

1 Time-dependent fitness effects can drive bet-hedging
2 populations extinct

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4 **Abstract**

5 To survive unpredictable environmental change, many organisms adopt bet-hedging
6 strategies that trade short-term population growth for long-term fitness benefits. Be-
7 cause the benefits of bet-hedging may manifest over long time intervals, bet-hedging
8 strategies may be out-competed by strategies maximizing short-term fitness. Here, we
9 investigate the interplay between two drivers of selection, environmental fluctuations
10 and competition for limited resources, on different bet-hedging strategies. We consider
11 an environment with frequent disasters that switch between which phenotypes they
12 affect in a temporally-correlated fashion. We determine how organisms that stochasti-
13 cally switch between phenotypes at different rates fare in both competition and survival.
14 When disasters are correlated in time, the best strategy for competition is among the
15 worst for survival. Since the time scales over which the two agents of selection act are

16 significantly different, environmental fluctuations and resource competition act in op-
17 position and lead populations to evolve diversification strategies that ultimately drive
18 them extinct.

19 Introduction

20 In the face of unpredictable environmental change, some organisms have evolved diver-
21 sification strategies that generate offspring poorly suited to the current environment,
22 but well-adapted to a different future environment [1, 2, 3]. For example, clonal bac-
23 terial lineages have evolved to produce both fast and slow growing phenotypes; the
24 latter can better survive lethal antibiotic exposure [4, 5]. Organisms that adopt these
25 strategies hedge their bets by sacrificing short-term increases in population expansion
26 for potential long-term population growth [3, 6]. The time interval over which the
27 long-term benefits of bet-hedging are realized depends in part on the frequency of
28 environmental change [7, 8, 9]. Frequent environmental change can impose immedi-
29 ate selection against organisms who do not bet-hedge [10], while hedging against rare
30 events may require long time periods [11]. Environmental change, however, will only
31 rarely be the sole driver of selection. Other processes, such as competition for limited
32 resources, may act on shorter time scales than environmental fluctuation, causing op-
33 timal bet-hedging strategies to go extinct before the long-term benefits are realized.
34 In this paper, we investigate the interplay between these two drivers of selection.

35 Bet-hedging is a well-known survival strategy, evolved by diverse organisms, to in-
36 crease fitness in risky, unpredictable environments [12, 13, 14, 15, 16, 17, 18, 19, 20].
37 For example, desert annuals delay germination in some seeds to hedge against across-
38 year variation in spring rainfall [1, 21]. Another example is the bacterial pathogen
39 *Haemophilus influenza*, in which a single clone generates offspring with diverse sur-
40 face antigens that increase the probability that some of the population will avoid de-
41 struction by the host immune response [22, 23]. Concomitant with the abundance of
42 bet-hedging, there are a wide array of molecular mechanisms for creating phenotypic

43 diversity, including contingency loci, stochastic gene expression, developmental insta-
44 bility, and asymmetric cell division [24, 25, 26, 27]. These diversification mechanisms
45 work together with reproductive strategies (e.g. asexual/sexual, clutch size) to enact
46 particular forms of bet-hedging [12]. Considering the gamut of bet-hedging strategies is
47 outside the scope of this paper, so for simplicity we will consider microbial bet-hedging,
48 which is the focus of a large body of theoretical research [11, 28, 29, 30, 31, 32, 33].

49 Microbial bet-hedging is usually equated with stochastic switching strategies whereby
50 a single genotype produces phenotypic heterogeneity in the absence of an apparent sig-
51 nal or regulatory response [10, 13, 24, 34, 35]. Mathematical models of microbial
52 bet-hedging typically assume that the organism switches reversibly between at least
53 two distinct phenotypic states, and that these distinct phenotypic states are each suited
54 to different possible environmental states. Such models align well with experimental
55 bet-hedging systems including CAP+/- phenotypes in *Pseudomonas fluorescens* [36],
56 antigen expression in *Salmonella* [37, 38], competence to non-competence switch for
57 DNA transformation in *Bacillus subtilis* [39], and galactose utilization in engineered
58 populations of *Saccharomyces cerevisiae* [40]. For the purposes of modeling, phenotypic
59 switch events are typically random and independent so that population-level hetero-
60 geneity follows a binomial or multinomial distribution, depending on the number of
61 phenotypic states. A key area where models differ is the way in which environments
62 fluctuate. For example, environmental fluctuations can occur randomly or after a fixed
63 amount of time [28, 31, 32, 40, 41] and they can be symmetric or asymmetric in terms of
64 how they switch and the selective pressure they exert [33, 41]. Whether or not stochas-
65 tic switching confers a fitness benefit depends on the precise nature of environmental
66 fluctuations.

67 In exponentially growing populations, the optimal rate of switching maximizes long-
68 term geometric mean fitness [1, 8, 9, 42]. Indeed, models with expanding populations
69 make it possible to calculate asymptotic growth rates [32]. The situation might be dif-
70 ferent if, along with environmental fluctuations, organisms face limitations in resources
71 so that there exists a carrying capacity that restricts population size. If the population

72 has not yet reached the carrying capacity, then each time an organism reproduces there
73 is one less opportunity for reproduction by others in the population [43]. This couples
74 the switching strategy of one organism to others, which could reward strategies that
75 deny reproductive opportunities to other switching types either in the current environ-
76 ment or some future environmental state. Furthermore, the finite limit of population
77 size allows for the possibility of extinction due to demographic stochasticity.

