Modeling dormancy: Optimal bet-hedging with delays in phenotypic switching

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Organisms face periods of environmental stress and nutrient scarcity. To overcome these harsh conditions, organisms can enter a low-metabolic state termed dormancy - either in response to or independent of changing conditions. The decoupling of dormancy from environmental state suggests that dormancy represents a bet hedging strategy. Previous theoretical work has shown that stochastically switching between active and dormant states at the individual level can maximize fitness at the population level in stochastic environments. However, such links make strong assumptions on time-scales related to switching between states and between environments. Here, we construct and analyze a dynamic model that couples environments with an organism's life cycle - including explicit time delays to reach dormancy. This model enables us to evaluate the contingency of optimal switching probabilities in fluctuating environments as a function of biological delays to reach dormancy. Stochastic environments are simulated using a multi-state Markov chain through which the mean and variance of environmental residence time can be adjusted. We find that optimal switching probabilities scale inversely with the mean environmental residence times, consistent with prior theory. We also find that increasing delays decrease optimal switching probabilities, an effect that can be influenced by the color of environmental noise. When environmental changes are rapid and uncorrelated, organisms should always invest in dormancy, the maximum population level fitness is obtained given low levels of switching between active and dormancy states. However when the environmental changes are slow and correlated, optimal dormancy initiation and termination probabilities increase insofar as the mean environmental persistent times are longer than the delay to reach dormancy. But, we also find that organisms should no longer initiate dormancy when delays to enter dormancy exceed those of mean environmental persistent times. These results show that the relationship between duration of switching and environmental residence are critical to predict if and how much a bet-hedging strategy benefits long-term fitness.

I. INTRODUCTION

Dormancy is a state of metabolic arrest which protects an individual organism against unfavorable environmental conditions including nutrient deprivation, changes in pressure, or temperature [1]. Organisms across all domains of life engage in dormancy including microbes, plants and animals. Several classic examples of dormant states include sporulation [2], seed dormancy [3], and hibernation [4]. Despite profound differences in physiological mechanisms, these examples each share the common feature of dimorphism in growth, reproduction, and survival. These examples also differ in both the triggers and mechanisms by which dormancy is initiated or terminated.

Triggers in and out of dormancy can be initiated involving an environmental sensing mechanism or randomly, i.e. independent of the environmental state. In practice, dormancy initiation and termination may include a mixture of both modes. Several examples showcasing the responsive nature of dormancy include sporulation in *Bacillus subtilis* and dormancy in bacteria like *Escherichia coli* or *Enterobacter*. Empirical evidence shows that each of these organisms initiate dormancy as a response to environmental stress factors or increased population density [5, 6]. There is also evidence that dormancy can be triggered in a seemingly random fashion. Stochastic entry and exit to and from dormancy has been documented in persister cells and soil microbes respectively [7–9].

Irrespective of organism, random switching between active and dormant states is often described as a bet-hedging strategy. A bet-hedging strategy refers to the investment in multiple phenotypes to reduce the potential loss suffered in future harsh environments. Plants have dormant seeds which germinate randomly, presumably to avoid transitioning during only periods that have brief windows favorable to growth [10, 11]. A variety of microorganisms employ a similar strategy in which cells exit dormancy at seemingly random times which allows population as a whole to sample a spectra of environmental conditions [12–14]. Bet-hedging strategies are hypothesized to lower the variance of possible outcomes, presumably to balance the benefits of optimal growth in good environments while avoiding collapse in bad environments.

While bet-hedging is often invoked in biology, there is little evidence that organisms utilize purely stochastic strategies. Many bet-hedging examples invoked in biology whether in microbes, plants or cellular gene expression

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also rely on a strong sensing and responsive mechanism. The lack of empirical evidence could stem from the fact that proving that phenotypic switching is stochastic can be experimentally challenging [15]. As such, the benefits of a purely bet-hedging strategy remain highly debated [16–18].

Early work done by Kelly on bet-hedging theory focused on computing the optimal betting in the context of gambling [19]. Kelly argues that an optimal betting strategy is one that decreases the variance of possible outcomes by maximizing the logarithm of the expected wealth. Kusell and Leibler took a more general approach and computed the optimal phenotypic switching in any type of stochastic environment, albeit of a minimum duration [20]. This result has been extended to biological settings, e.g. to compute the optimal investment in dormancy of a temperate phage [21]. While these works have examined different environmental settings, the modelling frameworks assume instantaneous switching between phenotypes. In reality, switching between active and dormancy can take a long time, comparable to or even longer than an individual's generation time. For example, in spore-forming bacteria it is common for organisms to reach dormancy over several hours, while having a relatively short generation time of 30 minutes [22, 23]. For other types of microbial dormancy, such as quiescence in persister cells or tumor cells, the time to reach dormancy is not as clearly defined. It can be however estimated that the time to reach quiescence is on the order of replication cycles because of the necessary changes in morphology and gene expression [24]. Depending on environmental fluctuations, this delay in phenoptypic switching could have a significant impact on the benefits and risks of a bet-hedging strategy.

In this paper, we extend the framework of bet-hedging models to explore the dynamic consequences of delays in reaching dormancy in correlated environments. Using Kelly's insight of maximizing the expected logarithmic wealth we optimize for the Lyapunov exponent or equivalently for the expected long-term growth rate of the population. By using a multi-state Markov chain to simulate environments we can vary environmental simulations from memory-less to periodic-like. Consistent with previous work, we find that optimal switching scales inversely with mean environmental residence times when phenotypic switching is instantaneous. However, transitioning to dormancy takes additional steps, the delays to reach dormancy and distribution of mean environmental residence times affect optimal switching probabilities in a non-monotonic fashion. As we explore, assessing bet hedging in the context of realistic delays and correlated environments can help deepen understanding of the drivers and constraints on the evolution of dormancy in biological systems.

II. METHODS

A. Summary

We propose a discrete stochastic model inspired by bet-hedging theory to compute the long-term fitness of a population in stochastic environments with two states: good or bad (see Figure 1 for an overview). Individuals can be active, dormant, or in transition from an active to a dormant state (Fig 1 D). In this model, dormancy represents a metabolically inactive state invulnerable to environmental stressors, hence dormant individuals do not reproduce or die over time. Active individuals reproduce during good times, but die at a constant rate during bad times. Transitory states represent the biological process of reaching dormancy, therefore individuals in transition states do not reproduce and also die during unfavorable environmental times. The transition states occur only between active and dormant states, with the inverse switch from dormant to active always taking one time step.

