Supporting Information for "Adapt or perish: Evolutionary rescue in a gradually deteriorating environment"

Loïc Marrec[1], Anne-Florence Bitbol[1,2*]

1 Sorbonne Université, CNRS, Institut de Biologie Paris-Seine, Laboratoire Jean Perrin (UMR 8237), F-75005 Paris, France
2 Institute of Bioengineering, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

* anne-florence.bitbol@epfl.ch

Contents

1 Fixation probability of mutants

1.1 Derivation

Here, we present the derivation of the fixation probability $p_{\rm fix}(i_0,t_0)$ of i_0 mutants present at time t_0 (Parzen 1999; Uecker and Hermisson 2011; Alexander and Bonhoeffer 2012), along similar lines as in (Uecker and Hermisson 2011). We assume that the number of wild-type microorganisms is initially much larger than the number of mutants ($N_W(t_0) \gg i_0$). As explained in the main text, the selective pressure due to the competition with the wild-type is felt by the mutants through their division rate $f_M(t)[1-N(t)/K]$, and in the initial phase where this competition is important, the total population size N(t) can be approximated by $N(t) \approx N_W(t)$. Thus, competition is felt through the effective mutant fitness $f_M^{\rm eff}(t) = f_M(t)[1-N_W(t)/K]$. In addition, we treat the number of mutants stochastically, but the number $N_W(t)$ of wild-type organisms deterministically (see Eq. 3 and Fig. 1).

The master equation that describes the evolution of the probability $P(i,t|i_0,t_0)$ of having i mutants at time t knowing that there are i_0 mutants at time t_0 is given by:

$$\frac{\partial P(i,t|i_0,t_0)}{\partial t} = f_M^{\rm eff}(t)(i-1)P(i-1,t|i_0,t_0) + g_M(i+1)P(i+1,t|i_0,t_0) - (f_M^{\rm eff}(t)+g_M)iP(i,t|i_0,t_0)\ . \tag{S1}$$

Eq. S1 allows to establish the partial differential equation satisfied by the probability generating function $\phi_{i_0,t_0}(z,t) = \sum_{i=0}^{+\infty} z^i P(i,t|i_0,t_0)$:

$$\frac{\partial \phi_{i_0,t_0}}{\partial t} = (z-1)(f_M^{\rm eff}(t)z - g_M)\frac{\partial \phi_{i_0,t_0}}{\partial z}\ . \tag{S2}$$

The method of characteristics then yields (Kendall 1948; Parzen 1999):

$$\phi_{i_0,t_0}(z,t) = \left[1 + \left(\frac{e^{\rho(t)}}{z-1} - \int_{t_0}^{t} f_M^{\rm eff}(u)e^{\rho(u)}{\rm d}u\right)^{-1}\right]^{i_0}\ , \tag{S3}$$

where:

$$\rho(t) = \int_{t_0}^{t}(g_M - f_M^{\rm eff}(u)){\rm d}u\ . \tag{S4}$$

Note that ρ depends on the number of wild-type microbes $N_W(t)$ and on the carrying capacity K only through the ratio $N_W(t)/K$, whose dynamics is system size-independent, i.e. independent from K (see Eq. 3).

The probability generating function ϕ_{i_0,t_0} allows to calculate the fixation probability $p_{\rm fix}(i_0,t_0)$ of i_0 mutants present at time t_0, through $p_{\rm fix}(i_0,t_0) = 1 - \lim_{t\to\infty} P(0,t|i_0,t_0) = 1 - \lim_{t\to\infty}\phi_{i_0,t_0}(0,t)$. This yields

$$p_{\rm fix}(i_0,t_0) = 1 - \left(\frac{g_M\int_{t_0}^{\infty} e^{\rho(t)}{\rm d}t}{1+g_M\int_{t_0}^{\infty} e^{\rho(t)}{\rm d}t}\right)^{i_0}\ , \tag{S5}$$

where we used:

$$\int_{t_0}^{t}(g_M - f_M^{\rm eff}(u))e^{\rho(u)}{\rm d}u = e^{\rho(t)} - 1\ . \tag{S6}$$

Since ρ does not depend on the carrying capacity K, as noted above, this is also true for $p_{\rm fix}$ (see Fig. S8A).

In the main text, we focus on the fixation probability of a single mutant that appears at time t_0, and denote it as $p_{\rm fix}(t_0) = p_{\rm fix}(1,t_0)$ (see Eq. 4, which corresponds to Eq. S5 with $i_0 = 1$).

1.2 Additional results

Fig. S1 shows the same data as in Fig. 2A for the fixation probability $p_{\rm fix}$ of G and S mutants versus their time of appearance t_0 in the deteriorating environment. However, here, t_0 is rescaled by the average extinction time τ_W of the wild-type population in the absence of mutation (see Fig. 1). This rescaling illustrates the convergence of $p_{\rm fix}$ toward asymptotes independent of n as τ_W is approached. These asymptotes correspond to the extinction probabilities of mutants that exist in the absence of competition: mutants fix unless their lineage undergoes rapid stochastic extinction.

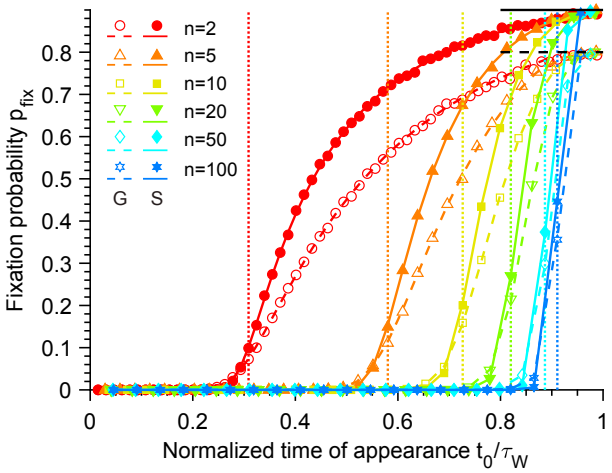

Fig S1. Fixation probability of mutants. Fixation probability p_{fix} of G and S mutants versus their time of appearance t_0 in the deteriorating environment, rescaled by the average extinction time τ_W of the wild-type population for different Hill coefficients n characterizing the steepness of the environment deterioration (see Eq. 1). Here, S mutants satisfy $m = n$, i.e. they have the same sensitivity to the environment as W organisms (see Eq. 2). Horizontal dashed line: $p_{\text{fix}} = 1 - g_G/f_G$. Horizontal solid line: $p_{\text{fix}} = 1 - g_S$. Markers correspond to averages over 10^4 replicate stochastic simulations. Dashed and solid lines correspond to numerical integrations of Eq. 4 for G and S mutants, respectively. Parameter values: $g_W = g_G = g_S = 0.1$, $K = 10^3$, $N_W^0 = 10$ and $\theta = 10^3$. Vertical dotted lines: $t_0 = \theta$. Main panels: linear scale; insets: semi-logarithmic scale. Same data as in Fig. 2A.

2 Application to different types of mutants

2.1 Antimicrobial resistance evolution

An important application of the study of evolutionary rescue regards antimicrobial resistance evolution, where rescue of the microbial population corresponds to the fixation of resistance. In line with our model comprising two types of individuals, let us consider sensitive wild type microbes W, and resistant mutants M. Furthermore, because we consider variable fitnesses and constant death rates (as throughout this work), we here model the effect of biostatic antimicrobials, and not biocidal ones. However, our model could easily be extended to the biocidal case. Let us assume that the concentration of antimicrobial gradually increases from 0 to some value which is above the minimum inhibitory concentration (MIC) of the sensitive strain but below the MIC of the resistant strain. Then, appearance and fixation of resistant mutants is necessary for the microbial population to be rescued. Let us model the fitness of resistant mutants M by

$$f_M(t) = \frac{f_M^0 - f_M^\infty}{1 + (t/\theta')^n} + f_M^\infty \,, \tag{S7}$$

which is equal to f_M^0 for $t = 0$ and tends to f_M^∞ for $t \to \infty$ (see Fig. S2). Because antimicrobial resistance often comes with a fitness cost in the absence of drug (Borman *et al.* 1996; Andersson and Hughes 2010; zur Wiesch *et al.* 2011), we will consider $f_M^0 < 1$. Since the final concentration is assumed to be above the mutant MIC, we have $f_M^\infty > g_M$, which ensures that a resistant population does not go extinct deterministically in the final environment. We further allow for the inflection point θ' to be different from that of f_W, which is θ (see Eq. 1), so that $\theta' > \theta$ may reflect the fact that M is less sensitive to the environment change than W. Indeed, compared to that of sensitive microorganisms, the dose-response curve of resistant microorganisms is usually shifted towards higher drug concentrations (Gullberg *et al.* 2011; Yu *et al.* 2018). Note that the functional forms taken for f_W and f_M (see Eqs. 1 and S7) are realistic e.g. in the case of a linear drug concentration increase with time, given the usual pharmacodynamics of antibiotics (Regoes *et al.* 2004).

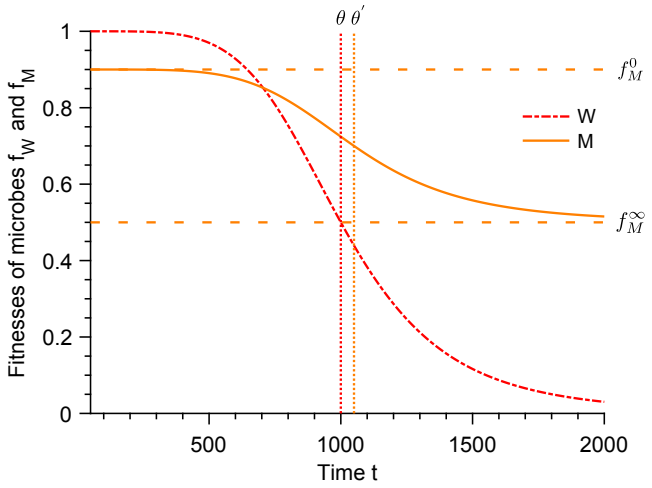

Fig S2. Fitnesses of the wild-type and mutant microbes in a model of antimicrobial resistance evolution. Fitnesses f_W and f_M of the wild-type sensitive microorganisms (W) and resistant mutants (M) versus time t (see Eqs. 1 and S7). Parameter values: $n = 5$, $\theta = 1000$, $\theta' = 1050$, $f_M^0 = 0.9$ and $f_M^\infty = 0.5$. Vertical dotted lines: $t = \theta$ and $t = \theta'$. Horizontal dashed lines: f_M^0 and f_M^∞.

Fig. S3 shows the results obtained for rescue within this model, and a comparison to the generalist (G) mutant with $f_G = 0.5$ studied in the main text. The agreement between our numerical simulations and our analytical predictions is very good. Larger values of θ' or of f_M^∞ increase the mutant fixation probability $p_{\rm fix}$ and the rescue probability p_r, consistently with the fact that they lead to higher mutant fitnesses. Despite minor quantitative differences associated to these parameter values, the rescue probability behaves qualitatively in the same way in this model as with the generalist mutant and as with the specialist mutant studied in the main text. This illustrates the generality of our findings with respect to the exact mutant fitness form, as long as the mutant is able to grow in the new environment and rescue the population.