78 Here, we examine the consequences of coupling and extinction, introduced through
79 a carrying capacity, on the evolution of microbial bet-hedging. We extend a previously
80 published model [12] in which phenotypes experience periodic disasters such as might
81 occur as the result of an adaptive immune response. We allow disasters to be correlated
82 in time and determine how switching strategies fare in competition and survival, i.e.
83 long-term fitness. When disaster risk is uncorrelated in time, the best competitive
84 strategy also maximizes long-term survival. The situation changes when disaster risk
85 is strongly correlated in time; the best strategy for competition is among the worst for
86 survival. Our results show that environmental fluctuations and resource competition
87 can lead to the evolution of diversification strategies that ultimately drive populations
88 extinct.

89 **Methods**

90 **Stochastic simulations**

91 We consider a population of genotypes that switch between two phenotypic states, A
92 and B. The defining characteristic of a genotype is its probability/rate of switching
93 between phenotypes, which we denote as p . We assume that the switch occurs stochas-
94 tically upon reproductive events so that each time an A or B reproduces there is a
95 fixed probability p that it yields a cell of the opposite type. The phenotypic states do
96 not differ in any fitness relevant trait other than susceptibility to risk. This risk man-
97 ifests in disasters that target either A or B phenotypes and removes them completely

98 from the population. We simulate the evolution of populations using a discrete time
99 approach.

100 At each time step, there is a probability that a disaster occurs. We use a disaster
101 probability of 10% for most results in this paper but explore the effects of changing this
102 probability on time scales in Figure 5. If a disaster occurs, we then determine which
103 phenotype it targets. A disaster targets the same phenotype as the previous disaster
104 with probability t_c and the alternate phenotype with probability $1-t_c$ (the first disaster
105 target is random). If $t_c = .5$ then the disaster targets a phenotype with no memory of
106 previous targets. For $t_c > .5$ there is an increased chance that the phenotype targeted
107 will be the same as before. In this way, the parameter t_c determines the duration of
108 an environment hostile towards A or B phenotypes and the temporal correlation of
109 disasters.

110 Following the potential disaster, there is an opportunity for population turnover
111 whereby a small fraction of the population is chosen for death. We use a default
112 population turnover probability of 10% for most results in this paper but show the
113 effects of changing this parameter in Figures 4 and 5. As a consequence of population
114 turnover, even if a disaster does not occur the population still evolves.

115 After the effects of a possible disaster and population turnover, the remaining or-
116 ganisms reproduce until the population is restored to a fixed size, the carrying capacity
117 N . For most results of the paper we consider $N = 1000$. Increasing this parameter
118 increases the duration of competitions and survival. The effects of different values of N
119 on Figure 4 are considered in the Supplementary material. Reproduction to carrying
120 capacity occurs through an iterative process whereby organisms are randomly chosen
121 to reproduce according to their frequency in the population. The discrete time step
122 ends once the carrying capacity is reached. We simulate the populations until one
123 genotype goes extinct or a maximum number of time steps occur, here 10^6 . Computer
124 simulations were conducted in the programming language julia and are provided in the
125 Supplementary material.

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Differential equation model

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As a complement to our stochastic simulations we consider a deterministic model that uses differential equations (Eqns 1) to model population regrowth following a disaster.

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The simulation is still split into discrete rounds of disasters and regrowth however these events do not occur probabilistically. Instead, disasters occur every round and

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target one phenotype for a fixed number of times. For example, there may be five

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rounds of disasters targeting A types followed by five rounds of disasters targeting B

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types. After each disaster the population regrows for a fixed amount of time, ($t = 100$,

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though we consider other values of t in the Supplementary material), with a constant

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rate of population turnover described by the parameter α . We compute the frequency

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of types that switch according to probability p_1 which is equal to $\frac{A_1+B_1}{A_1+B_1+A_2+B_2}$ after

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1000 environmental cycles. The differential equations were solved using Matlab and

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computer code is provided in the Supplementary material.

$$\begin{aligned} R &= \left(1 - \frac{A_1 + B_1 + A_2 + B_2}{N}\right) & (1) \\ \frac{dA_1}{dt} &= R(1 - p_1)A_1 + Rp_1B_1 - \alpha A_1 \\ \frac{dB_1}{dt} &= R(1 - p_1)B_1 + Rp_1A_1 - \alpha B_1 \\ \frac{dA_2}{dt} &= R(1 - p_2)A_2 + Rp_2B_2 - \alpha A_2 \\ \frac{dB_2}{dt} &= R(1 - p_2)B_2 + Rp_2A_2 - \alpha B_2 \end{aligned}$$

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Results

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Survival

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In our model, the probability of switching phenotypes determines whether an organism

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can survive the challenge of repeat disasters. We vary the probability of repeat disasters

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(t_c) from 0 to 1 and compute for each value of t_c the number of times out of 1000

144 stochastic simulations a switching strategy survives 10^6 rounds of potential disasters,
145 population turnover, and regrowth (see Figure 1). For fast switching probabilities,
146 $p \geq .1$, genotypes rarely go extinct (less than 1% of the time). In contrast, for slow
147 switching probabilities, $p \leq .025$, all organisms went extinct before the end of 10^6
148 rounds. For switching probabilities in between these values, e.g. $p = .05$ and $p =$
149 $.075$, there is a non-monotonic relationship between t_c and the frequency of extinction.
150 Genotypes are less likely to go extinct at the extremes of t_c , i.e. close to 0 or 1, as
151 compared to intermediate values, e.g. $t_c = .65$.