We use a Markov chain described in Figure 1 A and B to model the environmental conditions and to vary the correlation between time steps. We refer to the length of time environments remain constant as the residence time. By varying the switching rates and the number of additional states in the extended environment model we can control the mean and shape of the residence time distribution. The population and environmental models are coupled as the reproduction and death rates in the dormancy model are dependent on the environmental state.

B. Dormancy model

We consider a two-state model in which individuals switch between active and dormant with initiation probability x and resuscitation probability y (Fig. 1 C and D). Active individuals grow at rate r during good times, but die a factor of d during bad times. Dormant individuals remain unchanged regardless of environment as they are sheltered during bad times and cannot reproduce during good times. In the multi-state model in panel D there are additional states between active and dormant to represent the delay it takes for active individuals to reach full refuge in dormancy. These transition states are labeled $I_1, I_2, ..., I_n$ with corresponding transition probabilities $i_1, i_2, ..., i_n$. Given a stochastic sequence of environmental conditions $\{E_1, E_2, ..., E_n\}$ we can write a set of equations describing the number of active, transitory, and dormant individuals as follows:

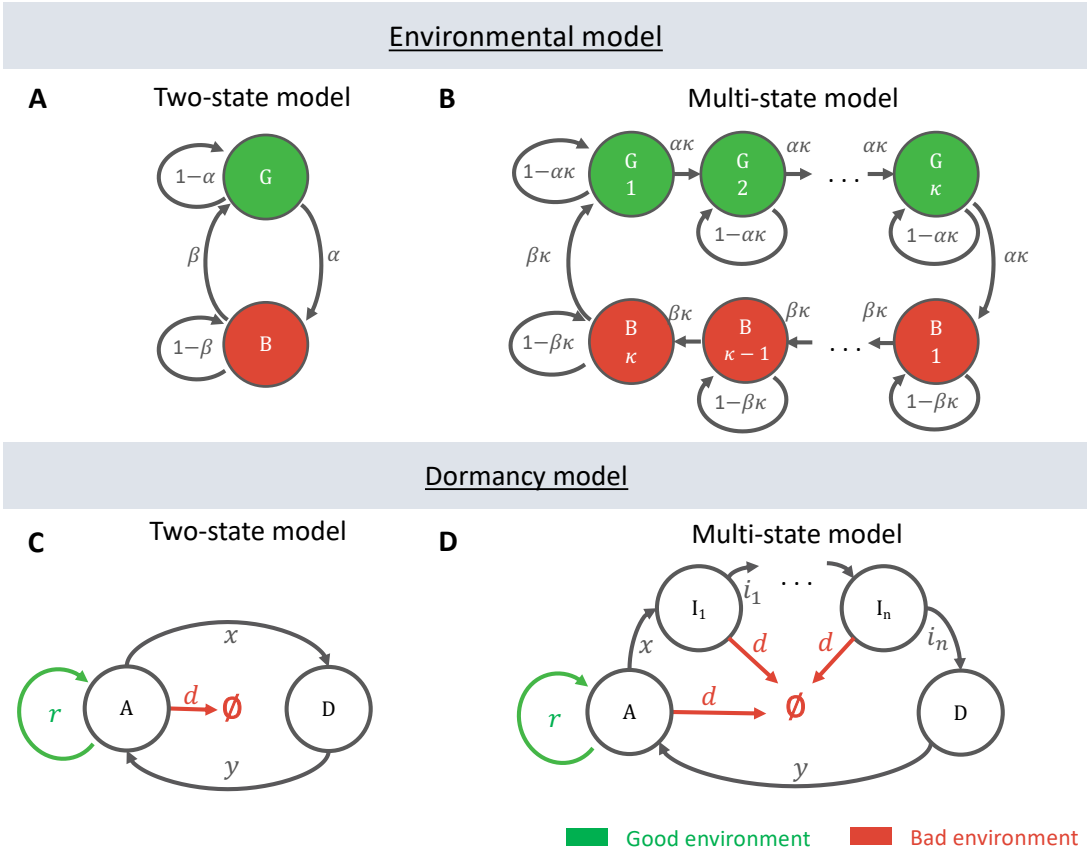

FIG. 1: **Schematic of environmental and dormancy models**. **A.** Environments change between good (G) and bad (B) based on a two-state Markov chain with switching probabilities α and β. **B.** Environments change between good (G) and bad (B) by passing through all intermediate states. There are κ good and bad intermediate states and the probability to advance through each intermediate state is $\alpha\kappa$, respectively $\beta\kappa$. This is a multi-state Markov chain and is an extension of the model in panel A. **C and D** Compartmental model of active cells A and dormant cells D. Initiation probability is x and resuscitation probability is y. The green arrows represent growth during good times and red arrows death during bad times. Active cells grow at rate r during good times and die at rate d during bad times. Dormant cells are not affected by environmental conditions. **C.** Classic dormancy model where switching between A and D is done in one time step. **D.** Extended model where switching between A and D involves passing through n intermediate transition states $I_1, I_2, ..., I_n$ with probabilities $i_1, i_2, ..., i_n$. All transition states are vulnerable to bad environments, but cannot grow during good environments.

Two-state model

$$A(t+1) = E(A, t+1) \cdot \left[(1-x) \cdot A(t) + y \cdot D(t)\right] \tag{1}$$

$$D(t+1) = x \cdot A(t) + (1-y) \cdot D(t) \tag{2}$$

Multi-state model

$$A(t+1) = E(A, t+1) \cdot \left[(1-x) \cdot A(t) + y \cdot D(t)\right] \tag{3}$$

$$I_1(t+1) = E(I, t+1) \cdot \left[x \cdot A(t) + (1-i_1) \cdot I_1(t)\right] \tag{4}$$

$$I_2(t+1) = E(I, t+1) \cdot \left[i_1 \cdot I_1(t) + (1-i_2) \cdot I_2(t)\right] \tag{5}$$

$$\dots$$

$$I_n(t+1) = E(I, t+1) \cdot \left[i_{n-1} \cdot I_{n-1}(t) + (1-i_n) \cdot I_n(t)\right] \tag{6}$$

$$D(t+1) = i_n \cdot I_n(t) + (1-y) \cdot D(t) \tag{7}$$

where $E(X,t)$ gives the multiplication factor for state $X \in \{A, I\}$ based on environmental condition E_t as follows:

$$E(A,t) = \begin{cases} r, & \text{if } E_t = Good \\ d, & \text{if } E_t = Bad \end{cases} \quad \text{and} \quad E(I,t) = \begin{cases} 1, & \text{if } E_t = Good \\ d, & \text{if } E_t = Bad. \end{cases} \tag{8}$$

The conditions for $E(X,t)$ are shown in Fig 1 C and D through the red and green arrows.

