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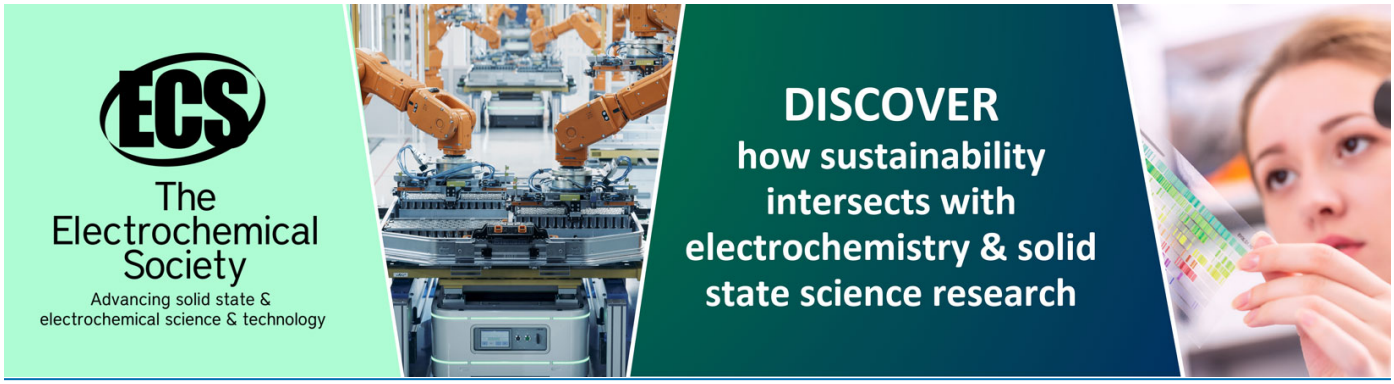

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Switching behaviour of two-phenotype bacteria in varying environment

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Abstract. An increasing interest in multi-phenotype species has stimulated both experimental and mathematical research. One example is bacteria which have two phenotypes and can make transitions from one phenotype to the other in response to variations in environmental conditions. We model a population of such bacteria subjected to a stochastic environmental input, which fluctuates between two conditions preferred by the phenotypes. Our interest in this model is how the average growth rate of the total population is affected by alterations to the environmental thresholds at which the transitions between phenotypes are allowed. Under certain conditions, we find that the bacteria achieve a maximum growth rate by adjusting their behavior to act in a similar manner to a non-ideal relay. In this scenario, memory helps to increase fitness. We then extend the model to include multiple competing species with different thresholds and examine the limit of distribution of population among these species and phenotypes as time increases. For this purpose, we formulate a reaction-diffusion model which involves non-ideal relays describing the evolution of the state of different species; and, a Preisach operator with time-dependent density function to account for the integral effect of the species on the environment. Formation of patterns and multiple stationary limits are shown numerically in the multi-species model.

1. Introduction

Long-term memory underpins genetic inheritance mechanisms and functioning of the immune system in higher organisms. Many regulatory networks exhibit complex dynamics and multi-stable states, also linked to memory. There is mounting evidence that microorganisms such as bacteria which have experienced different environmental histories may respond differently to current conditions and that an environmental memory can grant fitness to bacteria in the evolutionary game. For example, history dependent behaviour was shown experimentally, and quantified in the information theory framework, in *B. subtilis* [1]. Environmental memory has been shown in DNA methylation in chemotaxing bacteria [2], genetic and epigenetic phase variation mechanisms in pathogenic bacteria [3,4] and switch-type bistable systems in regulatory networks [5–8]. Further work focuses on designing biological memory switches such as a heritable switch with multiple states which are encoded into the DNA sequence [9].

Simple bacterial systems are an attractive test bed for developing understanding of adaptation mechanisms which help organisms to survive and improve fitness in a fluctuating environment. One example is bacteria capable of switching behaviours, phenotype, or state in response

to fluctuations of external conditions if different phenotypes are well adapted to different conditions. In particular, *E. coli* generate multistability of gene expression states under different perturbations [10–13].

A number of conceptual, technically simple, mathematical models have been proposed to understand how certain switching strategies can help bacteria to increase fitness, which is often measured by the net population growth rate. The hybrid linear differential model proposed in [14] shows that a dynamically heterogeneous bacterial population can sometimes achieve a higher growth rate than a homogeneous one provided that the rate of a transition between phenotypes is comparable to, or lower than, the rate of variations of the environment. In this case, bacteria can anticipate sudden fluctuations of the environment by having a subpopulation ready in an appropriate phenotype before the environment changes to a state favouring this phenotype. This effect is more pronounced for predictable environments, such as periodic, but was also shown to be present for stochastic environments in narrower parameter ranges [14]. The optimal heterogeneous distribution between phenotypes is achieved dynamically by allowing some positive rate of transitions from the currently most favoured phenotype to an unfavoured one.