152 At t_c close to 1 there are long periods of disasters targeting the same phenotype.
153 In the extreme case where $t_c = 1$ disasters never switch phenotypes, so as long as an
154 organism diversified into two phenotypes at least once it would survive. As t_c decreases
155 from 1 the probability of extinction increases because disasters more frequently switch
156 between phenotypes.

157 At the opposite extreme, with t_c close to 0, disasters frequently switch between
158 targeted phenotypes. While this seems like a challenging environment to survive, it
159 is actually easier than an environment with longer periods of disasters targeting the
160 same phenotype. The reason is that extinction in these simulations occurs through a
161 lack of phenotypic diversification: an organism exists entirely in one phenotypic state
162 when a disaster strikes that phenotype. After a disaster annihilates one phenotype, say
163 A , the surviving phenotype, B , has a certain number of reproductive events in which
164 to diversify. The probability that a B fails to produce at least one of the opposite
165 phenotype, A , is $(1 - p)^m$ where p is the switching probability and m is the number
166 of reproductive events. The expected number of A types produced is mp , assuming
167 that the B phenotype is the only one who gets to reproduce. Now, there are $N - mp$
168 organisms of type B and mp of type A . This sets the stage for why an environment
169 with $t_c = 0$ is easier to survive than one with an intermediate value of $t_c = .65$.

170 If the next disaster switches targets and annihilates the B type, as would be the
171 case if $t_c = 0$, then the A types would have $N - mp$ opportunities to diversify and
172 produce a B type. The chance of failure here is $(1 - p)^{N - mp}$. If, instead, t_c were greater

173 than zero then there is a chance that the disaster would target the same phenotype as
174 before, and annihilate any new A types produced. This would give the B phenotypes
175 only mp opportunities to diversify and produce an A . The chance of failure in this case
176 is $(1 - p)^{mp}$. The difference between these two chances of failures can be many orders
177 of magnitude: if, for instance, $p = .05$, $m = 500$, and $N = 1000$ then the probability
178 of not diversifying goes up from $1.91 * 10^{-20}\%$ to 27.7%.

179 **Competition**

180 If the only selective pressure were long-term survival, then the probability of switching
181 should be high to avoid extinction. However, there are often other forms of selection
182 acting on populations. We now consider what happens when there is competition in the
183 form of another genotype present in the population. We vary the probability of repeat
184 disasters (t_c) from 0 to 1 and compute for each value of t_c which switching strategy is
185 the best in pairwise competitions. The best strategy is the one that drives competitors
186 extinct more often than it, itself, goes extinct. The optimal probability of switching
187 decreases the more a disaster is likely to target the same phenotype, i.e. the higher
188 the value of t_c (see Figure 2A). If the disasters frequently switch phenotypes such that
189 $t_c \leq 0.50$ then the best strategy in pairwise competitions is to rapidly diversify and
190 switch phenotypes often. Thus, in this regime the optimal switching probability is
191 $p = 1$.

192 If, instead, disasters seldom switch the phenotype they target ($t_c \gg .5$) then
193 there is a cost to phenotypic diversification. Consider the case in which a disaster has
194 removed all of the A phenotypes. As the B phenotypes reproduce to reach the carrying
195 capacity any A types they produce will likely be lost to the next disaster. On the other
196 hand, failing to diversify at all, $p = 0$, will lead to the genotype going extinct should the
197 disaster switch the phenotype it targets. When risk is correlated in time, the optimal
198 switching strategy must strike a balance between diversifying too much into the form
199 that the disaster is targeting and not diversifying at all. As a point of reference from

200 Figure 2A, if $t_c = 0.99$ then the optimal switch probability that strikes this balance is
201 $p = 0.01$. These results echo earlier studies of bet-hedging populations in the absence
202 of carrying capacity [3, 6, 44].

203 Although the optimal switching strategy changes with the probability of repeat
204 disaster (t_c), it is unclear how poorly a suboptimal switching strategy performs. To
205 test this, we picked the best switching strategies for $t_c = .5$ ($p = 1$) and $t_c = .99$
206 ($p = .01$) and competed them against the optimal switching strategies for a range of t_c
207 values (see Figure 2B). The performance quickly drops off such that if either strategy
208 is competed against the optimal strategy at a t_c different by $.1$, it wins less than 10%
209 of the time. Furthermore, $p = 1$ competes as unsuccessfully against $p = .01$ at $t_c = .99$
210 as $p = .01$ competes against $p = 1$ at $t_c = .5$ – they each win less than 1% of the time.