In this work we set $i_1 = i_2 = ... = i_n = 1$ meaning n transition states add a delay of n time steps to go from active to dormant. It is assumed that individuals in transition states cannot reproduce during good times, but are vulnerable to bad times and die at the same rate as active individuals.

C. Environmental model

The environment switches between good and bad states. In a good state, active individuals reproduce at rate r and in a bad state, active and transitioning individuals die at a rate d. Dormant individuals do not grow in good environments but they also do not die in bad environments. Environments change between good and bad following a Markov process shown in Fig. 1, where the baseline model in panel A represents a two-state Markov chain with switching between good and bad states and the extended model in panel B is a multi-state Markov chain with additional states. These additional states are good or bad and individuals grow or die based on the same rules as in the two-state model. By introducing these states, we introduce different types of residence time distributions in good/bad states.

If we denote with E_t the environment at time t, we can write the equations for the Markov chains in Fig. 1 as follows:

Two-state model

$$\begin{aligned} P\big(E_{t+1} = B | E_t = G\big) &= \alpha & P\big(E_{t+1} = G | E_t = B\big) &= \beta \\ P\big(E_{t+1} = G | E_t = G\big) &= 1-\alpha & P\big(E_{t+1} = B | E_t = B\big) &= 1-\beta \end{aligned}$$

Multi-state model

$$\begin{aligned} P\big(E_{t+1} = G_{i+1} | E_t = G_i\big) &= \alpha\kappa & P\big(E_{t+1} = B_1 | E_t = G_\kappa\big) &= \alpha\kappa \\ P\big(E_{t+1} = G_i | E_t = G_i\big) &= 1-\alpha\kappa & P\big(E_{t+1} = G_\kappa | E_t = G_\kappa\big) &= 1-\alpha\kappa \end{aligned}$$

$$\begin{aligned} P\big(E_{t+1} = B_{i+1} | E_t = B_i\big) &= \beta\kappa & P\big(E_{t+1} = G_1 | E_t = B_\kappa\big) &= \beta\kappa \\ P\big(E_{t+1} = B_i | E_t = B_i\big) &= 1-\beta\kappa & P\big(E_{t+1} = B_\kappa | E_t = B_\kappa\big) &= 1-\beta\kappa, \end{aligned}$$

where G and B are the good and bad environmental states in the two state model and G_i and B_i are the i^{th} good and bad state in the multi-state model. Both Markov chains have a steady-state distribution

$$[G^*, B^*] = \big[\frac{\beta}{\alpha+\beta}, \frac{\alpha}{\alpha+\beta}\big], \tag{9}$$

meaning that on average the environment will be good $\frac{\beta}{\alpha+\beta}$ of the time and bad $\frac{\alpha}{\alpha+\beta}$ of the time. We maintain the fraction of bad times equal to the fraction of good times by keeping the ratio $\alpha/\beta = 0.5$ constant, although this ratio can be changed between 0 and 1. We can vary $\alpha = \beta$ between 0 and 1 to obtain fast switching environments for higher values or slow switching environments for lower values.

In the two-state model, the distribution of environmental residence time is exponential with mean α^{-1} and β^{-1} respectively. For simplicity, we set the number of additional states to be the same in the good and bad states κ. Because $\alpha/\beta = 0.5$, let τ be the average length of time environments remain constant. As we increase the number of additional states in the multi-state model, the distribution becomes more narrow but maintains the same mean τ (Fig. S1). Note that minimum residence time is anti correlated to the variance of residence time. When κ increases environments become more predictable and the distribution of residence time becomes more narrow (Fig. S1). We distinguish the following two parameters which we will use from now on to describe environmental conditions:

i. Mean residence time $\tau = \alpha^{-1} = \beta^{-1}$

ii. Minimum residence time κ.

The multi-state model includes a key constraint. Because all additional states need to be traversed to switch environments, we restrict our attention to models where $\tau > \kappa$.

Given that $\tau = \alpha^{-1} = \beta^{-1}$, κ has an upper limit of $\alpha^{-1} = \beta^{-1}$ and when that limit is reached environments are no longer stochastic and become periodic. In this work we use $\tau \in \{2, 4, 6, 8, 10, 20\}$ and $\kappa \in \{1, 2, m-2, m-1\}$, where m denotes the maximum value κ can take which is τ. Additionally given $\tau > \kappa$, not all pairs of (τ, κ) are feasible. The unfeasible cases, e.g. $\tau = 2$ and $\kappa = 2$, will be shown as 'unfeasible' in figures.

D. Expected Lyapunov exponent

To compute the expected logarithmic growth rate, we use the Lyapunov exponent formula as a proxy for fitness:

$$r = \frac{1}{t} \log \left(\frac{N(t)}{N(0)} \right) \tag{10}$$

where $N(t) = A(t) + I_1(t) + ... + I_n(t) + D(t)$ is the total size of the population at time t. A value of $t = 500$ time steps is used. We compute the Lyapunov exponent 1000 times for different simulations of the environment and take the mean to obtain the expected value.

Variable name	**Description**	**Value**
$\tau = \alpha^{-1} = \beta^{-1}$	Average environmental residence time	[2, 4, 6, 8, 10, 20]
n	Delay to reach dormancy	[0,1,2,4,6,8,10]
κ	Environmental predictability	[1,2,μ-2, μ-1]
x	Dormancy initiation probability	$0 \leq x \leq 1$
y	Dormancy resuscitation probability	$0 \leq y \leq 1$
d	Death factor	.5
r	Growth factor	2
m	Maximum value of κ w.r.t. τ	τ

TABLE I: Model variables

E. Code availability

All simulations were carried out in MATLAB v 2020a. Scripts are available on Github at https://github.com/WeitzGroup/Bet_hedging_dormancy.