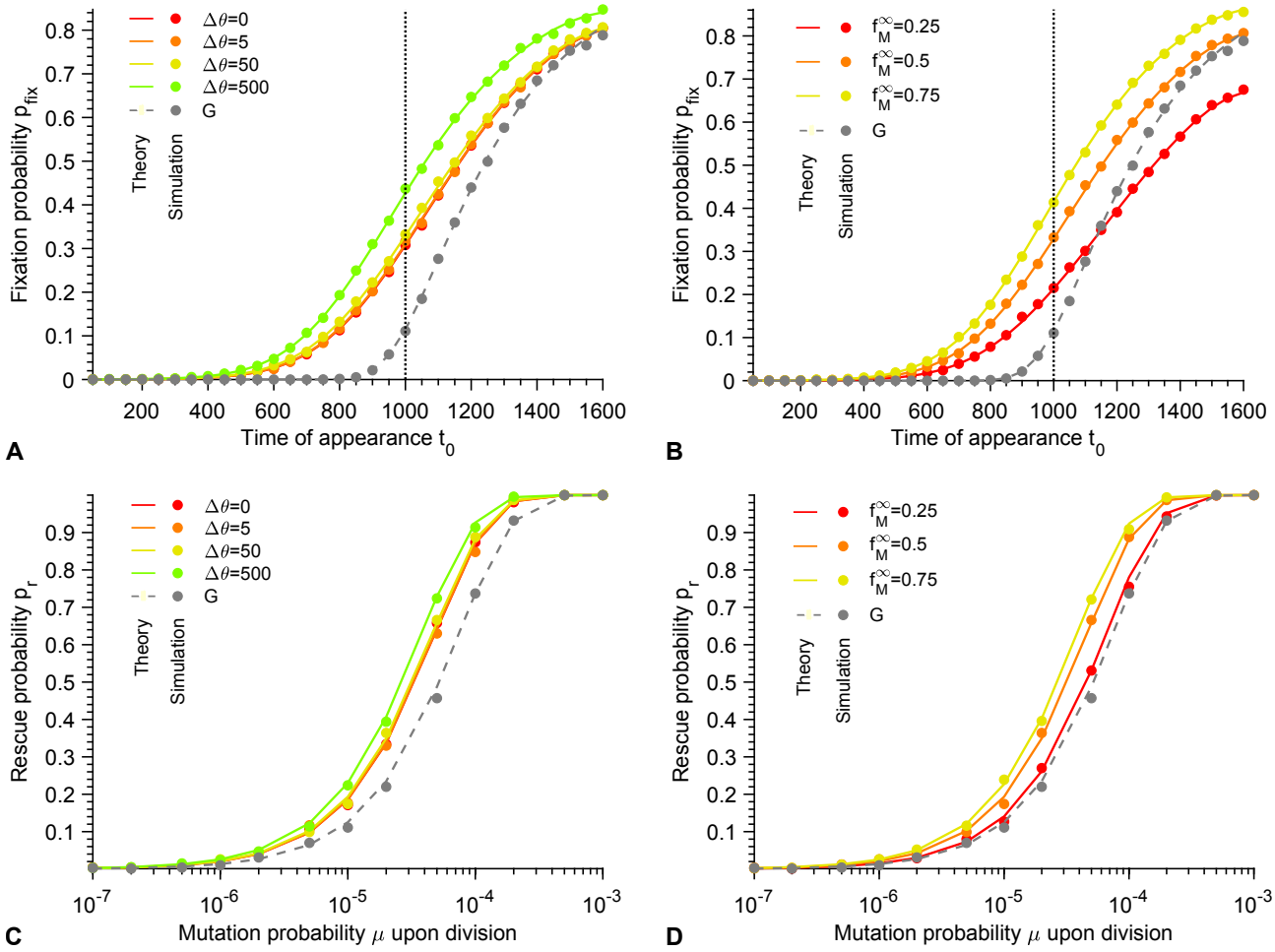

Fig S3. Fixation probability of mutants and probability of rescue in a model of antimicrobial resistance evolution. A. Fixation probability $p_{\rm fix}$ as a function of the time of appearance of the mutants t_0 for mutants M with different values of $\Delta\theta = \theta' - \theta$ and $f_M^\infty = 0.5$ (see Eqs. 1 and S7) and for generalist (G) mutants with $f_G = 0.5$. Vertical dotted line: $t_0 = \theta$. **B.** Same as in panel A, but with $\Delta\theta = 50$ and different values of f_M^∞. **C.** Rescue probability p_r as a function of the mutation probability μ upon division for mutants M with different values of $\Delta\theta = \theta' - \theta$ and $f_M^\infty = 0.5$ (see Eqs. 1 and S7) and for generalist (G) mutants with $f_G = 0.5$, as in panel A. **D.** Same as in panel C, but with $\Delta\theta = 50$ and different values of f_M^∞, as in panel B. In all panels, markers correspond to the average over $10^3 - 10^4$ replicate stochastic simulations, and dashed curves correspond to our analytical predictions. Parameter values: $g_W = g_M = g_G = 0.1$, $f_M^0 = 0.9$, $K = 10^3$, $N_W^0 = 10$, $n = 5$ and $\theta = 10^3$.

2.2 Additional results for various generalist mutants

In the main text, we consider generalist (G) mutants with fitness $f_G = 0.5$, corresponding to the case of specialist (S) mutants with $m = 0$ (see Eq. 2). Fig. S4 shows results obtained for various values of f_G that satisfy $f_G > g_G$, ensuring that the mutant can grow and rescue the population. Mutant fixation and rescue are more difficult for smaller values of f_G, but the overall behavior remains similar and is well described by our analytical predictions.

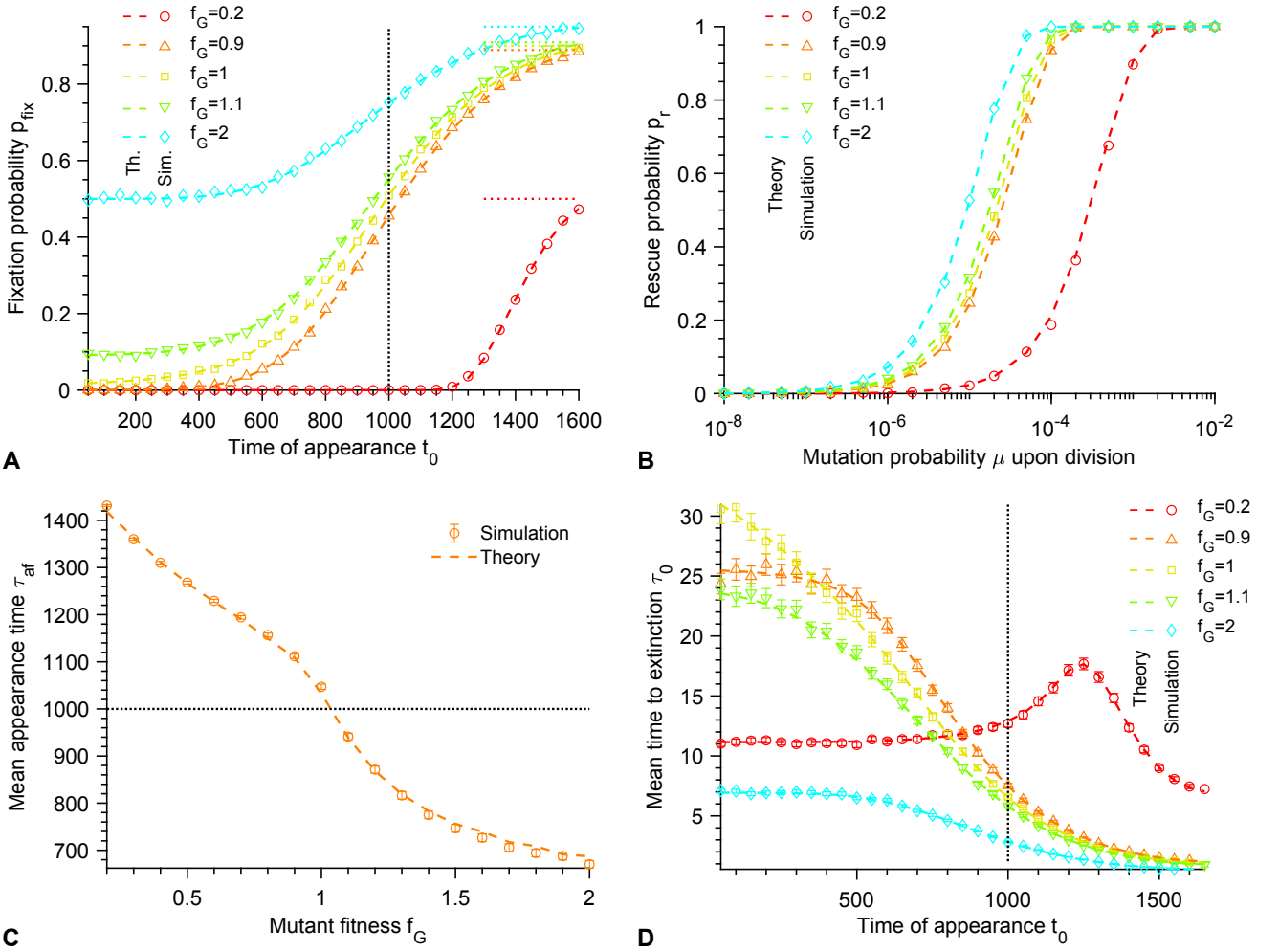

Fig S4. Additional results for generalist mutants. A. Fixation probability p_{fix} as a function of the time of appearance of the mutants t_0 for different fitnesses f_G of G mutants (in the rest of the paper, $f_G = 0.5$). Vertical dotted line: $t_0 = \theta$. Horizontal dotted lines: $p_{\text{fix}} = 1 - g_G/f_G$. **B.** Rescue probability p_r as a function of the mutation probability μ upon division for different fitnesses f_G. **C.** Mean appearance time τ_{af} of a mutant that fixes as a function of the fitness f_G for the mutation probability upon division $\mu = 10^{-5}$. Vertical dotted line: $\tau_{\text{af}} = \theta$. **D.** Mean time to extinction τ_0 as a function of the time of appearance of the mutants t_0 for different fitnesses f_G. Vertical dotted line: $t_0 = \theta$. In all panels, markers correspond to the average over $10^3 - 10^4$ replicate stochastic simulations, error bars (in panels C and D, often smaller than markers) are 95% confidence intervals and dashed curves correspond to our analytical predictions. Parameter values: $g_W = g_G = 0.1$, $K = 10^3$, $N_W^0 = 10$, $n = 5$ and $\theta = 10^3$.

3 Robustness of the results to different initial conditions

In Fig. S5, we show that our results are robust to varying N_W^0 as long as it is not very small, since starting with $N_W^0 = 10$ (as is done throughout) gives the same results as starting with $N_W^0 = K[1 - g_W/f_W(0)] = 0.9K$, which corresponds to the stationary population size in the initial environment within a deterministic description (see Eq. 3).