211 Due to the stochastic nature of these competitions, suboptimal strategies can occa-
212 sionally beat optimal strategies. To understand what happens in these competitions,
213 we investigate the competition between $p = 1$ and $p = .01$ at $t_c = .99$. On the rare
214 occasions that $p = 1$ wins, the dynamics of disasters show frequent change in the tar-
215 getted phenotype, mimicking an environment with a lower value of t_c in which $p = 1$ is
216 more adaptive (see Figure 3A). In contrast, the more typical scenario is that disasters
217 infrequently switch the target phenotype and thereby penalize strategies that adopt
218 rapid phenotypic diversification (see Figure 3B). The trajectory of this extinction shows
219 that each disaster gives an incremental numerical advantage to the slower switching
220 strategy. This acts as a steady drain which ultimately leads the $p = 1$ genotype to
221 extinction.

222 The different trajectories in Figure 3A and 3B demonstrate the two ways in which
223 organisms can go extinct during competition in our mathematical model. The first way
224 is through a lack of phenotypic diversification as was discussed in the “Survival” section
225 and is how the fast switcher beats the slow switcher (see Figure 3C). The second way
226 is through population turnover and is how the slow switcher defeats the fast switcher
227 (see Figure 3D). Extinction due to population turnover occurs during the death and
228 replacement phase of our simulations. A consequence of replacement is that there are

229 fluctuations in population abundances. If each organism has a probability α to be
230 chosen for replacement, i.e. death, then the probability a population of m organisms
231 goes extinct in a single round of replacement is α^m . In order for this form of extinction
232 to be realized a genotype must be rare, i.e. m must be small.

233 Although genotypes could become rare randomly through a set of unfortunate re-
234 placement events, usually it occurs because of a particular sequence of disasters. For
235 instance, there could be a sequence of sudden switches in the phenotype targeted for
236 disaster which would leave genotypes that switch infrequently as the rare type. Alter-
237 natively when disasters repeatedly target a single phenotype then the genotype that
238 switches frequently can become rare. The latter case befalls the genotype with $p = 1$ in
239 an environment with $t_c = .99$. To illustrate how this happens, consider two genotypes
240 with switching probabilities p_1 and p_2 that just experienced a disaster eliminating all
241 m of one phenotype. In the growth back to carrying capacity, we assume for simplic-
242 ity that they evenly split the remaining spots in the population, i.e. $\frac{m}{2}$ reproductive
243 events are allotted to each genotype after the first disaster. Over k disasters and no
244 replacement other than growth back to carrying capacity, then the genotype with a
245 switch probability of p_1 will gain an amount shown in Eqn. 2.

$$(1-p_1)\frac{m}{2} + (1-p_1)\frac{m}{2}\frac{(p_1+p_2)}{2} + \dots + (1-p_1)\frac{m}{2}\frac{(p_1+p_2)^k}{2^k} = (1-p_1)\frac{m}{2}\frac{1 - \left(\frac{p_1+p_2}{2}\right)^k}{1 - \frac{p_1+p_2}{2}} \quad (2)$$

246 Thus, the genotype with p_1 will have $\frac{1-p_1}{1-p_2}$ as much of the m pool as the genotype with
247 p_2 . If one genotype switches with $p = 1$ then the other will eventually get the entire
248 pool of m . This route to rarity is particularly effective if m is close to the carrying
249 capacity N . Once a type is rare then population turnover can lead it to extinction.

250 The route to extinction that relies on population turnover is not unique to our
251 stochastic simulation model. We can reformulate our model such that population
252 growth occurs deterministically according to a set of differential equations (see Meth-
253 ods: Differential equation model, and Eqn. 1). These equations consider continuous
254 population turnover rather than discrete rounds as was the case in the stochastic sim-

255 ulations. If populations grow for a fixed time according to these equations and then
256 experience disasters that reset the A or B phenotypes back to 0 then we find that the
257 amount of population turnover, i.e. the value of the α parameter, determines whether
258 a slow ($p_1 = .01$) or fast ($p_2 = 1$) switcher wins (see Figure 4). This is because follow-
259 ing a disaster, the initial growth of a genotype is determined by $R(1 - p) - \alpha$ which
260 decreases with larger switching probabilities p . Indeed, for $p = 1$ this term is negative
261 and the genotype drops in frequency for a short time. If disasters happen frequently
262 and target the same phenotype then this α can be the dominant force in determining
263 the winner.

264 We return to our stochastic model to weigh the competing pressures of competition
265 and survival. In an environment of $t_c = .99$ a strategy of $p = .01$ always goes extinct
266 when considered in isolation (Figure 1) and yet it is the best strategy for competition
267 (Figure 2). The reason for this seeming contradiction is a significant difference in time
268 scales (see Figure 5A). The time it takes $p = .01$ to go extinct is at least ten times
269 greater than the time it takes to win a competition. Thus, while we expect $p = .01$ to
270 go extinct eventually, it has enough time to outcompete faster switchers with $p = 1$.

271 The different time scales for competition and survival can be adjusted by chang-
272 ing parameters such as the rate of population turnover (see Figure 5B) or disaster
273 probability (see Supplementary material). By decreasing the probability of population
274 turnover (similar to α in the differential equation model), we can increase the time it
275 takes for the slow switcher ($p = .01$) to win the competition against a fast switcher
276 ($p = 1$). Similarly, the decreased value of population turnover gives less opportunities
277 to diversify and so reduces the survival time. The net effect is that the survival time
278 scale is shorter than the time scale for competition. As a result, the slow switcher goes
279 extinct before winning the competition (see Figure 5C).