III. RESULTS

A. Population dynamics and fitness change based on switching probabilities

We first evaluate how populations with different initiation and resuscitation probabilities grow and die in an unpredictable environment. A stochastic environment of 50 time steps is simulated based on the classic Markov model in Fig. 1 A with values of $\alpha = \beta = 0.5$. The population dynamics are shown in Fig. 2 A for three values of switching probabilities between 0 and 1. Populations grow during good times (green shading) and die during bad times (red shading). Each of the different populations has a fitness value calculated via the associated Lyapunov exponent shown in panel B which is used as a proxy for fitness. In panel B we also show the Lyapunov exponent for other values of switching probabilities and note that the population with $x = y = 0.5$ yields the highest fitness.

By varying $(x, y) \in [0, 1]^2$ we generate a fitness map based on the initiation probability on the x-axis and resuscitation probability on the y-axis (Fig. 3 enlarged heatmap). This fitness map is concave and has a global maximum $(x^*, y^*) = (0.5, 0.5)$ shown with a red marker. The pair $(x^*, y^*) = (0.5, 0.5)$ are the optimal switching probabilities which maximize the fitness of the population given parameters $\tau = 2$, $\kappa = 1$ and delay $n = 0$. The same type of fitness map is shown in the rest of Figure 2 for different values of mean residence time τ and minimum residence time κ. Notice that all the fitness maps in Figure 3 are concave, hence we obtain an optimal pair of dormancy switching probabilities for each value of $\tau \in \{2, 3, 4, 5, 6, 7\}$ and $\kappa \in \{1, 2, 3, 4, 5, 6\}$. These results suggest that the fitness of a population is smooth with respect to the initiation and resuscitation probability and monotonically decreases as (x, y) pair is further away from the optimal value.

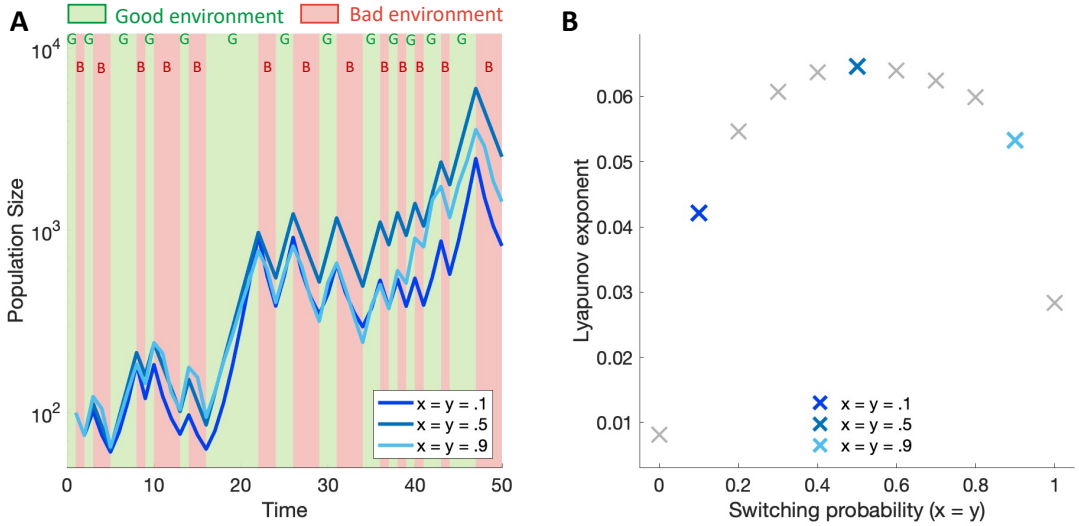

FIG. 2: **Population dynamics and Lyapunov exponent in the two-state dormancy model A.** Three populations with different initiation x and resuscitation y probabilities are shown in blue lines and environmental conditions are shown in red and green shaded areas which are also labeled G or B. The environmental and dormancy models used are the two-state models from Fig. 1 panels A respectively C with $\tau = \alpha^{-1} = \beta^{-1} = 2$. **B.** The corresponding Lyapunov exponent for each of the blue lines in panel A is shown for $x = y$ switching probabilities on the x-axis. The formula used to compute the Lyapunov exponent is shown in equation (10).

B. The relationship between optimal switching without delays and residence time distributions

Next, we evaluate the relationship between optimal switching probabilities identified in the prior section against the environmental residence time. We show the optimal pairs of dormancy switching probabilities from Fig. 3 against τ and κ in Figure 4 A and B respectively. First we note that the optimal initiation is equal to the optimal resuscitation, hence only one line is used to show $x^* = y^*$. Optimal switching decreases with τ, suggesting an inverse relationship between mean residence time and switching probabilities (Fig 4 A). We also note that this inverse relationship strengthens as the minimum residence time κ increases and environments become more predictable. For higher values