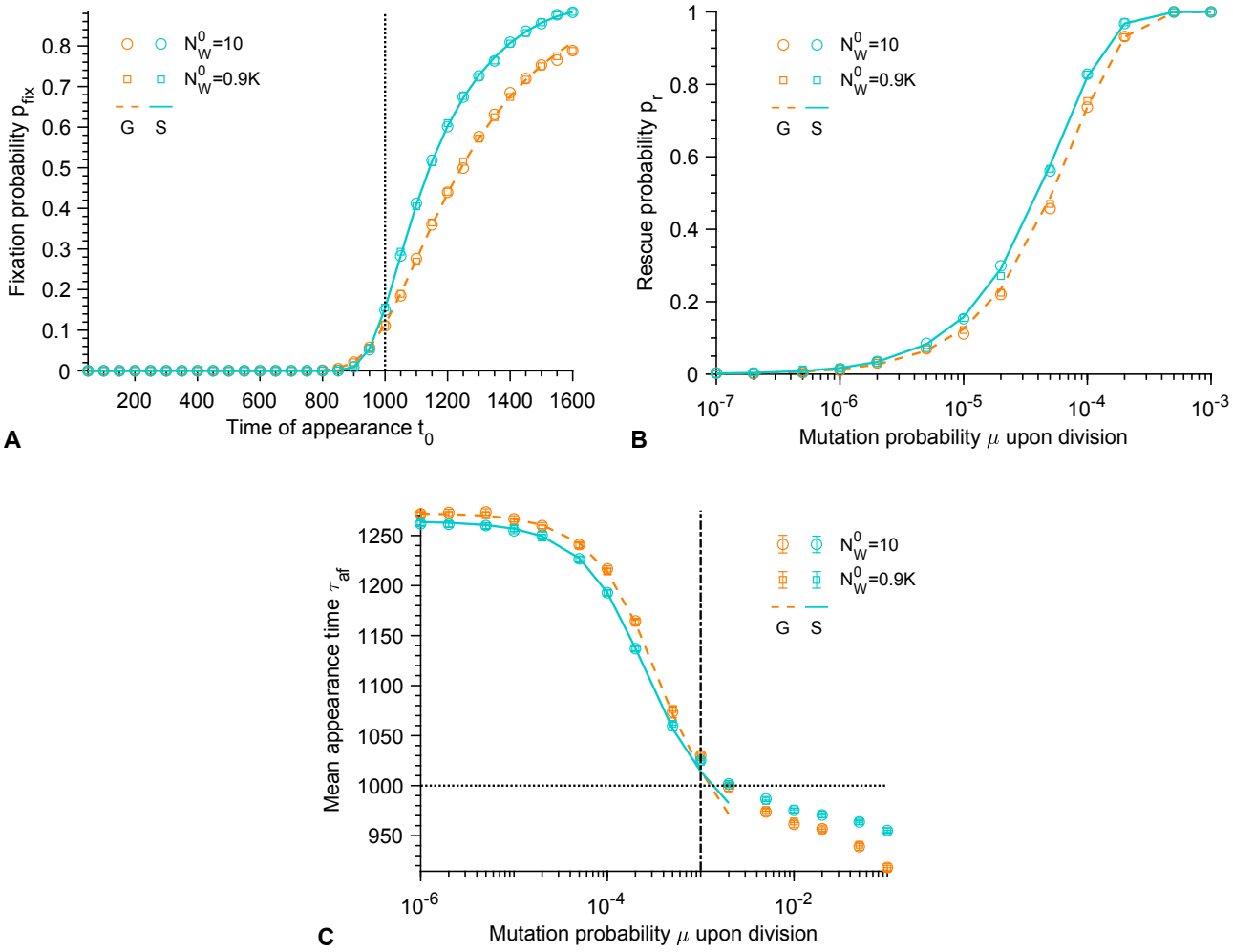

Fig S5. Impact of the initial number N_W^0 of wild-type organisms on rescue. A. Fixation probability $p_{\rm fix}$ of G and S mutants versus their time of appearance t_0 in the deteriorating environment, for $N_W^0 = 10$ and $N_W^0 = 0.9K$. Vertical dotted line: $t_0 = \theta$. **B.** Rescue probability p_r of different types of mutants versus the mutation probability μ upon division, for $N_W^0 = 10$ and $N_W^0 = 0.9K$. G mutants and S mutants are considered. **C.** Mean time $\tau_{\rm af}$ of appearance of a G or S mutant that fixes versus μ, for $N_W^0 = 10$ and $N_W^0 = 0.9K$. Horizontal dotted line: $\tau_{\rm af} = \theta$. Vertical dash-dotted line: $K\mu = 1$. In all panels, the Hill coefficient characterizing the steepness of the environment deterioration (see Eq. 1) is $n = 5$. Furthermore, S mutants satisfy $m = n$, i.e. they have the same sensitivity to the environment as W organisms (see Eq. 2). Markers correspond to averages over $10^3 - 10^4$ replicate stochastic simulations. Dashed and solid lines correspond to our analytical predictions for G and S mutants, respectively. Parameter values: $g_W = g_G = g_S = 0.1$, $K = 10^3$ and $\theta = 10^3$.

4 Additional results regarding the appearance of mutants

4.1 Appearance of mutants during the environment deterioration

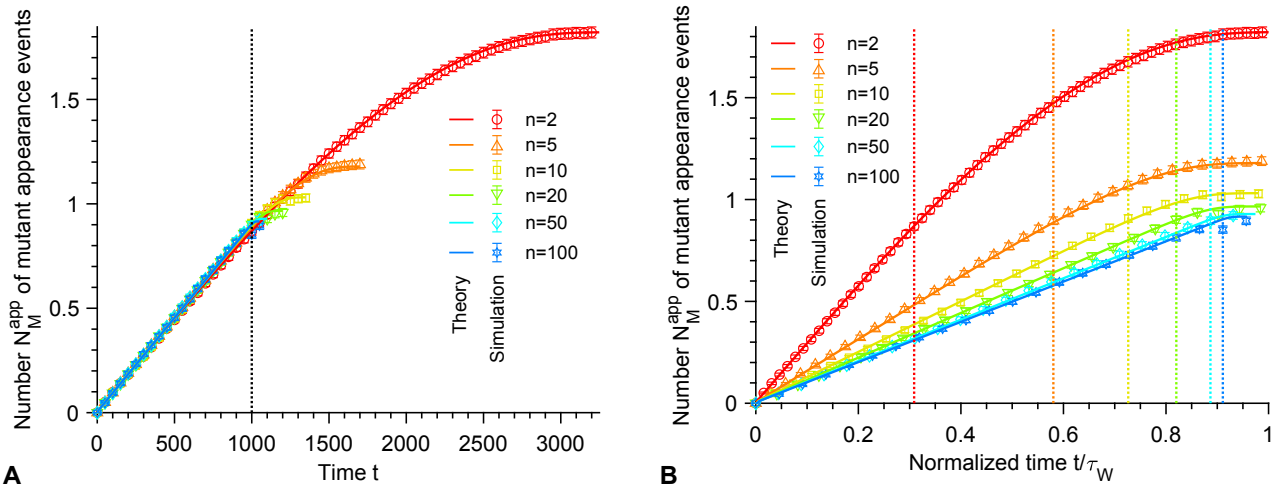

Fig S6. Appearance of mutants. A. Average number N_M^{app} of mutant appearance events that can occur between times 0 and t, plotted versus time t, for different Hill coefficients n characterizing the steepness of the environment deterioration. Vertical dotted line: $t = \theta$. Markers correspond to averages over 10^4 replicate stochastic simulations ("Simulation"), where mutants that appear are replaced immediately by wild-type organisms to avoid any mutant fixation events and count all potential mutant appearance events. Solid lines correspond to numerical integrations of $N_M^{app}(t) = \int_0^\infty N_W(t) f_W(t)(1 - N_W(t)/K)\mu dt$ ("Theory"), which corresponds to the number of mutants that appear, assuming that $N_M(t) \ll N_W(t)$ when they appear (see main text above Eq. 7). **B.** Same data, rescaled by the average extinction time τ_W of the wild-type population in the absence of mutation. Vertical dotted lines: $t = \theta$. Parameter values: $g_W = 0.1$, $K = 10^3$, $\theta = 10^3$, $\mu = 10^{-5}$ and $N_W^0 = 10$. Data is shown for $t < \tau_W$.

4.2 Time of appearance of the mutants that fix

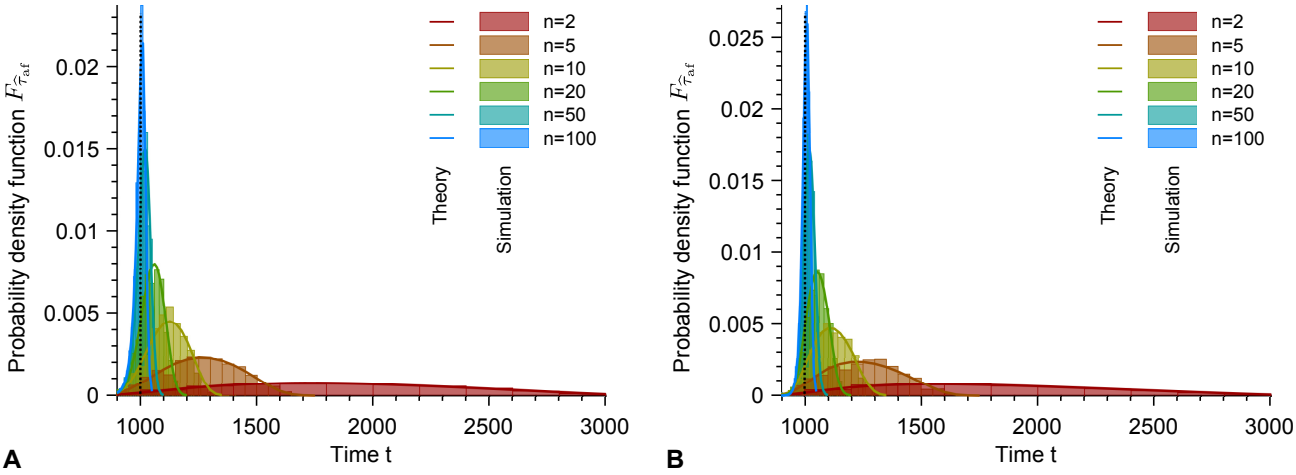

Fig S7. Probability density function of the time of appearance of the mutants that fix. Probability density function $F_{\widehat{\tau}_{\rm af}}$ of the time $\widehat{\tau}_{\rm af}$ of appearance of a mutant that fixes versus time t, for different Hill coefficients n. Results for the generalist (G) and specialist (S) mutants are shown in panels **A** and **B**, respectively. Vertical dotted line: $t = \theta$. Histograms are computed over 10^3 replicate stochastic simulations ("Simulation"). Solid lines correspond to numerical integrations of Eq. 11 ("Theory"). Parameter values: $g_W = g_G = g_S = 0.1$, $K = 10^3$, $\theta = 10^3$, $\mu = 10^{-5}$, $n = m = 5$, and $N_W^0 = 10$.