280 So far the cases considered have all been competitions between only two genotypes
281 in an environment with fixed t_c . To see if populations of potentially many genotypes can
282 evolve to respond to the selective pressure imposed by the value of t_c , we implement an
283 evolutionary simulation in which genotypes mutate to give rise to new genotypes with a

284 new characteristic switch rate. The mutation probability is 10^{-3} and a new switching
285 probability is chosen from a uniform distribution from 10^{-5} to 1. We begin each
286 simulation with a clonal population whose switch rate is $p = .0001$. The population
287 goes through rounds of death and reproduction in a fixed environment (t_c) for 100K
288 iterations or until the population goes extinct. Figure 6A shows evolution within a
289 $t_c = .99$ environment. The average probability of switching from 1000 simulations
290 evolves to the optimal switching probability $p = .01$ but all go extinct prior to 80K
291 rounds. This contrasts sharply with evolution in a $t_c = .5$ environment in which only
292 6 of 1000 simulations went extinct (Figure 6B). All other simulations lasted the entire
293 duration with an average switching probability close to the optimal of $p = 1$.

294 The speed of adaptation and general results are further confirmed in Figures 6C
295 and D when populations experience an environmental shift. Figure 6C shows the
296 evolution of a population that survived $t_c = .99$ (a rare event) and is subsequently
297 transferred to a different environment with $t_c = .5$. In $t_c = .99$, the population
298 evolves to the optimal switch probability: $p = .01$. As the environment changes to
299 $t_c = .5$, the population adapts by evolving to a switch rate close to the optimal of
300 $p = 1$. The population remains at a high switch rate and survives for the rest of the
301 simulation, 100K iterations. The reverse environmental fluctuation is shown in Figure
302 6D: a population evolving in $t_c = .5$ is transferred to an environment with $t_c = .99$.
303 In this simulation, the population evolves to $p > .7$ in $t_c = .5$. When the environment
304 shifts to $t_c = .99$, the population evolves to $p = .01$ and fluctuates before ultimately
305 going extinct. In this scenario, the drive to respond to competition left the winning
306 genotypes vulnerable to extinction from unpredictable environmental stress.

307 Discussion

308 Stochastic phenotype switching is a canonical microbial bet-hedging strategy that in-
309 creases fitness and long-term survival in unpredictable environments [6, 10, 13, 24, 34,
310 35]. However, the long time scales over which some bet-hedging strategies are manifest

311 may conflict with other selective pressures. We uncover such an evolutionary tension
312 between the timescales at which bet-hedging traits are adaptive. We study a math-
313 ematical model where environmental disasters select for diversification bet-hedging
314 strategies, i.e. organisms switch between phenotypes to survive stochastic selection.
315 We find that in environments where the type of disaster is positively correlated in
316 time, switch rates that optimize competitiveness were favored over the short-term,
317 while those that allow genotypes to avoid extinction were favored over the long-term.
318 Since the time scale for competition is shorter than that for survival, populations evolve
319 better competitive bet-hedging strategies, but this ultimately leaves them vulnerable
320 to extinction.

321 The model presented in this paper has four key elements: genotypes that switch
322 between phenotypes, disasters that annihilate a specific phenotype, population turnover
323 caused by non-disaster death, and regrowth back to a carrying capacity. These elements
324 are quite general and may appear in many real biological systems. Ecologically, one
325 can think of our model as being a description of free-living bacteria that risk exposure
326 to lytic phage capable of infecting only one of the two host phenotypes [45, 46], or
327 bacteria living in a host risking detection by the immune system. These disasters
328 occur stochastically, but the type of disaster (favoring either A or B cells) may be
329 correlated in time. Furthermore, population expansion may be limited by the available
330 space and resources found in the environment or host. Interestingly, in the bacteria-host
331 scenario, if the host continually mounts a response against the most abundant bacterial
332 phenotype then this would be similar to an environment $t_c = 0$ when “disasters”,
333 i.e. immune responses, continually switch between targeted phenotypes. In this case,
334 the survival probability of a switching organism actually increases when compared to
335 environments with intermediate values of t_c .

336 In the absence of temporal correlation of disasters, the strategy that maximizes
337 short-term fitness also maximizes long-term survival ($p = 1$ in $t_c = .5$ wins in com-
338 petitions and never goes extinct). In contrast, when risk is correlated in time, the
339 strategy that maximizes short-term competitive fitness becomes one of the worst for

340 long-term survival, and vice versa. Over short time periods selection favors traits that
341 increase reproductive success. When risk is correlated in time slower rates of stochastic
342 switching increase fecundity and competitive fitness because offspring of the opposite
343 phenotype are likely to be killed by the next disaster. The downside of slower switching
344 organisms is that they are far more susceptible to extinction (see Figure 1). Slower
345 stochastic switching thus exhibits strong time-dependent fitness effects in our model,
346 being advantageous over the short-term but costly over long time periods (see Figure
347 5). Importantly, in our simulations fast-switching strains capable of long-term survival
348 in high t_c environments were driven extinct during competition by slower switching
349 strains that then promptly went extinct following a disaster (see Figure 6).