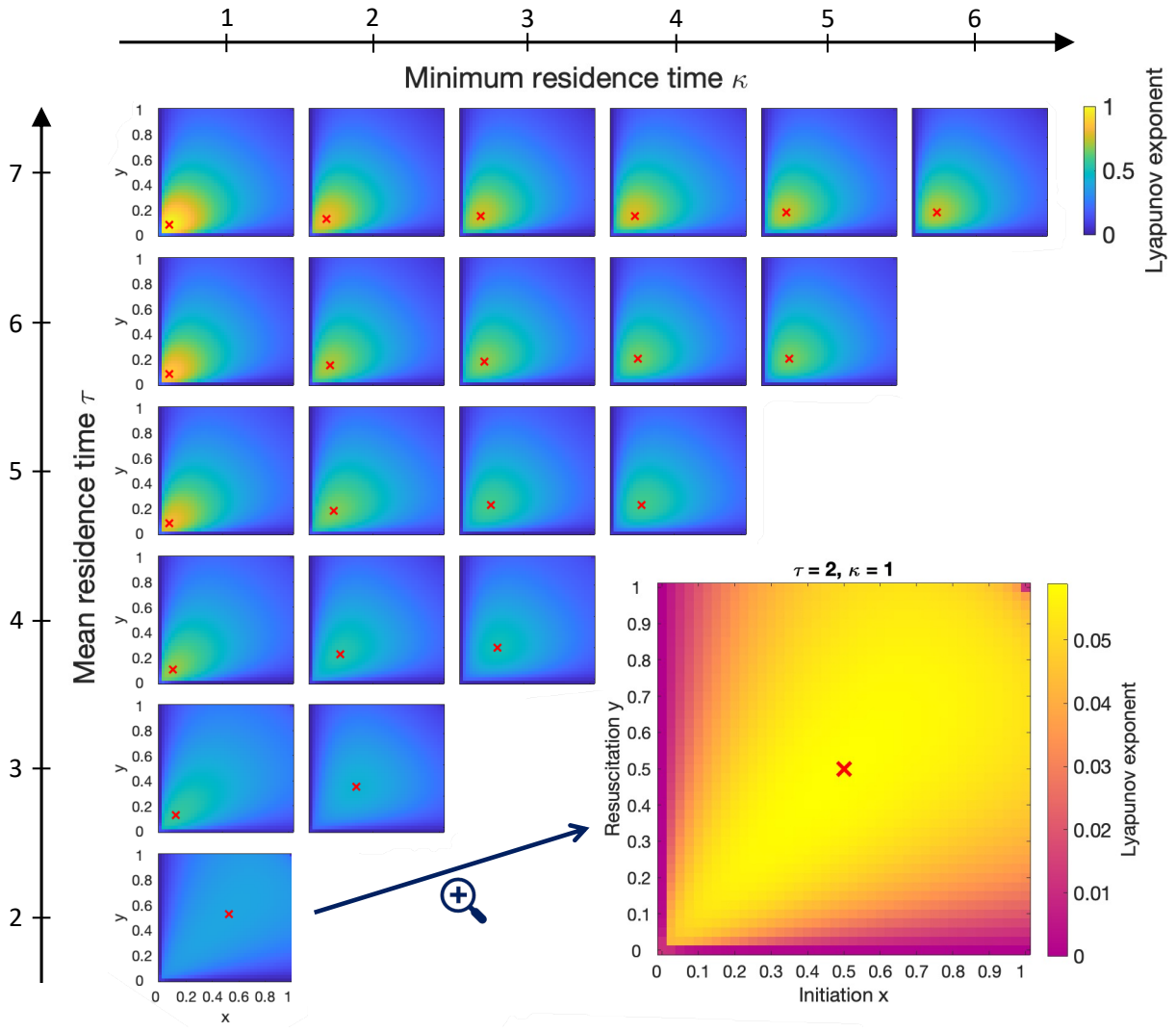

FIG. 3: **Fitness maps for instantaneous dormancy when varying mean and minimum residence time** Each heatmap shows the Lyapunov exponent based on the initiation probability on the x-axis and resuscitation probability on the y-axis. The highest fitness is marked with a red x. The simulations are done for mean residence time $\tau \in \{2, 3, 4, 5, 6, 7\}$, minimum residence time $\kappa \in \{1, 2, 3, 4, 5, 6\}$ and no delays between active and dormant states ($n = 0$). Because $\tau \geq \kappa$ the bottom right part of the figure is not feasible. Instead a magnified version of the $\tau = 2, \kappa = 1$ heatmap is shown. The values for switching probabilities are between 0 and 1 with an increment of 0.025 and a total of 500 runs is used for each heatmap. In each case, the Lyapunov exponent shown is the average of the exponent for each run.

of $\kappa \in \{max-2, max-1\}$ the optimal switching approaches τ^{-1}. This observation is consistent with previous findings (Kusell, 2005) that optimal phenotypic switching rates are equal to the inverse of environmental times in the limit of sufficiently persistent environments.

Having shown how optimal switching depends on mean residence time in Figure 4 A, we now evaluate the impact of minimum residence time. We show the same optimal switching values as in panel A, but plotted against the minimum residence time κ in panel B. As κ increases, the variance of environmental times decreases. Optimal switching increases as environments are more predictable and this observation is stronger for faster switching environments, i.e. for lower values of τ. We conclude that in the absence of delays, the shape of the residence time distribution affects the optimal bet-hedging strategy only when environments switch frequently between good and bad times.

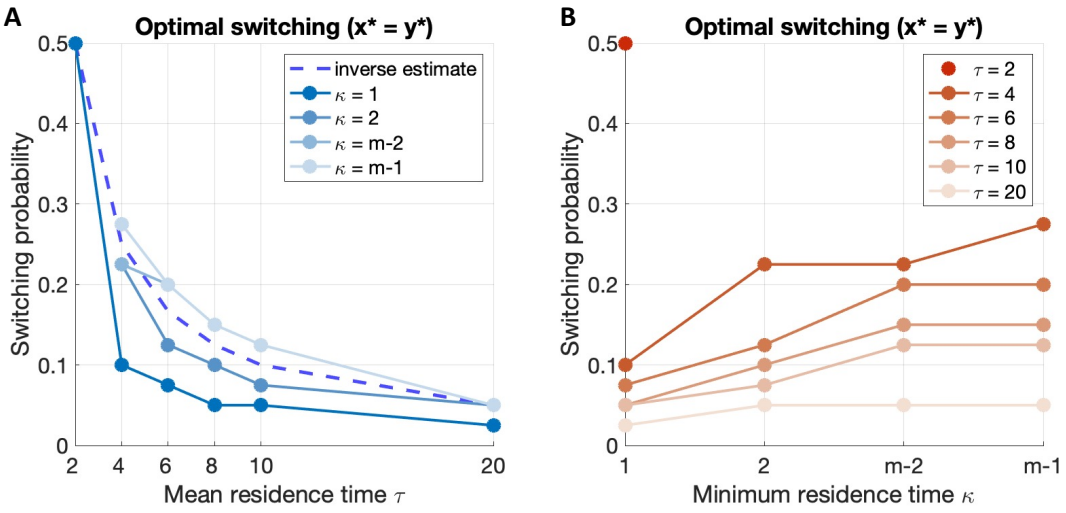

FIG. 4: **Impact of the mean residence time τ and minimum residence time κ on optimal switching with no delays A and B.** Optimal switching x^* and y^* are computed based on the location of the red x in Fig. 3 and shown against the mean residence time τ in panel **A** and against the minimum residence time κ in panel **B**. Note that $x^* = y^*$, hence one plot is representative of both optimal initiation and resuscitation probabilities. The optimal switching is shown for each value of κ in **A** and τ in **B**, with lower values of κ and τ being more opaque. The missing data points in both panels correspond to the case of $\kappa \geq \tau$, specifically when $\tau = 2$ and $\kappa \in \{2, max - 2, max - 1\}$. The theoretical estimate from [20] is the inverse of the environmental times and is shown in a dashed line. The dormancy model considered has no delays between A and D.