5 Results for the impact of population size on rescue

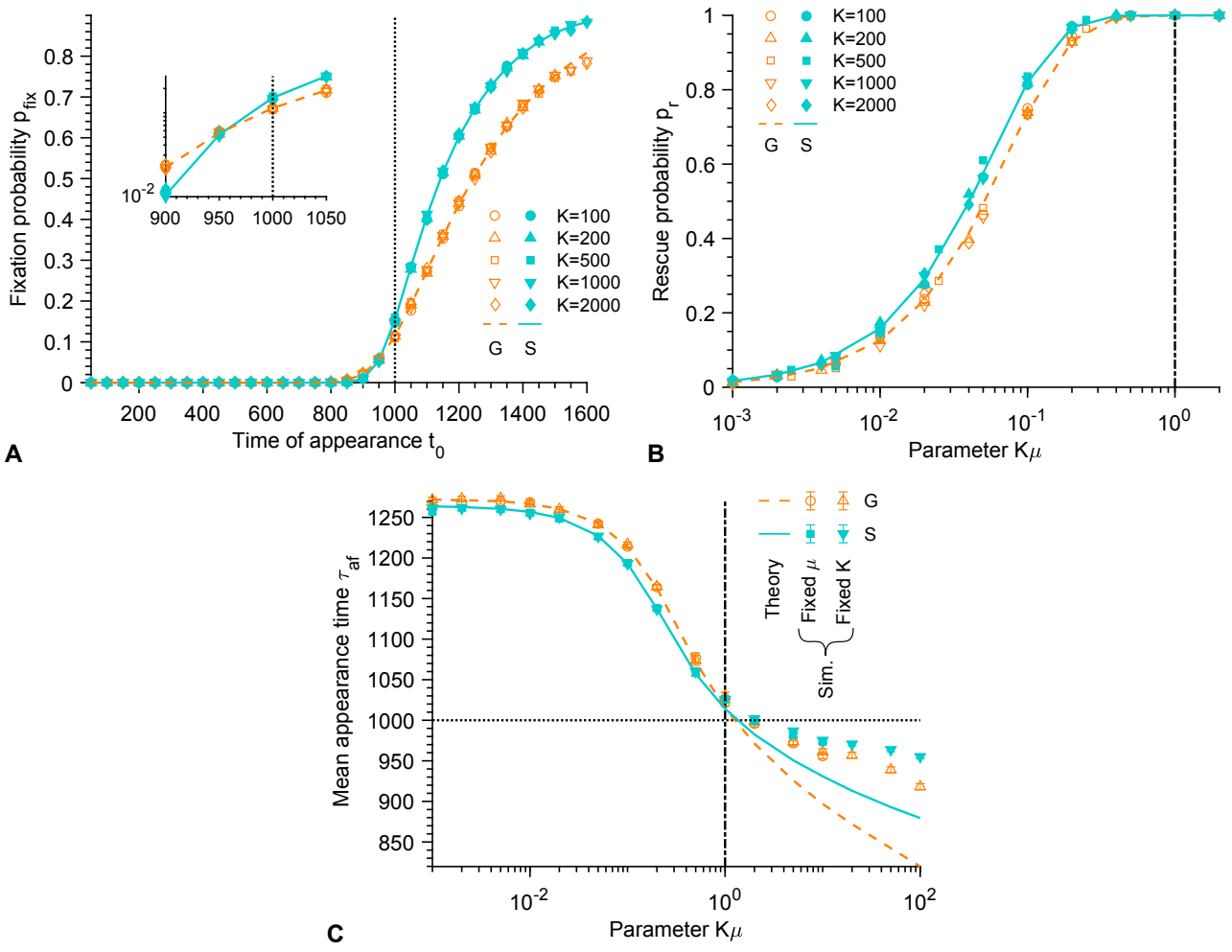

Fig S8. Impact of population size on rescue. A. Fixation probability $p_{\rm fix}$ of G and S mutants versus their time of appearance t_0 in the deteriorating environment, for different carrying capacities K. Vertical dotted line: $t = \theta$. Main panel: linear scale; inset: semi-logarithmic scale. **B.** Rescue probability p_r of different types of mutants versus the product $K\mu$ of the carrying capacity K and the mutation probability μ upon division, for different carrying capacities K. G mutants and S mutants are considered. Vertical dash-dotted line: $K\mu = 1$. **C.** Mean time $\tau_{\rm af}$ of appearance of a G or S mutant that fixes versus $K\mu$. Simulation results are shown both for a fixed mutation probability upon division $\mu = 10^{-5}$ and a variable carrying capacity K, and for a fixed $K = 10^3$ and a variable μ. Horizontal dotted line: $\tau_{\rm af} = \theta$. Vertical dash-dotted line: $K\mu = 1$. In all panels, the Hill coefficient characterizing the steepness of the environment deterioration (see Eq. 1) is $n = 5$. Furthermore, S mutants satisfy $m = n$, i.e. they have the same sensitivity to the environment as W organisms (see Eq. 2). Markers correspond to averages over $10^3 - 10^4$ replicate stochastic simulations ("Sim."). Dashed and solid lines correspond to our analytical predictions ("Theory") for G and S mutants, respectively. Parameter values: $g_W = g_G = g_S = 0.1$, $N_W^0 = 10$ and $\theta = 10^3$.

6 Extinction time of mutants that do not fix

In the case where the mutant that appears does not fix, how long does its lineage take to go extinct? As for the fixation probability $p_{\rm fix}$, the time of extinction of a mutant will depend on its time of appearance t_0. The average time of extinction is the average of the first-passage time $\widehat{\tau}_0^{'}$ to the state $i = 0$ where i denotes the number of mutants. Then, we can compute the probability $dp(\widehat{\tau}_0^{'} \in [t, t + {\rm d}t] \,|\, i_0, t_0)$ that $\widehat{\tau}_0^{'}$ belongs to the interval $[t, t + {\rm d}t]$, provided that the initial number of mutants is i_0 at time t_0:

$$dp(\widehat{\tau}_0^{'} \in [t, t + {\rm d}t] \,|\, i_0, t_0) = P(0, t + dt|0, \infty; i_0, t_0) - P(0, t|0, \infty; i_0, t_0) \ , \tag{S8}$$

where $P(0, t|0, \infty; i_0, t_0)$ is the probability to have 0 mutant at time t, provided that the initial number of mutants is i_0 at time t_0 and the final number is $i_\infty = 0$, corresponding to extinction. Using Bayes' theorem and the Markov property yields

$$P(0, t|0, \infty; i_0, t_0) = \frac{P(0, t|i_0, t_0)\, P(0, \infty|0, t; i_0, t_0)}{P(0, \infty|i_0, t_0)} = \frac{P(0, t|i_0, t_0)\, (1 - p_{\rm fix}(0, t))}{1 - p_{\rm fix}(i_0, t_0)} = \frac{P(0, t|i_0, t_0)}{1 - p_{\rm fix}(i_0, t_0)} \, , \tag{S9}$$

where we have employed $p_{\rm fix}(0, t) = 0$, as having 0 mutant is an absorbing state of the system. Thus,

$$dp(\widehat{\tau}_0^{'} \in [t, t + {\rm d}t] \,|\, i_0, t_0) = \frac{P(0, t + {\rm d}t|i_0, t_0) - P(0, t|i_0, t_0)}{1 - p_{\rm fix}(i_0, t_0)} = \frac{1}{1 - p_{\rm fix}(i_0, t_0)} \frac{{\rm d}P(0, t|i_0, t_0)}{{\rm d}t} {\rm d}t \ . \tag{S10}$$

We can now express the mean time of extinction $\tau_0^{'} = \langle \widehat{\tau}_0^{'} \rangle$ of a mutant that appeared at t_0 using Eq. S10 as

$$\tau_0^{'} = \int_{t_0}^{\infty} t \, dp(\widehat{\tau}_0^{'} \in [t, t + {\rm d}t] \,|\, i_0, t_0) = \frac{1}{1 - p_{\rm fix}(i_0, t_0)} \int_{t_0}^{\infty} t \frac{{\rm d}P(0, t|i_0, t_0)}{{\rm d}t} {\rm d}t \ . \tag{S11}$$

The previous equation can be rewritten using the probability generating function $\phi_{i_0,t_0}(z, t) = \sum_{i=0}^{+\infty} z^i P(i, t|i_0, t_0)$ by noting that $P(0, t|i_0, t_0) = \phi_{i_0,t_0}(0, t)$:

$$\tau_0^{'} = \frac{1}{1 - p_{\rm fix}(i_0, t_0)} \int_{t_0}^{\infty} t \, \frac{\partial \phi_{i_0,t_0}}{\partial t}(0, t) \, {\rm d}t \ . \tag{S12}$$

Using Eqs. S3 and S6 and introducing $\Lambda(t) = g_M \int_{t_0}^{t} e^{\rho(u)} {\rm d}u$ then yields

$$\tau_0^{'} = \frac{i_0 g_M}{1 - p_{\rm fix}(i_0, t_0)} \int_{t_0}^{\infty} t e^{\rho(t)} \frac{\Lambda^{i_0 - 1}(t)}{(1 + \Lambda(t))^{i_0 + 1}} {\rm d}t \ . \tag{S13}$$

Numerical integration of Eq. S13 is discussed in section 9 below.

Fig. S9 shows the average lifetime $\tau_0 = \tau_0^{'} - t_0$, or time to extinction, of the lineage of a single mutant ($i_0 = 1$) that finally goes extinct, versus the time t_0 when this mutant appears during the environment degradation. We obtain a very good agreement between the results of our stochastic simulations and our analytical prediction in Eq. S13. For $t_0 < \theta$, mutants are less fit than wild-type organisms, and S mutants are less fit than G mutants (see Eq. 2). Conversely, for $t_0 > \theta$, mutants are fitter than wild-type organisms, and S mutants are fitter than G mutants: hence, S mutants are always more extreme than G mutants. Because of this, intuition based e.g. on the fixation times within the Moran process (Ewens 1979; Teimouri and Kolomeisky 2019; Teimouri *et al.* 2019) with constant population size make us expect that S mutants will have their fates sealed faster, and thus will get extinct faster provided that they are destined for extinction (note that related results exist in the framework of the Wright-Fisher model, see e.g. (Maruyama and Kimura 1974)). This is indeed what we obtain (see Fig. S9). In particular, the largest extinction time is obtained close to $t_0 = \theta$, where G and S mutants are neutral. In addition, for $t_0 \ll \theta$, S mutants have a fitness $f_S \approx 0$ (see Eq. 2). Then, they generally go extinct in about one generation, i.e. in $\tau_0 \approx 10$ time units (in our simulations, the death rate, which sets the division rate when the population is close to its steady-state size $K(1 - g_W/f_W)$, is taken equal to 0.1): this is what is obtained in Fig. S9. Still for $t_0 \ll \theta$, G mutants are such that $f_G = 0.5$ while $f_W \approx 1$ (see Eq. 1): then, the extinction time of the mutant lineage can be obtained within the framework of the Moran process assuming a constant population size $K(1 - g_W/f_W)$: it yields $\tau_0 \approx 15$ (Ewens 1979), consistently with Fig. S9. Furthermore, Fig. S9A shows that for $t_0 < \theta$, the bigger the Hill coefficient n characterizing the steepness of the environment degradation (see Eq. 1), the smaller the mean time to extinction. In particular, as long as $t_0 < \theta$, we have $f_S \approx 0$ and $f_W \approx 1$, and therefore the results obtained just before for $t_0 \ll \theta$ hold. Finally, Fig. S9B shows that τ_0 does not depend on the carrying capacity K. This can be understood from Eq. S13, given that $p_{\rm fix}$ is independent from K, as well as ρ, as explained in Section 1.

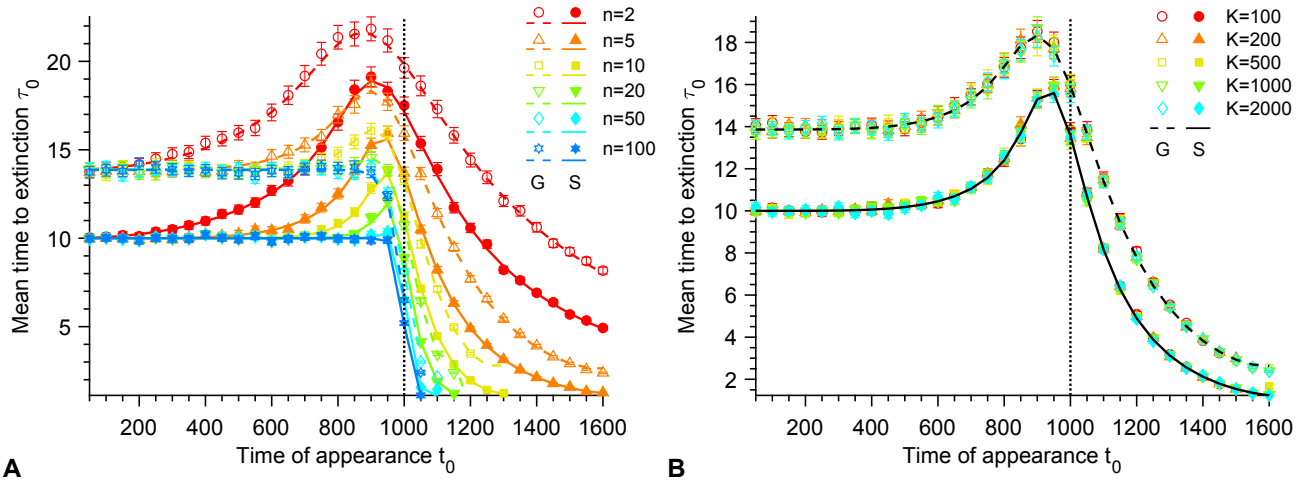

Fig S9. Mean time to extinction. A. Mean time to extinction τ_0 of G and S mutants versus their time of appearance t_0 in the deteriorating environment, for $K = 10^3$ and for different Hill coefficients n characterizing the steepness of the environment deterioration (see Eq. 1). **B.** Mean time to extinction τ_0 of G and S mutants versus their time of appearance t_0 in the deteriorating environment, for different carrying capacities K and a fixed Hill coefficient $n = 5$ characterizing the decay of f_W (see Eq. 1). In both panels, markers correspond to averages over $10^3 - 10^4$ replicate stochastic simulations. Solid (resp. dashed) curves correspond to numerical integrations of Eq. S13 for S (resp. G) mutants. Here, S mutants satisfy $m = n$, i.e. they have the same sensitivity to the environment as W organisms (see Eq. 2). Parameter values: $g_W = g_G = g_S = 0.1$, $N_W^0 = 10$ and $\theta = 10^3$. Vertical dotted lines: $t_0 = \theta$.