If the rate of transitions between phenotypes is higher than the rate of environment variations, then, under the assumptions of the model studied in [14], the maximal fitness is achieved by the responsive switching strategy whereby all the bacteria switch to the currently most favoured phenotype. However, if the responsive strategy is penalised, then it can be not optimal. The penalty can be associated with the cost of sensing the environment as bacteria have to maintain some sensory machinery to respond to changes. Another linear hybrid differential model, where the cost of sensing was implemented as an explicit reduction in the growth rates, shows that stochastic switching can confer more fitness to the population than the responsive switching in slowly varying environments [15]. This result, as well as the results in [14] for faster environments, support the idea that diversity (heterogeneity) can help improve fitness in varying conditions, that is the view very well established in ecology.

Memory can also grant fitness to bacteria. For instance, past phosphate limitation was shown to lead to a faster response to successive periods of phosphate limitation in *E. coli*, and this faster response was suggested to be survival enhancing [16]. An advantage of using strategies with memory can be shown in the framework of the game theory [17–19] applied to models where bacteria are considered as players in an evolutionary game [7, 15, 20].

Differential models proposed in [14, 15] are memoryless in slowly varying environmental conditions. In the adiabatic limit when the ratio of environment variation rate and the switching rate between phenotypes tends to zero, the state of the system is completely determined by the state of the environment. In this paper, using a modification of the model proposed in [14], we show that a long-term bistability type memory can increase fitness of bacteria in a stochastically varying environment. Our model includes a cost of switching in the form of a temporary inhibition of the reproductive activity in bacteria undergoing a transition to a different phenotype. We show that the memory confers fitness when the rates of the environment variation and switching are comparable. In this state, the system achieves dynamic heterogeneity, which is consistent with the results in [14]. However, a static memory in our model persists in the limit of slow environments. The memory is characterised by a responsiveness parameter α; the value $\alpha = 0$ corresponds to a memoryless system.

This paper has two parts. After characterising the type of persistent memory which ensures the maximal net growth rate of a population of bacteria in the first part of the paper, we discuss a model where populations with different α compete for nutrients.

More specifically, in the first part, we consider a linear model of a growing population of bacteria, which respond to variations of external conditions (environment) by switching between two phenotypes. We demonstrate a possibility of a scenario where memory can help achieve

better fitness. The effect of external conditions is modelled by varying the availability of nutrients and, by this, the growth rate of each phenotype; fitness is measured by the average growth rate of the total population. It is assumed that each phenotype consumes a different type of food, for example, one consumes lactose, the other consumes glucose. A mixture of the two nutrients is supplied at a constant rate, while the proportion of the two ingredients in the mixture, measured by a variable E, varies in time. Bacteria sense changes in E and thus, by changing to the phenotype for which more food is available, can potentially increase the growth rate of the population. In this way, the system is similar to the model studied in [14]. However, instead of the binary environment, we use a continuous input $E(t)$ and assume the threshold type response of bacteria. Namely, bacteria decide to switch their phenotype after E passes a certain threshold value. Importantly, the threshold value E_1 for switching from phenotype one to phenotype two can be different from the threshold value E_2 for inverse switching. The equality $E_1 = E_2$ corresponds to memoryless bacteria, while the case $E_1 \neq E_2$ indicates the presence of memory as a bacterium has to know (remember) its phenotype in order to decide whether to switch or not at a certain value of E. This is the type of memory of a non-ideal relay (bistable switch) [21].

Some *in vitro* experimental studies give evidence that the process of changing phenotype can be stressful for bacteria. In particular, bacteria may not reproduce within a period of time preceding, during, or following this process.[1] If this is the case, a delay in growth appears to be a natural cost associated with phenotype switching. Assuming such a cost in our model, we will show that having memory can be an advantage for bacteria living in a stochastically varying environment. The memory, by introducing the difference between the thresholds, prevents switching when E varies in the interval $E_1 < E < E_2$ around the value $E_T = 0.5$ with equally available nutrients. This somewhat conservative strategy may increase the population's growth rate as small random fluctuations of E near the point E_T can keep more sensitive (responsive) bacteria, such as memoryless bacteria with $E_1 = E_2 = E_T$, or bacteria with $E_1 \approx E_2 \approx E_T$, in a transition non-reproductive state forever, thus stopping the growth. We will describe the optimal strategy of bacteria as a probabilistic binary switch with memory. At the same time, it can be shown that in a deterministic environment with a predictable pattern of variation (for example, a periodic environment) the most responsive memoryless switching strategy can be optimal.