C. Delays to reach dormancy reduce the fitness and optimal switching probabilities in a population

We next investigate how delays to reach dormancy affect a population by using the multi-state dormancy model introduced in Fig. 1 D (see Methods for full details). Whereas in previous sections we used a dormancy model with no delays, we compute the Lyanpunov exponents for delay $n = 1$ and show the results in Figure 5. Note that Figures 3 and 5 are identical aside from parameter n, i.e. the populations in Figure 5 take one extra step to reach dormancy. When comparing the heatmaps with and without dormancy, we note that the addition of one time step to reach dormancy reduces the population fitness for all values of κ and τ. When comparing the enlarged heatmaps for $\tau = 2, \kappa = 1$, the addition of one delay reduces the highest possible fitness by about 50% and the optimal switching probabilities change 10-fold from $(x^*, y^*) = (.5, .5)$ to $(x^*, y^*) = (.05, .05)$. Overall, the inclusion of delays to reach dormancy significantly reduces the long-term growth and leads to lower optimal switching probabilities throughout the parameter space explored in $\tau - \kappa$.

Building on this finding, we compute the optimal switching probabilities for other values of τ, κ and n and plot them against the delay to reach dormancy in Fig. 6. We note that the optimal initiation is equal to the optimal resuscitation within a small tolerance of 0.025 in the switching probability - likely due to stochastic effects, hence we show only one line for $x^* = y^*$. Both the initiation and resuscitation probabilities decrease as delays to reach dormancy increase until the optimal switching becomes $x^* = y^* = 0$ when the delays are too high (Fig. 6 A). This trend holds for all values of τ, however the reduction in optimal switching is more drastic for faster changing environments with lower mean residence time. The associated Lyapunov exponent also decreases as delays increase from almost 0.15 when $n = 0$ to ≈ 0.01 when $n = 10$ (Fig. 6 B). Delays to reach dormancy have a stronger effect on the fitness when the mean residence time τ is higher. Altogether our findings suggest that increasing delays to reach dormancy decrease long-term fitness and decrease the optimal switching rate between active and dormant states - although the low levels of switching are retained.

D. Optimal switching increases with environmental predictability unless delays are too large

So far we have discussed how residence time distribution affects the classic bet-hedging strategy with no delays in section III B and separately how delays affect the fitness and optimal switching strategies in section III C. In this last section we investigate the larger picture about the combined effect of residence time distribution and delays to reach dormancy on optimal switching and long-term fitness. To do so, we compute the optimal switching for all values of τ, κ and n in Fig. 7 and group the results in 4 panels based on minimum residence time κ. As the value of κ increases,

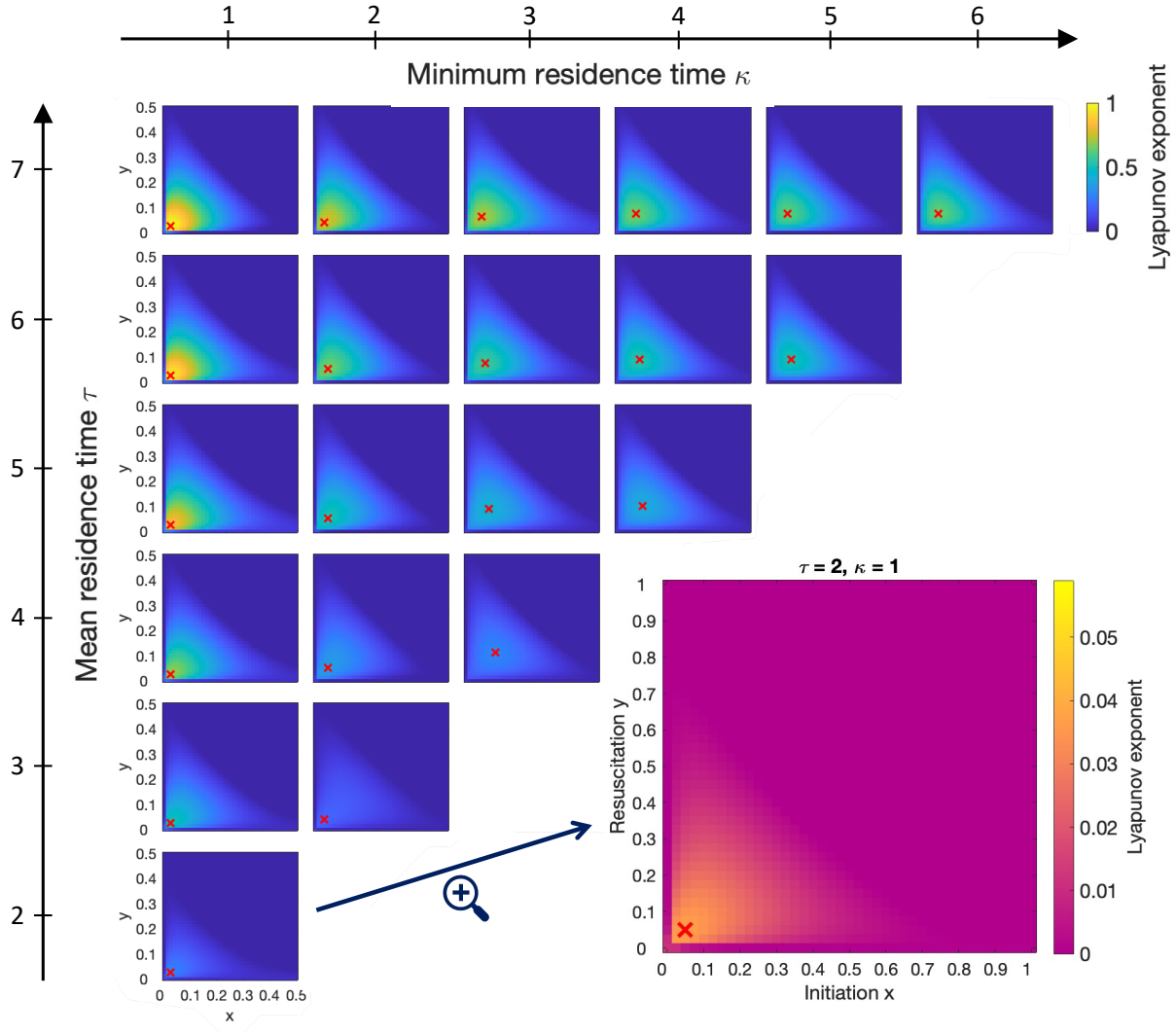

FIG. 5: **Fitness maps for multi-state dormancy model when varying mean and minimum residence time** Similar to Fig. 3, each heatmap shows the Lyapunov exponent based on the initiation probability on the x-axis and resuscitation probability on the y-axis. The only difference from 3 is that the dormancy model used here has one additional transition state ($n = 1$). The same values are used for τ and κ and a magnified version of the $\tau = 2, \kappa = 1$ heatmap is shown in the unfeasible area. The values for switching probabilities are between 0 and 1 with an increment of 0.025 and a total of 1000 runs is used for each heatmap.

environments become more predictable. As before, we find that $x^* = y^*$ within a small tolerance of 0.025 for all values of κ, τ and n.