7 Analytical approximations for a sudden environment degradation

Here, we derive analytical approximations for the fixation probability $p_{\rm fix}$, the probability $p_{\rm r}$ of rescue and the mean time $\tau_{\rm af}$ of appearance of a mutant that fixes in the case of a sudden environment degradation. We thus consider that the Hill coefficient n describing the decay of W fitness f_W tends to infinity (see Eq. 1), as well as m, which describes the increase of S mutant fitness f_S (see Eq. 2), i.e. $n, m \to \infty$. Then, the fitness transition around $t = \theta$ is very abrupt, and we therefore consider that $f_W = 1$ and $f_S = 0$ if $t < \theta$ while $f_W = 0$ and $f_S = 1$ if $t > \theta$.

As soon as $f_W = 0$, i.e. for $t > \theta$, W microbes stop dividing. In a deterministic description, their number decreases exponentially according to the function $N_W(t) = N_W^e e^{-g_W(t-\theta)}$, where $N_W^e = K(1-g_W)$ is the equilibrium size of the fully wild-type population if $f_W = 1$, i.e. for $t < \theta$. For analytical convenience, we make the approximation that $N_W(t) = N_W^e$ if $t < \theta + \tau_{1/2}$ and $N_W(t) = 0$ otherwise, where $\tau_{1/2}$ is the time such that $N_W(\tau_{1/2}) = K/2$ (i.e. $\tau_{1/2} = \ln(2N_W^e/K)/g_W$). While the exact choice of $\theta + \tau_{1/2}$ as a threshold is somewhat arbitrary, it is important to choose a threshold that reflects the decay timescale of the W population. Indeed, it allows to effectively take into account the demographic pressure that mutants undergo because of the presence of W organisms during the decline of the W population. Considering a threshold θ instead of $\theta + \tau_{1/2}$ would lead one to underestimate the demographic pressure on mutants and thus to overestimate their fixation probability. Conversely, considering a threshold $\theta + \tau_0$, where τ_0 is the mean time of W population extinction when W microbes no longer divide, would lead one to overestimate the demographic pressure on mutants and thus to underestimate their fixation probability.

7.1 Fixation probability

7.1.1 Generalist mutant

Let us first focus on the fixation probability $p_{\rm fix}^G(t_0)$ of a single generalist (G) mutant that appears at time t_0. Recall that the fitness of G mutants is constant. In most of our work, we take $f_G = 0.5$, but here, for the sake of generality, we will retain f_G in our expressions, assuming that $f_G > g_G$. Within our approximation, the fate of a mutant will strongly depend on whether $t_0 < \tilde{\theta} = \theta + \tau_{1/2}$ or $t_0 > \tilde{\theta}$. We start from Eq. 4, which reads

$$p_{\rm fix}^G(t_0) = \frac{1}{1 + g_G \int_{t_0}^{\infty} e^{\rho_G(t)} {\rm d}t}. \tag{S14}$$

Two regimes need to be distinguished:
- If $t < \tilde{\theta}$, then $N_W(t) = K(1 - g_W)$;
- If $t \geq \tilde{\theta}$, then $N_W(t) = 0$.

For $t_0 < \tilde{\theta}$, Eq. 5 yields

$$\rho_G(t) = \begin{cases} -\left(f_G g_W - g_G\right)(t - t_0) & \text{if } t_0 < t < \tilde{\theta}, \\ -(f_G - g_G)(t - t_0) + f_G(1 - g_W)(\tilde{\theta} - t_0) & \text{if } t_0 < \tilde{\theta} < t. \end{cases} \tag{S15}$$

Thus, Eq. S14 simplifies as:

$$p_{\text{fix}}^G(t_0) = \frac{(f_G - g_G)(f_G g_W - g_G)}{f_G g_W (f_G - g_G) - e^{-(g_G - f_G g_W)(t_0 - \tilde{\theta})} f_G g_G (1 - g_W)} \ . \tag{S16}$$

For $t_0 > \tilde{\theta}$, $N_W = 0$, and Eq. 5 yields

$$\rho_G(t) = -\left(f_G - g_G\right)(t - t_0) \ . \tag{S17}$$

Then, Eq. S14 gives

$$p_{\text{fix}}^G(t_0) = 1 - g_G/f_G \ , \tag{S18}$$

which corresponds to the probability that the mutant lineage survives rapid stochastic extinction in a constant-rate birth-death process, in the absence of competition (Ovaskainen and Meerson 2010; Coates *et al.* 2018; Marrec and Bitbol 2020). This makes sense, because within our approximation, $t_0 > \tilde{\theta}$ formally corresponds to introducing a mutant in the absence of any W individual.

Let us summarize Eqs. S16 and S18:

$$p_{\text{fix}}^G(t_0) = \begin{cases} \frac{(f_G - g_G)(f_G g_W - g_G)}{f_G g_W (f_G - g_G) - e^{-(g_G - f_G g_W)(t_0 - \tilde{\theta})} f_G g_G (1 - g_W)} & \text{if } t_0 < \tilde{\theta} \ , \\ 1 - g_G/f_G & \text{if } t_0 > \tilde{\theta} \ . \end{cases} \tag{S19}$$

7.1.2 Specialist mutant

Let us now turn to the fixation probability $p_{\text{fix}}^S(t_0)$ of a single specialist (S) mutant that appears at time t_0. Again, we start from Eq. 4, which reads

$$p_{\text{fix}}^S(t_0) = \frac{1}{1 + g_S \int_{t_0}^{\infty} e^{\rho_S(t)} \mathrm{d}t}. \tag{S20}$$

Note that we assume $g_S < 1$. Three regimes need to be distinguished:
- If $t < \theta$, then $N_W(t) = K(1 - g_W)$ and $f_S(t) = 0$;
- If $\theta < t \leq \tilde{\theta}$, then $N_W(t) = K(1 - g_W)$ and $f_S(t) = 1$;
- If $t \geq \tilde{\theta}$, then $N_W(t) = 0$ and $f_S(t) = 1$.

If $t_0 < \theta$, Eq. 5 yields

$$\rho_S(t) = \begin{cases} g_S(t - t_0) & \text{if } t_0 < t < \theta, \\ g_S(\theta - t_0) + (g_S - g_W)(t - \theta) & \text{if } \theta < t < \tilde{\theta}, \\ g_S(\theta - t_0) + (g_S - g_W)(\tilde{\theta} - \theta) + (g_S - 1)(t - \tilde{\theta}) & \text{if } \tilde{\theta} < t \ . \end{cases} \tag{S21}$$

Note that the second term in the second and the third lines of the previous equation both vanish if $g_S = g_W$. In this case, Eq. S20 simplifies as:

$$p_{\text{fix}}^S(t_0) = \frac{e^{-g_S(\theta - t_0)}(1 - g_S)}{1 + g_S(1 - g_S)(\tilde{\theta} - \theta)} \ . \tag{S22}$$

If $\theta < t_0 < \tilde{\theta}$, Eq. 5 yields

$$\rho_S(t) = \begin{cases} (g_S - g_W)(t - t_0) & \text{if } t_0 < t < \tilde{\theta}, \\ (g_S - g_W)(\tilde{\theta} - t_0) + (g_S - 1)(t - \tilde{\theta}) & \text{if } \tilde{\theta} < t \ . \end{cases} \tag{S23}$$

If in addition $g_S = g_W$, Eq. S20 then gives

$$p_{\rm fix}^S(t_0) = \frac{1-g_S}{1+g_S(1-g_S)(\tilde{\theta}-t_0)} \ . \tag{S24}$$

If $t_0 > \tilde{\theta}$, Eq. 5 yields

$$\rho_S(t) = (g_S - 1)(t - t_0) \ . \tag{S25}$$

Thus, Eq. S20 simplifies as:

$$p_{\rm fix}^S(t_0) = 1 - g_S \ . \tag{S26}$$

Again, this is the probability that the mutant lineage escapes rapid stochastic extinctions, in the absence of any competition.

Let us summarize Eqs. S22, S24 and S26:

$$p_{\rm fix}^S(t_0) = \begin{cases} \frac{e^{-g_S(\theta-t_0)}(1-g_S)}{1+g_S(1-g_S)(\tilde{\theta}-\theta)} & \text{if } t_0 < \theta \ , \\ \frac{1-g_S}{1+g_S(1-g_S)(\tilde{\theta}-t_0)} & \text{if } \theta < t_0 < \tilde{\theta} \ , \\ 1-g_S & \text{if } \tilde{\theta} < t_0 \ . \end{cases} \tag{S27}$$

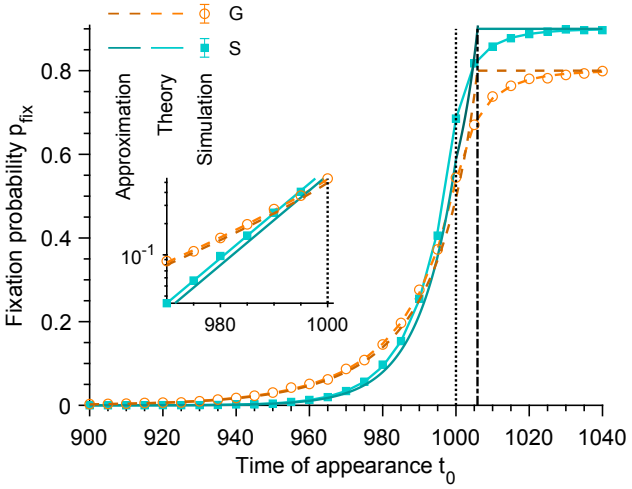

Fig S10. Fixation probability for a sudden environment degradation. Fixation probability $p_{\rm fix}$ of S or G mutants versus their time of appearance t_0 in the deteriorating environment, for Hill coefficients $n, m \to \infty$ (see Eqs. 1 and 2) corresponding to an instantaneous, stepwise, environment change. Markers correspond to averages over 10^4 replicate stochastic simulations. Light dashed (resp. solid) curves correspond to our analytical predictions in Eq. 4 for G (resp. S) mutants. Dark dashed (resp. solid) curves correspond to our approximations in Eq. S19 (resp. Eq. S27) for G (resp. S) mutants in the different regimes discussed. Vertical dotted line: $t_0 = \theta$. Vertical dash-dotted line: $t_0 = \tilde{\theta} = \theta + \tau_{1/2}$. Parameter values: $g_W = g_G = g_S = 0.1$, $K = 10^3$, $N_W^0 = 10$, $n = m = 10^{10}$, $\theta = 10^3$ and $\tau_{1/2} = 5.9$. Main panel: linear scale; inset: semi-logarithmic scale.

Fig. S10 shows that Eqs. S19 and S27 provide good approximations in the appropriate regimes, i.e. for t_0 substantially smaller or larger than θ. (Our approximation that the decay of the W population occurs instantaneously is least valid when t_0 is close to θ.)

7.2 Rescue probability

Now, let us focus on the rescue probability p_r, which satisfies $p_\mathrm{r} = 1 - e^{-\Sigma}$ (see Eq. 9), where Σ is given by Eq. 10. Since here $f_W(t) = 0$ for $t > \theta$ and $f_W(t) = 1$ for $t < \theta$, Eq. 10 simplifies into

$$\Sigma = \mu N_W \left(1 - \frac{N_W}{K}\right) \int_0^\theta p_\mathrm{fix}(t)\mathrm{d}t = \mu K (1 - g_W) g_W \int_0^\theta p_\mathrm{fix}(t)\mathrm{d}t \ , \tag{S28}$$

where we have employed $N_W = K(1 - g_W)$. Thus, we obtain a simplified formula for the rescue probability:

$$p_\mathrm{r} = 1 - \exp\left(-\mu K (1 - g_W) g_W \int_0^\theta p_\mathrm{fix}(t)\mathrm{d}t\right) \ , \tag{S29}$$

which holds both for generalist and for specialist mutants.