350 Most prior models studying stochastic switching in fluctuating environments con-
351 sider continuous populations that grow without limits [1, 8, 9, 32, 42]. This has two
352 major effects relevant to the study of bet-hedging: first, it eliminates the risk of extinc-
353 tion caused by environmental fluctuations, and second, it decouples competing lineages
354 so that the behavior of one lineage has no effect on the absolute fitness of competitors
355 within the same population. We relax both of these constraints and find that imposing
356 a carrying capacity on the population radically changes the ability for natural selec-
357 tion to favor the bet-hedging strategy that maximizes long-term fitness. By enforcing
358 a lower limit on the probability of extinction, a carrying capacity allows extinction to
359 play a powerful demographic role in shaping life history evolution. Without a carrying
360 capacity, populations could expand to the point that extinction is no longer a threat.

361 In addition to affecting survival, carrying capacities are also instrumental in com-
362 petition. By limiting opportunities for reproduction, a carrying capacity couples the
363 fitness consequences of one strain's switching strategy to its competitors. Specifically,
364 the effects of employing one strategy determines the number of available reproductive
365 events for the other strategy— either in the same round of growth, or a future round.
366 As a result, strains with higher short-term fitness, but lower long-term fitness, can
367 displace competitors (see Figure 6). These competitive effects should become more in-
368 fluenial if one phenotype reproduces slower than another, as is the case with bacterial

369 persistence [5]. Optimal fitness with bacteria persistence balances a trade-off between a
370 fast-growing/antibiotic-susceptible phenotype and a dormant/antibiotic-resistant phe-
371 notype [6]. Imposing a carrying capacity on a population of microbes hedging against
372 antibiotic exposure via persistence would create an additional tradeoff in which pro-
373 duction of dormant cells would limit the number of other cells that could be produced.
374 These tradeoffs also exist in systems with regular, predictable environmental change
375 as might be found in experimental populations of *Pseudomonas fluorescens* [43]. The
376 only requirements are a limit to population growth and organisms that can produce
377 more than one phenotype with different reproductive rates.

378 The stochastic phenotype switching considered in this paper fits within the hier-
379 archical model of bet-hedging advanced by Andrew Simons [47]: stochastic switching
380 itself is a primary bet-hedging trait that effectively improves fitness in unpredictable,
381 fluctuating environments, while rapid switch rates can be a second-order bet-hedging
382 trait beneficial only over long time periods. With this view, organisms that do not
383 switch phenotypes are quickly driven extinct by environmental fluctuations. Long-
384 term selection clearly favors switch rates rapid enough to avoid extinction, but this
385 works against short-term selection for slow switching imposed by competition. De-
386 pending on the switch rates, there may be a significant time scale asymmetry between
387 these selective agents. This asymmetry, coupled with the very real possibility of ex-
388 tinction during early-phase competition, may limit the ability of natural selection to
389 favor higher-level bet-hedging strategies that maximize long-term fitness.

390

Figures

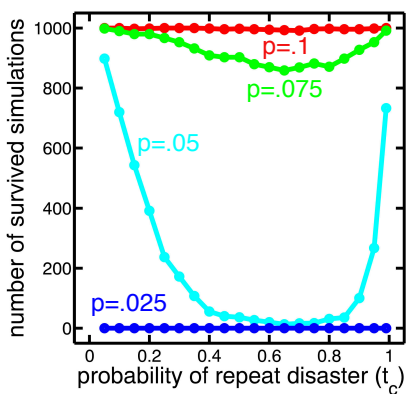


Figure 1: **Survival as a function of the probability of switching and the probability of a repeat disaster.** The number of extinctions out of 1000 for genotypes with different switch probabilities is shown as a function of the probability that a disaster repeats the phenotype it targets. Fast switchers $p \geq .1$ rarely go extinct while slow switchers $p \leq .025$ always go extinct. Intermediate values of p show a non-monotonic relationship in which extinction reaches a maximum around $t_c = .65$.

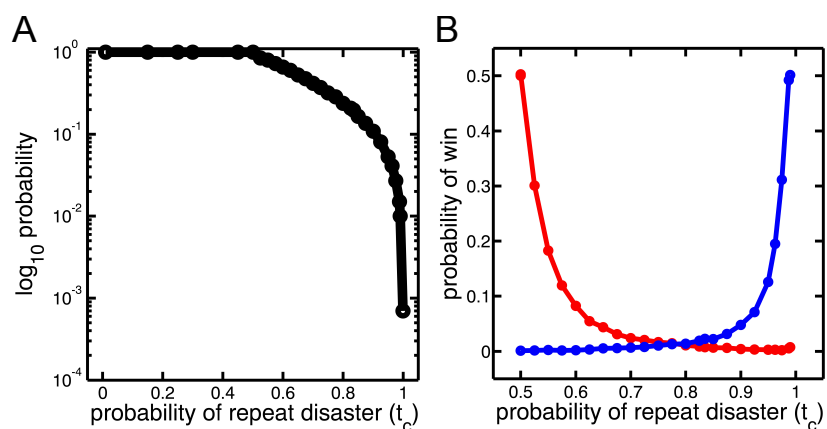


Figure 2: **Optimal switching strategy versus the probability that a disaster targets the same phenotype** **A)** The switching probability that beats all others in pairwise competitions is shown as a function of the probability of repeat disasters t_c . The switching probability decreases with increasing value of t_c . **B)** A switch probability of $p = 1$ (red) or $p = .01$ (blue) is competed against the optimal switch probability for a range of t_c values (on the horizontal axis). Each strategy quickly drops in performance, as measured by the number of wins, by a factor of more than 5 with a .1 change in t_c .