First we make note of results that are consistent with the ones from previous sections, but hold true for a larger range of parameters. Consistent with the results in section III C, optimal switching decreases as delays increase and this remains valid for all values of τ and κ. We also notice that, similar to the results discussed in section III B, switching probabilities are more dependent on the mean residence time τ as the value of κ is higher. Optimal switching probabilities tend to be equal to the smallest nonzero value for lower values of κ of 1 or 2. However when κ is higher there is a stronger correlation between $x^* = y^*$ and both the environmental residence time and the delay to reach dormancy, τ and n, respectively. Indeed when $\kappa = 1$, all but four values are equal to 0.05 or 0.025, whereas for $\kappa = max - 1$ most intermediate values between 0 and 0.275 are obtained several times (compare Figure 7 A vs. Figure 7 D).

We further investigate how the optimal switching probabilities change with minimum residence time and notice a binary behaviour based on mean residence time τ and delay to reach dormancy n:

1. Optimal switching increases with κ when $\tau > n + 2$ (compare the top of each panel in Figure 7).
2. Optimal switching decreases with κ when $\tau \leq n + 2$ until it reaches 0 or 0.025 when $k = max - 1$(compare the bottom of each panel in Figure 7).

Note that when $\kappa = max - 1$, environmental times often stay constant for exactly $\tau - 1$ time steps. If $\tau = n + 2$,

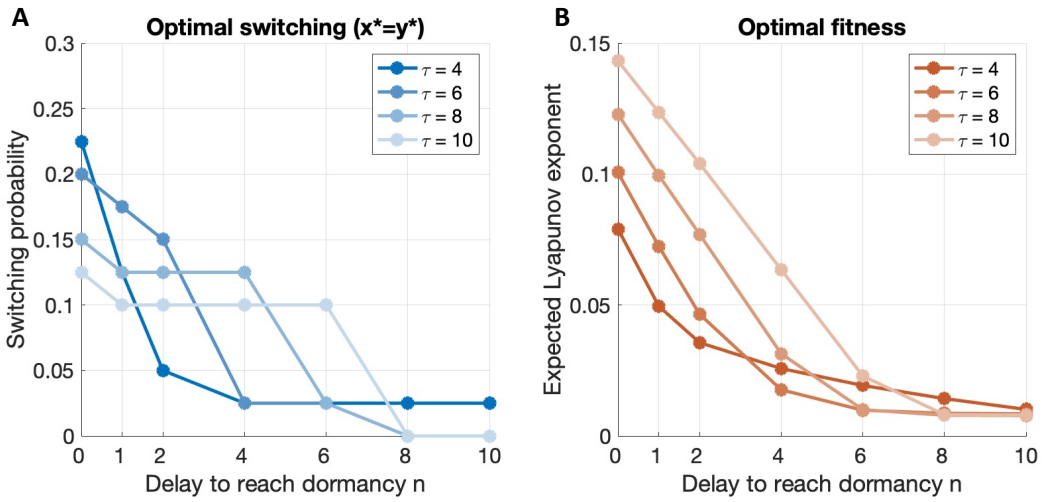

FIG. 6: **Effects of delays to reach dormancy on highest fitness and optimal switching probabilities A.** Optimal switching probabilities are computed for all values of τ, κ and delays and plotted against the delays to reach dormancy on the x-axis. Note that $x^* = y^*$ within a small tolerance of 0.025, hence one plot is representative of both optimal initiation and resuscitation probabilities. The optimal switching is shown for several values of τ, with lower values of τ being more opaque. **B.** The corresponding fitness for the optimal switching probabilities is shown against the delay to reach dormancy on the x-axis. The fitness is shown for the same values of τ as in panel **A**, with lower values of τ being more opaque. Both panels use a value of $\kappa = max - 2$.

then environments remain constant for exactly $\tau - 1 = n + 1$ time steps which coincides with the number of steps needed to transition between active and dormant (recall that delay 0 still takes one time step). In other words, if by the time dormancy is reached the environmental condition has changed, it would be more beneficial not to engage into dormancy at all. If there is some uncertainty regarding how soon the environments will change, i.e. smaller values of κ, dormancy might still be beneficial even if the delays are longer than mean environmental residence times. However, when environments are highly correlated, the relationship between length of delays n and mean environmental residence times κ determines whether dormancy is a favorable strategy or not.