Specifically, in the case of a generalist mutant, Eq. S19 yields

$$\int_0^\theta p_\mathrm{fix}^G(t)\mathrm{d}t = \frac{1}{f_G g_W} \log\left(\frac{g_G(1 - g_W)e^{(g_G - f_G g_W)\tilde{\theta}} - g_W(f_G - g_G)}{g_G(1 - g_W)e^{(g_G - f_G g_W)\tilde{\theta}} - g_W(f_G - g_G)e^{(g_G - f_G g_W)\theta}}\right) \ . \tag{S30}$$

And in the case of a specialist mutant, Eq. S27 gives

$$\int_0^\theta p_\mathrm{fix}^S(t)\mathrm{d}t = \frac{(1 - e^{-g_S\theta})(1 - g_S)}{g_S + g_S^2(1 - g_S)(\tilde{\theta} - \theta)} \ . \tag{S31}$$

Fig. S11A shows that there is a good agreement between our approximated analytical predictions and our numerical simulation results. Moreover, we observe that the transition between small and large values of p_r occurs for μK of order 1. Indeed for abrupt environment degradations such that W fitness gets to 0 right at the transition point θ, preexisting mutants are necessary to ensure rescue.

In a previous work (Marrec and Bitbol 2020), we proposed an expression for the probability of extinction of a microbial population subjected to a periodic presence of antimicrobial in the weak-mutation regime $K\mu \ll 1$. We then assumed that the antimicrobial was instantaneously added and removed from the environment, which thus corresponds to instantaneous environment changes. For a perfect biostatic antimicrobial that completely stops growth, wild-type fitness goes to 0 in the presence of antimicrobial, corresponding to the case studied here. When in addition the alternation period is long enough for extinction to occur at the first phase with antimicrobial if no resistant mutants preexist, our prediction in Eq. 1 of (Marrec and Bitbol 2020) gives a good approximation of our present results, as shown by Fig. S11B. Therefore, the present work generalizes this prediction beyond the weak-mutation regime $K\mu \ll 1$. Note that in (Marrec and Bitbol 2020) we made the assumption $K\mu \ll 1$ in particular when calculating the probability that at least one mutant be present when antimicrobial is added. Indeed, we expressed it as as the ratio of the average lifetime of a mutant lineage (destined for extinction in the initial environment) to the average time of appearance of a new mutant lineage. This assumes that at most one mutant lineage is present in the population.

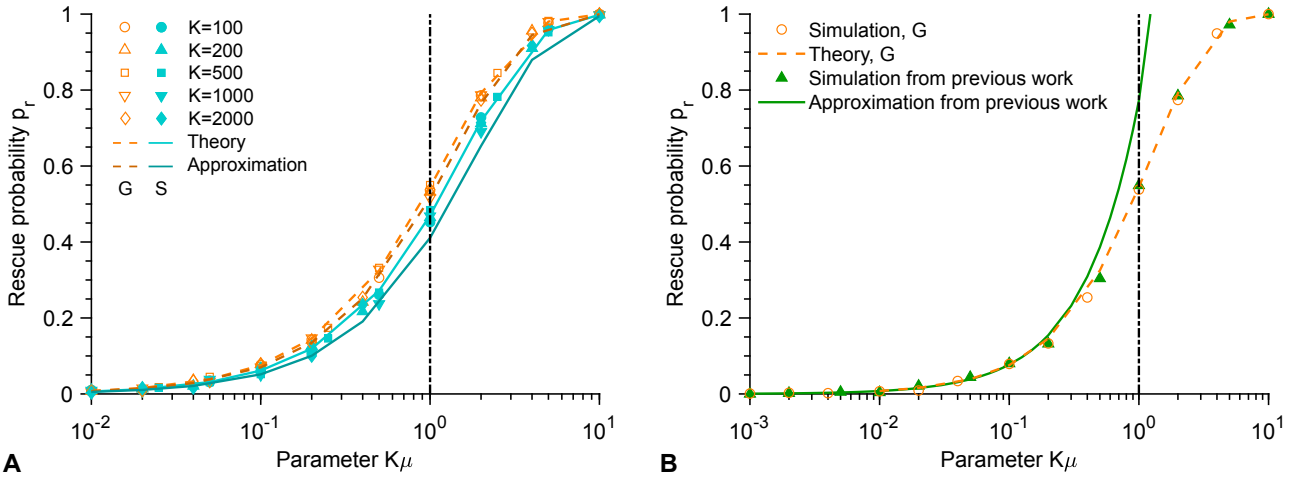

Fig S11. Rescue probability for a sudden environment degradation. A. Rescue probability p_r versus the product $K\mu$ of the carrying capacity K and the mutation probability μ upon division, for different carrying capacities K. Markers correspond to averages over 10^4 replicate stochastic simulations. Light dashed (resp. solid) curves correspond to our analytical predictions in Eq. 9 for G (resp. S) mutants. Dark dashed (resp. solid) curves correspond to our approximations, corresponding to Eq. S29 with Eq. S30 (resp. Eq. S31) for G (resp. S) mutants, with $\tau_{1/2} = 5.9$. **B.** Rescue probability p_r versus $K\mu$. The present results for G mutants are compared to those of our previous work (Marrec and Bitbol 2020) for $K = 10^3$. Markers correspond to averages over $10^3 - 10^4$ replicate stochastic simulations. Dashed orange curve: analytical prediction in Eq. 9 for G mutants. Solid green curve: analytical prediction $p_\mathrm{r} = 1 - p_0$ with p_0 in Eq. 1 of (Marrec and Bitbol 2020), valid for $K\mu \ll 1$. Vertical dash-dotted lines in both panels: $K\mu = 1$. Parameter values: $g_W = g_G = g_S = 0.1$, $N_W^0 = 10$, $n = m = 10^{10}$, $\theta = 10^3$.

7.3 Appearance time of a mutant that fixes

Finally, we derive an approximated analytical prediction for the mean time of appearance τ_af of a mutant that fixes in the population before it goes extinct. Let us recall that the probability density function of $\tilde{\tau}_\mathrm{af}$ satisfies $F_{\tilde{\tau}_\mathrm{af}}(t) = (1/p_\mathrm{r})(\mathrm{d}p_\mathrm{af}/\mathrm{d}t)$ (see Eq. 11 and above). Thus, for an abrupt environment degradation such that $f_W(t) = 0$ for $t > \theta$, the mean time of appearance τ_af is given by:

$$\tau_\mathrm{af} = \int_0^\theta t F_{\tilde{\tau}_\mathrm{af}}(t)\mathrm{d}t = \frac{1}{p_\mathrm{r}}\int_0^\theta t\frac{\mathrm{d}p_\mathrm{af}}{\mathrm{d}t}\mathrm{d}t = \theta - \frac{1}{p_\mathrm{r}}\int_0^\theta p_\mathrm{af}(t)\mathrm{d}t = \theta - \frac{1}{p_\mathrm{r}}\int_0^\theta (1 - e^{-\sigma(t)})\mathrm{d}t \ , \tag{S32}$$

where we have performed an integration by parts, employed Eq. 8 (and the formula for $p_\mathrm{af}(t)$ just above it), and used $p_\mathrm{af}(\theta) = p_\mathrm{r}$ (see Eq. 9, and recall that here, $f_W(t) = 0$ for $t > \theta$). Using Eq. 12 with $f_W = 1$ and $N_W = K(1 - g_W)$ for $t < \theta$, we have

$$\sigma(t) = \mu K g_W(1 - g_W)\int_0^t p_\mathrm{fix}(u)\mathrm{d}u \ . \tag{S33}$$

Eq. S32 is valid for both generalist and specialist mutants. One just needs to compute p_r by using Eq. S29 with Eq. S30 (resp. Eq. S31) for G (resp. S) mutants and p_fix by using Eq. S19 (resp. Eq. S27) for G (resp. S) mutants.

Fig. S12 shows that there is a very good agreement between our approximated analytical predictions and the results of our numerical simulations in the weak-to-moderate mutation regime $K\mu \lesssim 1$ where our analytical derivations were conducted (see main text, "Rescue probability" section). Recall also that τ_af only depends on K and μ via $K\mu$ (see main text).

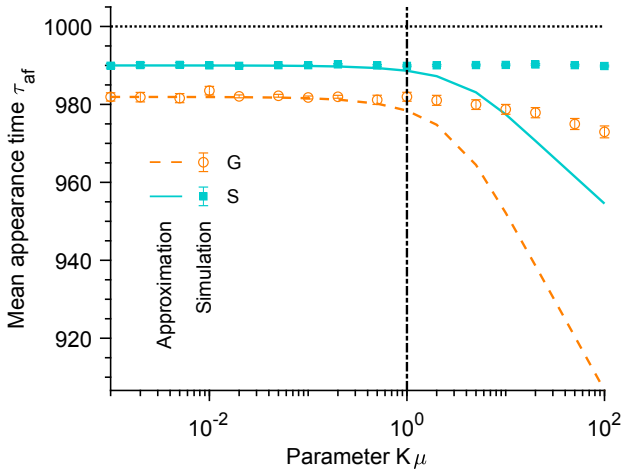

Fig S12. Mean time of appearance for a sudden environment degradation. Mean time $\tau_{\rm af}$ of appearance of a G or S mutant that fixes versus the product $K\mu$ of the carrying capacity K and the mutation probability μ. Here, μ was varied at constant carrying capacity $K = 10^3$. Horizontal dotted line: $\tau_{\rm af} = \theta$. Vertical dash-dotted line: $K\mu = 1$. Markers correspond to averages over 10^3 replicate stochastic simulations ("Simulation"). Dashed and solid lines correspond to our analytical predictions ("Theory") for G and S mutants, respectively (see Eq. S32). Parameter values: $g_W = g_G = g_S = 0.1$, $N_W^0 = 10$, $m = n = 10^{10}$, $\theta = 10^3$ and $\tau_{1/2} = 5.9$ and $\theta = 10^3$.

8 From the stochastic model to the deterministic limit

In our analytical calculations, we consider the deterministic description for the population of W organisms (see Eq. 3). Here, we present a full derivation of the deterministic limit of the stochastic model for large population sizes. This derivation is similar to those of (Traulsen *et al.* 2005; Traulsen and Hauert 2009; Marrec and Bitbol 2018) that address the case of the Moran model.

In a fully wild-type (W) population, the probability $P(j,t|j_0)$ of having j W microorganisms at time t, knowing that j_0 W microorganisms were present at time $t = 0$, satisfies the master equation

$$\begin{aligned}\frac{\partial P(j,t|j_0)}{\partial t} &= f_W(t)\left(1-\frac{j-1}{K}\right)(j-1)P(j-1,t|j_0) + g_W(j+1)P(j+1,t|j_0) \\ &\quad - \left[f_W(t)\left(1-\frac{j}{K}\right)+g_W\right] jP(j,t|j_0)\ .\end{aligned} \tag{S34}$$

Let us introduce $x = j/K$ and $\rho(x,t|x_0) = KP(j,t|j_0)$, and perform a Kramer-Moyal expansion (Van Kampen 1981; Gardiner 1985), which focuses on the regime $1/K \ll x$. To first order in $1/K$, one obtains the following diffusion equation (Ewens 1979) (also known as Fokker-Planck equation or Kolmogorov forward equation):

$$\frac{\partial \rho(x,t|x_0)}{\partial t} = -\frac{\partial}{\partial x}\left\{\left[f_W(t)x(1-x) - g_W x\right]\rho(x,t|x_0)\right\} + \frac{1}{2K}\frac{\partial^2}{\partial x^2}\left\{\left[f_W(t)x(1-x) + g_W x\right]\rho(x,t|x_0)\right\}\ . \tag{S35}$$

Note that the first term on the right hand-side of this equation corresponds to the selection term (known as the drift term in physics), while the second one corresponds to the genetic drift term (known as the diffusion term in physics).