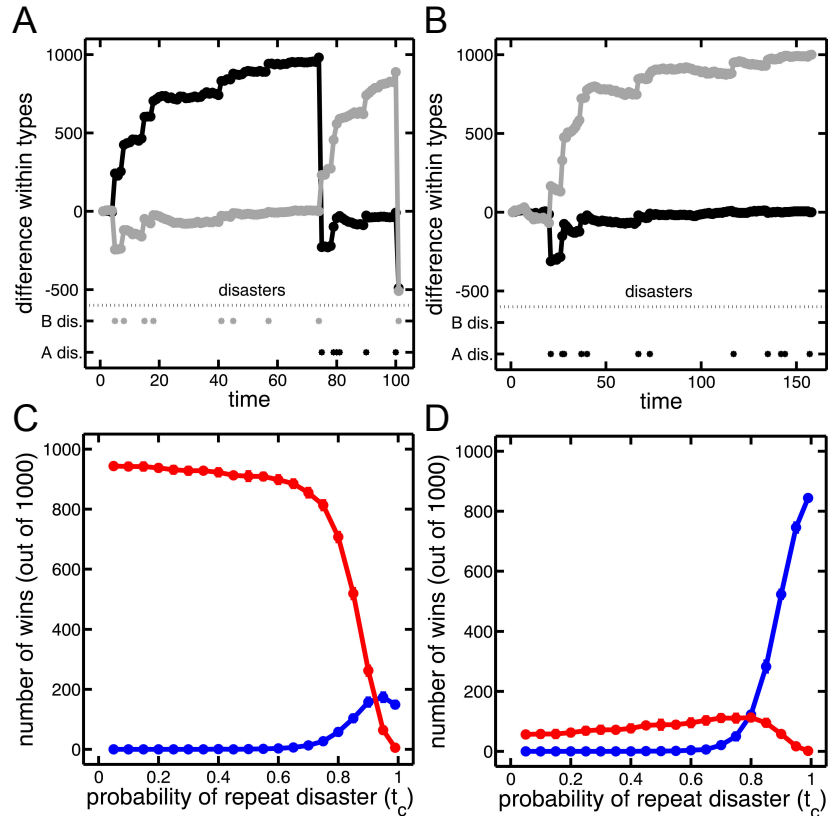


Figure 3: **Characteristic manner different switching strategies win.** **A)** The difference between A (gray) and B types (black) of a slow ($p = .01$) and fast ($p = 1$) switching strategy, e.g. $A_{\text{slow}} - A_{\text{fast}}$, are plotted over the course of many disasters with $t_c = .99$. The phenotype targeted by the disaster is shown at the bottom. The faster switching phenotype wins because the disasters switch targets and mimic an environment with a lower t_c . **B)** Here, the slow switching phenotype wins as repeated disasters slowly diminish the fast switching population. **C)** The number of wins (out of 1000) decided by a disaster switching phenotypes is shown as a function of the probability of repeat disasters. The fast switcher ($p = 1$, red) wins most of the competitions over the slow switcher ($p = .01$, blue) in this manner. **D)** Similar to C) except population turnover causes genotypes to win. In comparison to C), the slow switcher ($p = .01$, blue) wins more than 80% of its victories in this manner. Thus, fast switchers tend to win when disasters target both A and B phenotypes in rapid succession while slow switchers tend to win via a longer draining process.

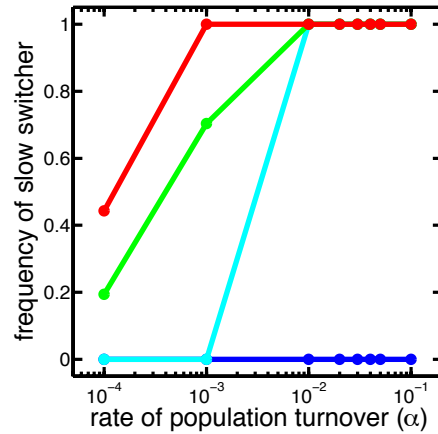


Figure 4: **Population turnover determines the winner in a differential equation model.** The frequency of the population composed of the slow switcher ($p = .01$) as opposed to the fast switcher ($p = 1$) is plotted against the rate of population turnover, α , in the differential equation model Eqn. 1. The different colors correspond to the number of disasters faced before the targeted phenotype is switched: 1 (blue), 5 (cyan), 10 (green), 25 (red). In this way the red line corresponds to a higher value of t_c than the blue. As the rate of population turnover increases, the slow switcher gains in frequency for all but the blue curve which corresponds to the lowest value of t_c . The minimal value of population turnover that leads to the slow switcher winning decreases with longer durations in environments, i.e. higher t_c values.