In the second part of the paper, we allow for variability of the switching thresholds in a population of bacteria. The thresholds in each species are assumed to be symmetric with respect to $E = E_T$, that is $E_1 = E_T - \alpha$, $E_2 = E_T + \alpha$, with α varying in different species. Having shown in the first part of the paper that there is an optimal $\alpha = \alpha_{opt}$ which maximises the growth rate, and that α_{opt} depends on the parameters of the system and food dynamics, we ask the question whether species with α close to α_{opt} will outgrow the others if they compete for food. That is, we are interested in how fitness and competition act to select a certain distribution of switching thresholds in the population.

For simplicity, we assume that switching is fast-the time of a transition from one phenotype state to the other is short compared to the characteristic time of the variation of environment. Hence, a population of bacteria with a given α is modelled by the classical deterministic non-ideal relay. For one model of competing populations with α ranging over an interval of values, we show the formation of patterns resulting from the evolution. Our simulations indicate that, depending on initial data, the solution can converge to different patterns. That is, there is no single winner of the competition, or a single limit distribution. The attractor seems to be a connected continual set of stationary distributions.

[1] In these experiments, a colony of bacteria grown in a Petri dish with one nutrient is swapped to a Petri dish with another nutrient. After a period of inactivity, or a shock, following the swap, bacteria start a transition to the other phenotype which is better fit for consuming the new type of food.

Our model is a system of reaction-diffusion equations containing discontinuous nonlinearities, the non-ideal relays, and a continuous integral of those. This integral can be interpreted as the Preisach operator [21] with a time dependent density (the density is a component of the solution describing the varying distribution of bacteria).

The first and the second parts of the paper constitute the two following sections. The paper ends with conclusions, including some discussion of the results and possible modifications and extensions of the models.

2. Model of a single population of two phenotype bacteria

2.1. Model formulation

The following model of two phenotype bacteria living in discretely switching binary environment was presented in [14]:

$$\tilde{x}' = \gamma_1\tilde{x} - \kappa_1\tilde{x} + \kappa_2\tilde{y}, \tag{1a}$$

$$\tilde{y}' = \gamma_2\tilde{y} - \kappa_2\tilde{y} + \kappa_1\tilde{x}. \tag{1b}$$

Here the function $\tilde{x}(t)$ is the population of bacteria in one of the phenotypes and $\tilde{y}(t)$ is the population in the other phenotype. The parameters γ_1, γ_2, κ_1 and κ_2 change whenever the environment changes state; γ_1 and γ_2 denote the growth rates of the phenotypes $\tilde{x}$ and $\tilde{y}$, respectively, in the current environment state; κ_1 and κ_2 are the transition rates between the two phenotypes.

In this work, we consider the case where the environment changes continuously within an interval of values, as opposed to discretely. We introduce the continuous variable E to denote which of the environmental states the system is currently in. The value of E is a measure of the relative abundance of one saturated environmental state over the other saturated state in the current intermediate (mixed) state. For example, if the environmental conditions that we consider are a glucose/lactose mix, then E would tell us how much glucose there was compared to lactose. We now make some definitions about the value of the variable E; we take the case of $E \leq 0$ to be the case where the phenotype $\tilde{x}$ is fully favoured, that is its growth rate is at its maximum and the growth rate of $\tilde{y}$ is at its minimum. Similarly, for $E \geq 1$ we have the case where the phenotype $\tilde{y}$ is fully favoured. Intermediate values of E give rise to partial favouring of one phenotype over the other. We define the value $E = 0.5$ as the environmental threshold, E_T, the point at which both phenotypes are equally favoured.

In case of discrete (binary) environment, as in [14], it is realistic to assume that the growth rates of the two phenotypes are discrete too and switch each time the environment switches. As we assume gradual changes of the environment between its continuous states, and there is only a partial favouring of one phenotype over the other, it seems natural to use functions that change the growth rate gradually as the environment fluctuates. With this in mind, we replace γ_1 and γ_2 in model (1) with functions Γ_1 and Γ_2 given by

$$\Gamma_1(E) = \begin{cases} \gamma_{unfit} + \sigma, & E \leq 0, \\ \gamma_{unfit} + \sigma(1-E), & 0 < E < 1, \\ \gamma_{unfit}, & E \geq 1, \end{cases} \tag{2a}$$

$$\Gamma_2(E) = \begin{cases} \gamma_{unfit}, & E \leq 0, \\ \gamma_{unfit} + \sigma E, & 0 < E < 1, \\ \gamma_{unfit} + \sigma, & E \geq 1, \end{cases} \tag{2b}$$

where γ_{unfit} is the growth rate when the environment is in the state that is unfavoured by the phenotype; σ is the benefit for the environment being in the state that is preferred by the phenotype, see Figures 1a and 1b. We assume a positive transition rate κ from a phenotype