In the limit $K \to \infty$, to zeroth order in $1/K$, one can neglect the diffusion term, yielding:

$$\frac{\partial \rho(x,t|x_0)}{\partial t} = -\frac{\partial}{\partial x}\left\{\left[f_W(t)x(1-x) - g_W x\right]\rho(x,t|x_0)\right\}\ . \tag{S36}$$

In this limit, one obtains an equation on the average population size (scaled by K), $\langle x(t)\rangle = \int_0^1 x\rho(x,t|x_0)dx$:

$$\frac{\partial\langle x\rangle}{\partial t} = \left[f_W(t) - g_W\right]\langle x\rangle - f_W(t)\langle x^2\rangle\ . \tag{S37}$$

Further assuming that the distribution of x is very peaked around its mean ($\langle x\rangle \approx x$) and in particular neglecting the variance ($\langle x^2\rangle \approx \langle x\rangle^2 \approx x^2$), which is acceptable for very large systems with demographic fluctuations, one obtains:

$$\frac{\partial x}{\partial t} = \left[f_W(t)(1-x) - g_W\right]x\ . \tag{S38}$$

Multiplying this ordinary differential equation by the carrying capacity K yields Eq. 3, where j is denoted by N_W.

9 Numerical integration methods

In this work, we derived analytical predictions for the fixation probability p_{fix}, the rescue probability p_r and the mean time of extinction τ_0' (see Eqs. 4, 9 and S13, respectively). Since these equations involve improper integrals, it is necessary to appropriately choose the values of the (finite) integral boundaries in order to obtain a good approximation of these improper integrals by numerical integration. These choices are discussed below. The built-in function `NIntegrate` from Wolfram Mathematica was then employed to perform numerical integrations.

First, in order to compute numerically p_{fix} from Eq. 4, let us introduce a parameter τ_1 such that:

$$p_{\text{fix}}(t_0) = 1 - \frac{g_M \int_{t_0}^{\infty} e^{\rho(t)} \mathrm{d}t}{1 + g_M \int_{t_0}^{\infty} e^{\rho(t)} \mathrm{d}t} \approx 1 - \frac{g_M \int_{t_0}^{t_0+\tau_1} e^{\rho(t)} \mathrm{d}t}{1 + g_M \int_{t_0}^{t_0+\tau_1} e^{\rho(t)} \mathrm{d}t} \ , \tag{S39}$$

One should choose τ_1 such that it is much larger than the mean time of extinction of the mutants τ_0'. Otherwise, some mutants destined for extinction will be considered as mutants that fix. Fig. S13A illustrates this point: for the parameters employed in this figure, the largest value of τ_0 is $\max(\tau_0) \sim 30$, and accordingly, we observe that for $\tau_1 \gg 30$, the agreement between the analytical prediction calculated numerically via Eq. S39 and the simulated data is very good.

Similarly, in order to compute numerically p_{r} from Eq. 9, we introduce a parameter τ_2 such that:

$$p_{\text{r}} = 1 - \exp\left[-\mu \int_0^{\infty} p_{\text{fix}}(t) N_W(t) f_W(t) \left(1 - \frac{N_W(t)}{K}\right) \mathrm{d}t\right] \approx 1 - \exp\left[-\mu \int_0^{\tau_2} p_{\text{fix}}(t) N_W(t) f_W(t) \left(1 - \frac{N_W(t)}{K}\right) \mathrm{d}t\right] \ , \tag{S40}$$

Choosing τ_2 so that it is larger than the mean time of spontaneous extinction of wild-type microbes should ensure that we capture the whole time range over which mutants can appear and fix. As can be seen in Fig. 1, for the parameter values chosen in Fig. S13B, the mean time of spontaneous extinction is ~ 1750. Indeed, Fig. S13B shows that a good agreement between numerical predictions and simulated data is obtained for $\tau_2 > 1750$.

Similarly, in order to compute numerically $\tau_0 = \tau_0^{'} - t_0$ from Eq. S13 with $i_0 = 1$, we introduce a parameter τ_3 such that:

$$\tau_0^{'} = \frac{g_M}{1 - p_{\text{fix}}(t_0)} \int_{t_0}^{\infty} \frac{t e^{\rho(t)}}{(1 + \Lambda(t))^2} \mathrm{d}t \approx \frac{g_M}{1 - p_{\text{fix}}(t_0)} \int_{t_0}^{t_0+\tau_3} \frac{t e^{\rho(t)}}{(1 + \Lambda(t))^2} \mathrm{d}t \ . \tag{S41}$$

The parameter τ_3 must be chosen so that it is larger than all times for which the probability density function of $\widehat{\tau}_0$ is significant. In practice, we may choose τ_3 as larger than the variance of the distribution of extinction times. Assuming that this distribution is exponential (it is close to exponential in simulations), one should choose $\tau_3 \gg \tau_0^2$. Accordingly, Fig. S13C demonstrates a very good agreement with simulated data for $\tau_3 \gg \max(\tau_0)^2 \sim 900$, where $\max(\tau_0)$ is the largest value of τ_0 for the parameters involved in this figure.

In practice, in each figure of this paper, we chose the values of τ_1, τ_2 and τ_3 so that they were large enough to satisfy the criteria outlined here in the worse case of the figure (i.e. the one requiring the largest value of this parameter).

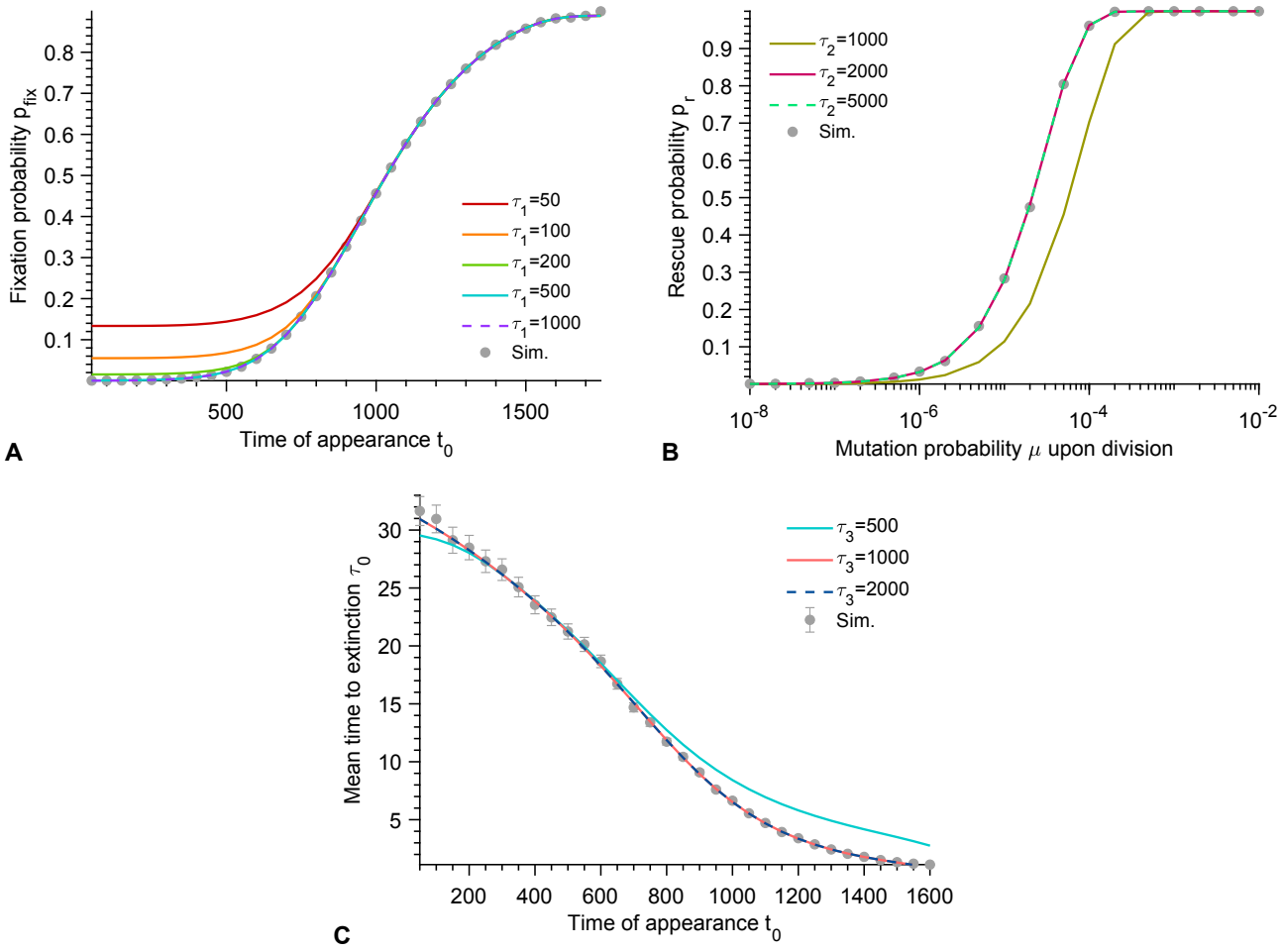

Fig S13. Robustness of parameters and numerical integrations. A. Fixation probability $p_{\rm fix}$ of G mutants versus their time of appearance t_0 in the deteriorating environment. Solid curves correspond to numerical integrations of Eq. S39 with different values of τ_1. **B.** Rescue probability $p_{\rm r}$ of a W population in a deteriorating environment by G mutants, versus mutation probability μ upon division. Solid curves correspond to numerical integrations of Eq. S40 with different values of τ_2. **C.** Mean time of extinction τ_0' of G mutants versus their time of appearance t_0 in the deteriorating environment. Solid curves correspond to numerical integrations of Eq. S41 with different values of τ_3. In all panels, gray markers correspond to averages over 10^3 replicate stochastic simulations, and error bars in panel C (often smaller than markers) to 95% confidence intervals. Parameter values: $f_G = 1$ (recall that generally we take $f_G = 0.5$), $g_W = g_G = g_S = 0.1$, $K = 10^3$, $N_W^0 = 10$, $n = 5$ and $\theta = 10^3$.

10 Numerical simulation methods

In this work, all numerical simulations are performed using a Gillespie algorithm (Gillespie 1977). Because the sampled time intervals Δt between successive individual event satisfy $\Delta t < 1$ (see Fig. S14), which is smaller than the timescales of all processes considered here, we neglect fitness variations between individual events. In practice, the sampled time intervals between each individual event tend to get larger close to extinction events, since the total number of microbes then substantially decreases, but even then, they remain smaller than 1. Note that, in order to take into account the time variability of fitness at a higher resolution than that of events, one could employ e.g. the approach described in (Thanh and Priami 2015). In the following, we provide details about the simulations used in each part of our work. Matlab implementations of our numerical simulations are freely available at `https://doi.org/10.5281/zenodo.3993272`.

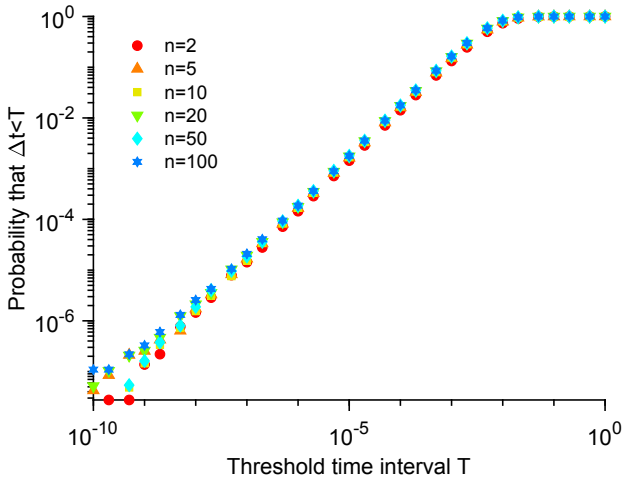

Fig S14. Time interval between two events. Probability that the sampled time interval Δt between two events in the Gillespie simulation is smaller than the threshold time interval T plotted versus T for different Hill coefficients n (see Eqs. 1). Markers correspond to the average over 10^2 replicate stochastic simulations of a purely W population ($\mu = 0$). Parameter values: $g_W = 0.1$, $K = 10^3$, $N_W^0 = 10$ and $\theta = 10^3$.