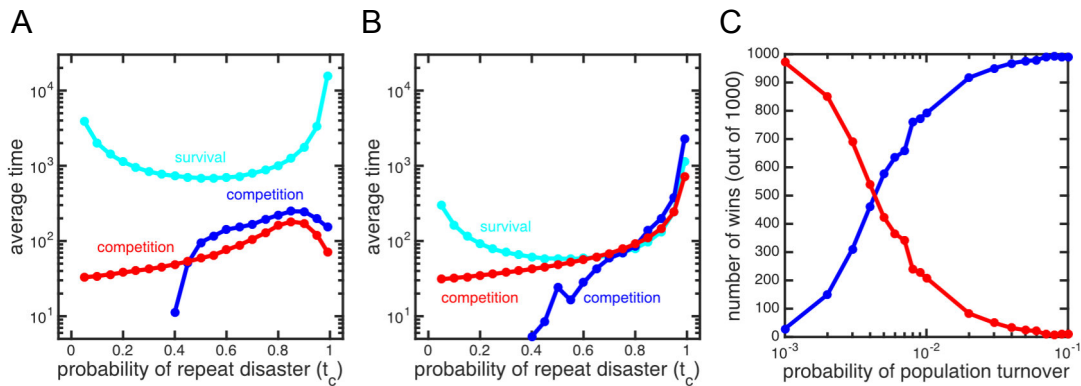


Figure 5: Time scale separation for survival and competition **A)** The time scales over which the selective pressures of survival and competition act are shown as a function of the probability of repeat extinction. Each time is an average of 10000 simulations. The time for the slow switching strategy ($p = .01$) to go extinct (cyan) is at least ten times longer than it takes either $p = .01$ (blue) or $p = 1$ (red) to win in competition. The fast switching strategy did not go extinct and so is not plotted. **B)** The same as in A) except that the probability of population turnover is 100 times lower. The time scale for competition at $t_c = .99$ is now longer than the time scale for survival. This means that the $p = .01$ strategy will go extinct before winning the competition. **C)** The number of wins out of 1000 for $p = .01$ (blue) or $p = 1$ (red) switchers is shown as a function of population turnover when $t_c = .99$. The lower value of population turnover in B) is where the shorter survival times dominate and fast switchers win more often. As population turnover increases to the value in A), the survival time scale becomes longer allowing competition to dominate and the slower switcher to win more frequently.

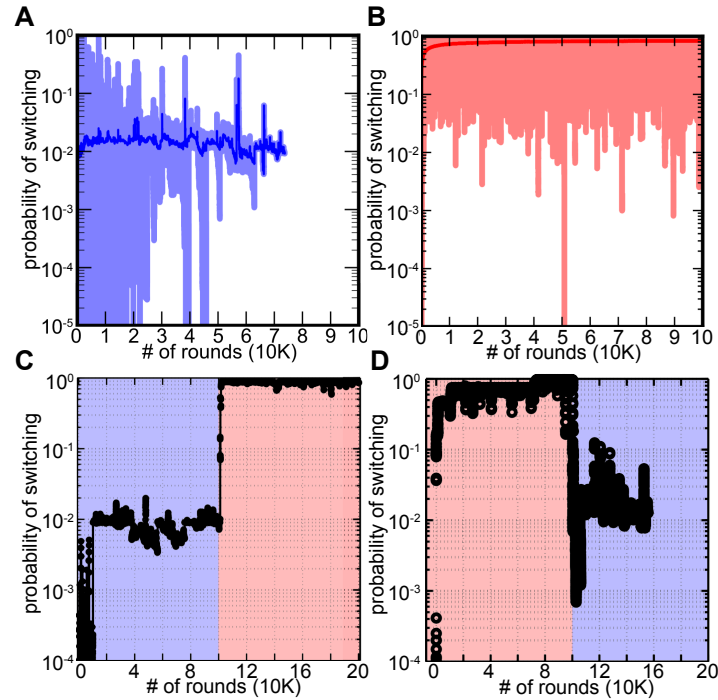


Figure 6: Evolution of switch rates in environments with different probabilities of repeat disasters. **A)** The average probability of switching over 1000 simulations of evolving populations (dark blue) is plotted over time in an environment with $t_c = .99$. The lighter area shows simulated populations removing the top and bottom 5%. Populations quickly evolve to $p = .01$ and then go extinct. **B)** Similar to A) but with $t_c = .5$ and a red scale for coloring. Populations evolve a probability of switching close to $p = 1$ and all but 6 out of 1000 survive the duration of the simulation. **C)** Similar to A) and B) but environments switch from $t_c = .99$ (blue) to $t_c = .5$ (red). It took many simulations to find a population that survived $t_c = .99$ but once it did, transfer to an environment with $t_c = .5$ saw the evolution of higher probabilities of switching close to the optimal $p = 1$ (average switch probability shown in black). **D)** Same as C) but in reverse order. The population average (black) evolves to the optimal competitive probabilities $p = 1$ in $t_c = .5$ (red) and $p = .01$ in $t_c = .99$ (blue) but ultimately goes extinct in $t_c = .99$.

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