to longer than average phases and thus
377 may facilitate extinction. Conversely, stochastic environmental fluctuations with a mean phase
378 duration that is longer than the mean survival time of the population in the harsh environment
379 very slightly increase the mean total extinction time and the rescue probability but do not
380 significantly affect the mean appearance time of a rescue mutant.

381 Relating our results to a public health perspective, our model may represent treatment
382 with biostatic drugs, which inhibit microbial division. Under this scenario, we evaluate the
383 risk of antimicrobial resistance evolution by *de novo* mutations during therapy [8, 51]. Similar
384 to previous theoretical work [47], we show that variation in antimicrobial concentration plays
385 a role in the evolution of resistance. For example, we find that deterministic rapid variations
386 favor the evolution of resistance over a constant environment. We extend [47] by showing that
387 rapid random environmental switches of the drug concentration decrease the risk of resistance
388 evolution. Furthermore, our analytical prediction for the probability of evolutionary rescue
389 is valid across the regimes of fast to slow environmental fluctuations, which complements the
390 work of [47], whose analytical results have been derived in the limit of extremely fast or slow
391 fluctuation regimes.

392 Long-term therapies involving multiple dosing are subject to imperfect adherence to treat-
393 ment, i.e., patients often fail to follow the exact treatment plan [52, 53, 54]. With this in mind,
394 dose missing was theoretically investigated in [21], which showed that non-adherence allows
395 resistant strains to grow. In our model, stochastic fluctuations may result from another form of
396 imperfect adherence: doses taken at irregular intervals. Surprisingly, our model suggests that
397 a biostatic antimicrobial treatment taken at irregular intervals may hinder resistance evolution
398 rather than accelerate it.

399 In summary, our theoretical work can inform the design of drug treatments that prevent
400 the evolution of resistance by choosing the best type of antimicrobial and the time interval
401 between each dose. A possible extension would be to compare two types of antimicrobial,
402 namely biostatic (i.e., hindering microbial division) and biocidal (i.e., killing microbes) [17, 19],
403 by including environment-dependent death rates. We expect that biocidal drugs accelerate
404 extinction compared to biostatic drugs while at the same time promoting evolutionary rescue.
405 That is because since biocidal drugs do not prevent cell division, more mutants appear, which
406 increases the probability of evolutionary rescue.

407 **High equilibrium population sizes and growth rates slow down extinction and fa-**
408 **vor evolutionary rescue.** Our model includes an explicit link between ecology, evolution,
409 and demography: environmental fluctuations impact the wild-type birth rate, affecting the
410 population size and the selective advantage of the mutant. Thus, our work does not rely on
411 the common assumption that ecology and evolution are uncoupled when studying the genet-
412 ics of adaptation [55]. This assumption was already relieved in theoretical studies that have
413 analytically predicted adaptation in a fluctuating environment inducing changes in either pop-
414 ulation size or selection coefficient, but not both together [12, 14, 38]. The analysis of our
415 eco-evolutionary model shows that the underlying growth type (i.e., the underlying growth
416 model) plays an essential role in the population's fate. Specifically, we show that growth types
417 with larger equilibrium sizes lengthen the mean survival time of the population in the harsh

418 environment, and growth types with higher growth rates decrease the probability of rapid ex-
419 tinction in the favorable environment. As a result, large equilibrium sizes and high growth
420 rates make the population persist longer and therefore favor evolutionary rescue.

421 Many mathematical growth models have been developed to describe population demography,
422 from the microscopic to the macroscopic scale [40]. Mathematical growth models allow, among
423 other things, the fitting of population dynamics data [56]. However, to date, there is no
424 universal model that best describes any data set [41]. Our work highlights that it is crucial
425 to correctly infer the growth type from empirical data when assessing the persistence of a
426 population undergoing environmental change. Although we focused on haploid populations,
427 our purely ecological results, such as extinction time, apply to diploid populations. Specifically,
428 our model can contribute to conservation biology by guiding natural population management.
429 For example, the birds' breeding season was shown to be impacted by climate change, resulting
430 in stochasticity in its duration [57]. Our model, combined with an inference of the growth type
431 of bird populations, could allow for predictions of the risk of extinction of such populations.

432 Possible extensions to our model carry the potential for additional applications in conser-
433 vation biology. For example, by introducing environment-dependent death rates, we may be
434 able to identify harvesting periods that should be respected to avoid the extinction of animal
435 populations [58]. Here, environmental fluctuations that increase the death rate may represent
436 fishing or hunting of animal species at specific periods of the year. Our model suggests that
437 stochastically varying fishing and hunting seasons may decrease population persistence and
438 accelerate extinction for purely population-dynamic reasons.

439 **No significant differences in the impact of an imperfectly harsh environment on**
440 **evolutionary rescue compared to a perfectly harsh environment.** Our model com-
441 pares the impact of a perfectly harsh environment (i.e., one that fully prevents births) to a
442 perfectly harsh environment (i.e., one that does not fully prevent births) on evolutionary res-
443 cue. We show no significant differences between the two harshness levels, especially for death
444 rates much larger than birth rates. Specifically, we prove that the mean survival time, and
445 thus the mean total extinction time, is similar for both perfectly and imperfectly harsh envi-
446 ronments. Although some births may occur in the imperfectly harsh environment, a mutant
447 appearance during this phase is unlikely. Thus, an imperfectly harsh environment does not
448 significantly favor evolutionary rescue compared to a perfectly harsh one.

449 This result means that our analytical results apply to an extensive range of scenarios where
450 populations are exposed to an environment that successively causes their decline and growth.
451 In particular, our analytical predictions for the perfectly harsh case are a good approximation
452 for the case where the environment does not fully prevent reproduction, which is likely to be
453 the case in nature. In the perfectly harsh case, we emphasize that our analytical predictions
454 are explicit and exact. They do not rely on a deterministic or diffusion approximation that has
455 been shown to poorly describe extreme events such as extinctions [39], although widely used in
456 population genetics [10].

457 In summary, the randomness of environmental fluctuations is essential to consider when
458 quantifying the persistence of a population, as is its growth type. Conversely, the harshness of
459 the environment does not significantly impact the persistence of the population as long as it
460 induces its decline.

461 Author Contributions

462 LM designed the study; LM performed the numerical and analytical work; LM and CB analyzed
463 and interpreted the data; LM and CB wrote and edited the manuscript.

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