10.1 Population decay in a deteriorating environment

In our simplest simulations, presented in Fig. 1, only W microorganisms were considered (no mutation, $\mu = 0$). For each replicate simulation, we saved the number of W individuals present at regular time intervals, i.e. at time points $0, \delta t, 2\delta t...$ The elementary events that can occur are:

- $W \to 2W$: Division of a wild-type microbe with rate $k_W^+ = f_W(t)(1 - N_W/K)$, where the value of $f_W(t)$ is taken at the time t of the last event that occurred.
- $W \to \emptyset$: Death of a wild-type microbe with rate $k_W^- = g_W$.

The total rate of events is $R = (k_W^+ + k_W^-)N_W$. Simulation steps are the following:

1. Initialization: The microbial population starts from $N_W = N_W^0$ wild-type microorganisms at time $t = 0$, and the value of f_W is set at $f_W(0)$.
2. The time increment Δt is sampled randomly from an exponential distribution with mean $1/R$, where $R = (k_W^+ + k_W^-)N_W$. The next event to occur is chosen randomly, with probabilities k/R proportional to the rate k of each event.
3. The time t is increased to $t = t + \Delta t$ and the event chosen at Step 2 is executed, i.e. N_W is updated. The value of f_W is also updated from $f_W(t)$ to $f_W(t + \Delta t)$.
4. The number of wild-type microbes N_W is saved at the desired time points falling between t and $t + \Delta t$.
5. We go back to Step 2 and iterate until the total number of microbes reaches zero ($N_W = 0$), corresponding to extinction.

10.2 Fixation probability and time of extinction of mutants

In our simulations concerning the fixation probability and the time of extinction of mutants, both wild-type microorganisms (W) and mutants (M) are considered, but no random mutations are allowed, i.e. $\mu = 0$. Indeed, the aim is to determine the fate of i_0 mutants that are introduced at a controlled time t_0 (generally we take $i_0 = 1$ to model the appearance of a single mutant). The elementary events that can occur are:

- $W \to 2W$: Division of a wild-type microbe with rate $k_W^+ = f_W(t)(1 - (N_W + N_M)/K)$, where the value of $f_W(t)$ is taken at the time t of the last event that occurred.
- $W \to \emptyset$: Death of a wild-type microbe with rate $k_W^- = g_W$.
- $M \to 2M$: Division of a mutant microbe with rate $k_M^+ = f_M(t)(1 - (N_W + N_M)/K)$, where the value of $f_M(t)$ is taken at the time t of the last event that occurred. Note that for G mutants, f_M is constant, but for S mutants, it varies in time.
- $M \to \emptyset$: Death of a mutant microbe with rate $k_M^- = g_M$.

The total rate of events is $R = (k_W^+ + k_W^-)N_W + (k_M^+ + k_M^-)N_M$. Simulation steps are the following:

1. Initialization: The microbial population starts from $N_W = N_W^0$ wild-type microorganisms and $N_M = 0$ mutant at time $t = 0$, and the values of f_W and f_M are set at $f_W(0)$ and $f_M(0)$, respectively.
2. The time increment Δt is sampled randomly from an exponential distribution with mean $1/R$, where $R = (k_W^+ + k_W^-)N_W + (k_M^+ + k_M^-)N_M$. The next event to occur is chosen randomly, with probabilities k/R proportional to the rate k of each event.
3. If $t + \Delta t \geq t_0$ for the first time, the time is set to $t = t_0$, i_0 wild-types microbes are replaced by i_0 mutants ($N_W = N_W - i_0$ and $N_M = N_M + i_0$) and the event determined at Step 2 is not executed. Otherwise, the time t is increased to $t = t + \Delta t$ and the event determined at Step 2 is executed, i.e. N_W or N_M is updated. The values of f_W and f_M (in the case of an S mutant) are also updated.
4. We go back to Step 2 and iterate until the total number of microbes is zero ($N_W + N_M = 0$), corresponding to extinction of the population, or there are only mutants ($N_W = 0$ and $N_M \neq 0$). In the latter case, we also check that the mutant lineage does not undergo rapid stochastic extinction by assessing whether it dies out or not before reaching a size of 100 individuals. If it reaches such a size, we consider that fixation of the mutant has occurred.

10.3 Rescue of a population by mutants

Finally, our simulations concerning the rescue of a population by mutants, both wild-type microorganisms (W) and mutants (M) are considered, with a probability μ of mutation from W to M upon division. The elementary events that can occur are:

- $W \to 2W$: Division without mutation of a wild-type microbe with rate $k_W^+ = f_W(t)(1-(N_W+N_M)/K)(1-\mu)$, where the value of $f_W(t)$ is taken at the time t of the last event that occurred.
- $W \to W + M$: Division with mutation of a wild-type microbe with rate $k_{WM} = f_W(t)(1 - (N_W + N_M)/K)\mu$.
- $W \to \emptyset$: Death of a wild-type microbe with rate $k_W^- = g_W$.
- $M \to 2M$: Division of a mutant microbe with rate $k_M^+ = f_M(t)(1 - (N_W + N_M)/K)$, where the value of $f_M(t)$ is taken at the time t of the last event that occurred. Note that for G mutants, f_M is constant, but for S mutants, it varies in time.
- $M \to \emptyset$: Death of a mutant microbe with rate $k_M^- = g_M$.

The total rate of events is $R = (k_W^+ + k_W^- + k_{WM})N_W + (k_M^+ + k_M^-)N_M$. Simulation steps are the following:

1. Initialization: The microbial population starts from $N_W = N_W^0$ wild-type microorganisms and $N_M = 0$ mutant at time $t = 0$, and the values of f_W and f_M are set at $f_W(0)$ and $f_M(0)$, respectively.

2. The time increment Δt is sampled randomly from an exponential distribution with mean $1/R$, where $R = (k_W^+ + k_W^- + k_{WM})N_W + (k_M^+ + k_M^-)N_M$. The next event to occur is chosen randomly, with probabilities k/R proportional to the rate k of each event.

3. The time t is increased to $t = t + \Delta t$ and the event determined at Step 2 is executed, i.e. N_W and N_M are updated. The value of f_W and f_M (in the case of an S mutant) are also updated.

4. We go back to Step 2 and iterate until the total number of microbes is zero ($N_W + N_M = 0$), corresponding to extinction of the population, or there are only mutants ($N_W = 0$ and $N_M \neq 0$), corresponding to fixation of the mutant and rescue of the population.

References

Alexander and Bonhoeffer 2012. Alexander, H. K. and S. Bonhoeffer, 2012 Pre-existence and emergence of drug resistance in a generalized model of intra-host viral dynamics. Epidemics **4:** 187–202.

Andersson and Hughes 2010. Andersson, D. I. and D. Hughes, 2010 Antibiotic resistance and its cost: is it possible to reverse resistance? Nat. Rev. Microbiol. **8:** 260–271.

Borman *et al.* 1996. Borman, A. M., S. Paulous, and F. Clavel, 1996, Mar Resistance of human immunodeficiency virus type 1 to protease inhibitors: selection of resistance mutations in the presence and absence of the drug. J. Gen. Virol. **77 (Pt 3):** 419–426.

Coates *et al.* 2018. Coates, J., B. R. Park, D. Le, E. Simsek, W. Chaudhry, and M. Kim, 2018, 03 Antibiotic-induced population fluctuations and stochastic clearance of bacteria. Elife **7**.

Ewens 1979. Ewens, W. J., 1979 *Mathematical Population Genetics*. Springer-Verlag.

Gardiner 1985. Gardiner, C. W., 1985 *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*. Springer.

Gillespie 1977. Gillespie, D. T., 1977 Exact stochastic simulation of coupled chemical reactions. J. Phys. Chem. **81:** 2340–2361.

Gullberg *et al.* 2011. Gullberg, E., S. Cao, O. G. Berg, C. Ilbäck, L. Sandegren, D. Hughes, and D. I. Andersson, 2011, Jul Selection of resistant bacteria at very low antibiotic concentrations. PLoS Pathog. *7*(7)**:** e1002158.

Kendall 1948. Kendall, D. G., 1948 On the Generalized "Birth-and-Death" Process. Ann. Math. Statist. *19*(1)**:** 1–15.

Marrec and Bitbol 2018. Marrec, L. and A.-F. Bitbol, 2018, Nov Quantifying the impact of a periodic presence of antimicrobial on resistance evolution in a homogeneous microbial population of fixed size. J. Theor. Biol. **457:** 190–198.

Marrec and Bitbol 2020. Marrec, L. and A.-F. Bitbol, 2020 Resist or perish: fate of a microbial population subjected to a periodic presence of antimicrobial. PLoS Comput. Biol. *16*(4)**:** e1007798.

Maruyama and Kimura 1974. Maruyama, T. and M. Kimura, 1974, 03 A Note on the Speed of Gene Frequency Changes in Reverse Directions in a Finite Population. Evolution *28*(1)**:** 161–163.

Ovaskainen and Meerson 2010. Ovaskainen, O. and B. Meerson, 2010 Stochastic models of population extinction. Trends Ecol. Evol. *25*(11)**:** 643 – 652.

Parzen 1999. Parzen, E., 1999 *Stochastic processes*. SIAM, Philadelphia.

Regoes *et al.* 2004. Regoes, R. R., C. Wiuff, R. M. Zappala, K. N. Garner, F. Baquero, and B. R. Levin, 2004, Oct Pharmacodynamic functions: a multiparameter approach to the design of antibiotic treatment regimens. Antimicrob. Agents Chemother. *48*(10)**:** 3670–3676.

Teimouri *et al.* 2019. Teimouri, H., M. P. Kochugaeva, and A. B. Kolomeisky, 2019, Dec Elucidating the correlations between cancer initiation times and lifetime cancer risks. Sci Rep *9*(1)**:** 18940.

Teimouri and Kolomeisky 2019. Teimouri, H. and A. B. Kolomeisky, 2019, Mar Theoretical investigation of stochastic clearance of bacteria: first-passage analysis. J R Soc Interface *16*(152)**:** 20180765.

Thanh and Priami 2015. Thanh, V. and C. Priami, 2015 Simulation of biochemical reactions with time-dependent rates by the rejection-based algorithm. J. Chem. Phys. **143:** 054104.

Traulsen *et al.* 2005. Traulsen, A., J. C. Claussen, and C. Hauert, 2005, Dec Coevolutionary dynamics: from finite to infinite populations. Phys. Rev. Lett. *95*(23)**:** 238701.

Traulsen and Hauert 2009. Traulsen, A. and C. Hauert, 2009 Stochastic evolutionary game dynamics. In H.-G. Schuster (Ed.), *Reviews of Nonlinear Dynamics and Complexity*, Volume II. Wiley-VCH.

Uecker and Hermisson 2011. Uecker, H. and J. Hermisson, 2011 On the Fixation Process of a Beneficial Mutation in a Variable Environment. Genetics *188*(4)**:** 915–930.

Van Kampen 1981. Van Kampen, N., 1981 *Stochastic Processes in Physics and Chemistry*. North-Holland.

Yu *et al.* 2018. Yu, G., D. Y. Baeder, R. R. Regoes, and J. Rolff, 2018, 03 Predicting drug resistance evolution: insights from antimicrobial peptides and antibiotics. Proc. Biol. Sci. *285*(1874).

zur Wiesch *et al.* 2011. zur Wiesch, P. A., R. Kouyos, J. Engelstadter, R. R. Regoes, and S. Bonhoeffer, 2011, Mar Population biological principles of drug-resistance evolution in infectious diseases. Lancet Infect Dis *11*(3)**:** 236–247.