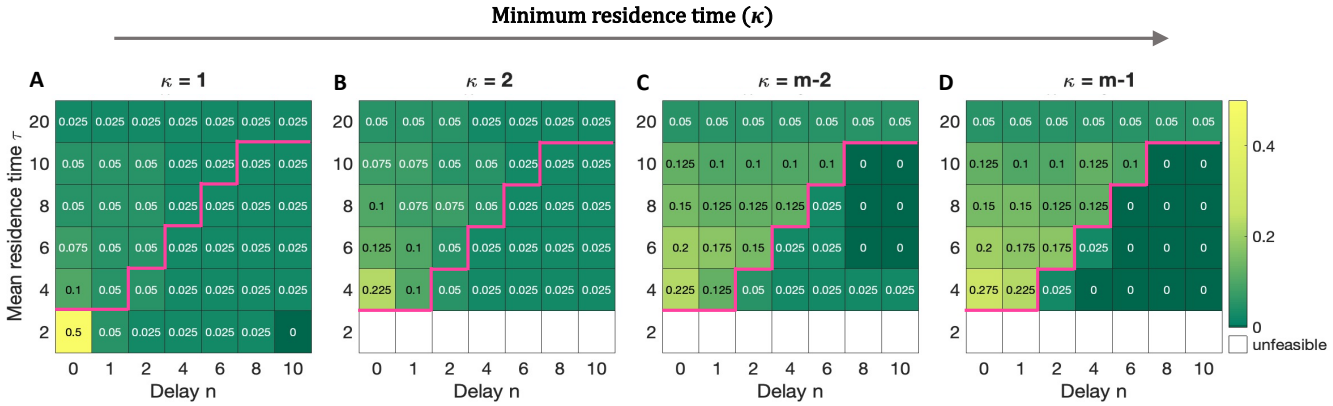

FIG. 7: **Optimal switching for all values of τ, κ and delays to reach dormancy** Each of the four maps shows the optimal switching probabilities based on the delay to reach dormancy n on the x-axis and mean environmental residence time τ on the y-axis. Each panel has a different environmental predictability with increasing values of κ from left to right. Given the constraint of $\tau > m$, unfeasible areas are left white. The magenta line in each panel represents the delimitation between $\tau + 2$ and n: above the line $\tau + 2 > n$ and below $\tau + 2 \leq n$. The values for switching probabilities are between 0 and 1 with an increment of 0.025 and a total of 1000 runs is used to find each optimal value.

IV. DISCUSSION

Using a stochastic model of individual growth and dormancy coupled to fluctuating environments, we find that delays in reaching dormancy have a large impact in reducing long-term population fitness and optimal switching probabilities. Delays in phenotypic switching increase the risk of investing in dormancy since transitory states are susceptible to harsh conditions, hence drastically changing the associated risks and benefits of a bet-hedging strategy. We also find that the balance between the length of delays, mean residence time and minimum residence time determines how much and whether dormancy is a beneficial bet-hedging strategy. Dormancy is no longer beneficial when delays are consistently longer than environmental residence times, but dormancy can be maintained at a low level when the distribution of environmental residence time is wide, i.e. environmental predictability is low. Thus while delays in phenotypic switching can have a drastic effect on optimal strategy, environmental predictability alone can lead to maintenance or loss of dormancy. These results show that all three components – environmental mean residence time, minimum residence time – and delays are essential in analyzing the benefits of dormancy as a stochastic strategy.

Previous work on phenotypic switching has focused on examining effects of the mean environmental residence time on optimal switching probabilities. In classic bet-hedging theory, environmental conditions change randomly and are not correlated. This memory-less environmental setup corresponds to the case of $\kappa = 1, \tau = 2$ and $n = 0$ in our work for which we obtain optimal switching probabilities consistent with the theoretical predictions from [21]. For environments that remain constant longer, i.e. higher values of κ, we replicate the findings by Kusell and Leibler that optimal switching probabilities are equal to the inverse of mean residence time [20]. By varying κ between 1 and τ we are able to see how the system behaves in between these limiting cases.

Our results underline the importance of considering dormancy life history traits when assessing optimal bet-hedging investment in a biological system. In the absence of a sensing mechanism, we predict that dormancy is favorable in unpredictable environments even when delays are relatively high. On the contrary, in more predictable environments dormancy is beneficial only if environments remain constant longer than the time needed to switch into dormancy. For organisms with with long delays to initiate dormancy, such as spore forming bacteria, our results suggest that stochastic entry and exit from dormancy is beneficial either in highly unpredictable environments or environments that switch infrequently between states. For organisms with lower delay, such as those entering a quiescent state, randomly initiating dormancy may be beneficial regardless of environmental conditions, however higher optimal dormancy switching is obtained in more predictable environments with larger values of κ.

We make several simplifying assumptions when modeling dormancy and the surrounding system. Environments are parameterized in a binary fashion as good or bad with fixed associated growth or death factors, whereas in reality environmental severity and organismal parameters can take more than two values. Additionally, we assume that dormancy is a pure bet-hedging strategy without taking into account a responsive switching mechanism based on available resources or population density [25–28]. Incorporating a sensing mechanism and exploring the trade-off between a stochastic and responsive strategy is one consideration that could make this work more readily applicable to microorganisms [29].

Our findings extend the previous efforts to analyze bet-hedging strategies by showing the importance of incorporating delays to reach dormancy. As we have shown, small changes in the mechanistic representation of dormancy and/or environmental conditions can have large effects on the benefits of particular bet-hedging strategies. Future work incorporating mixed strategies, direct competition between populations, and sensing-based initiation and exiting of dormancy could further provide valuable insight about the benefits and robustness of evolutionary strategies to respond to fluctuating environments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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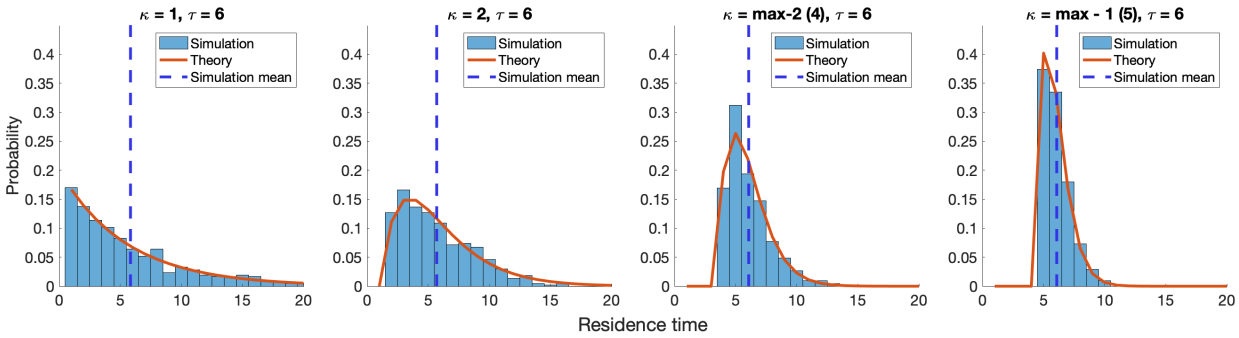

FIG. S1: **Probability density function of residence time** Each of the four plots shows the PDF of residence time with the same mean $\tau = 6$ and values of κ between 1 and 5. Simulations of environments have 5000 time steps and are shown in the blue histogram. The mean residence time of the simulated environments is shown with a dotted blue line. A theoretical functions computing the PDF based on the Markov process in Fig. 1 B is shown in orange.