unfavoured by the environment to the favoured phenotype; and, the zero transition rate from the favoured phenotype. The transition rate changes when E reaches a threshold value. That is, we assume that the parameters κ_1 and κ_2 in (1) are step functions of E,

$$\kappa_1(E) = \begin{cases} 0, & E \leq E_T + \alpha, \\ \kappa, & E > E_T + \alpha, \end{cases} \tag{3a}$$

$$\kappa_2(E) = \begin{cases} \kappa, & E \leq E_T - \alpha, \\ 0, & E > E_T - \alpha, \end{cases} \tag{3b}$$

see Figures 1c and 1d. Note that if $\alpha > 0$, then no transitions occur as long as $E_T - \alpha < E(t) < E_T + \alpha$.

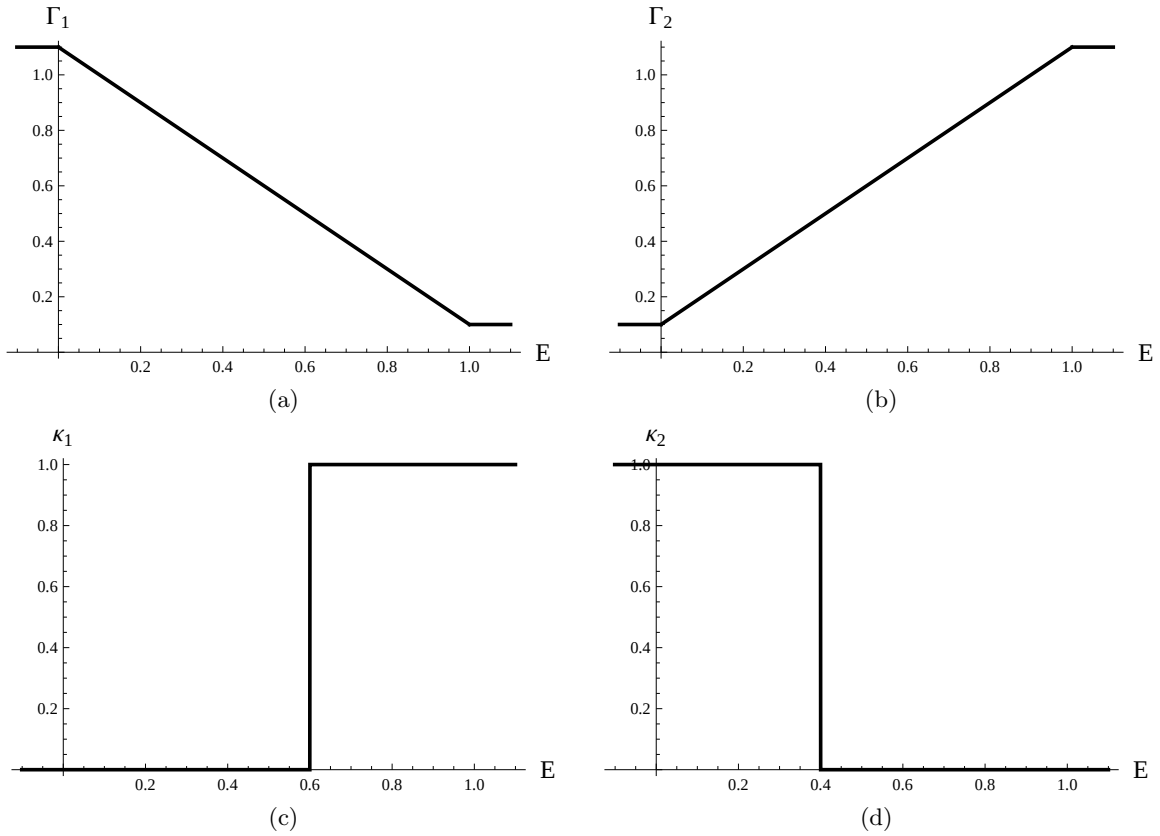


Figure 1: Functions (2) and (3).

In model (1) there is no penalty for a bacteria switching from one phenotype to another. This assumption is justified, in particular, if the time taken for the bacteria to change phenotype is shorter than the time between the occurrence of these transitions as is the case studied in [14]. The alternative case is when a cost of the transition is incorporated into a model. We make the assumption that when a bacterium begins to change phenotype it undergoes a period of shock during which it does not reproduce. To model this behaviour, we introduce two new population groups $\tilde{z}$ and $\tilde{w}$, which represent intermediate states in the transition from the phenotype $\tilde{x}$ to the phenotype $\tilde{y}$ and vice versa, respectively. That is, when a bacterium in the phenotype $\tilde{x}$ undergoes a transition to the phenotype $\tilde{y}$, it first enters the population $\tilde{z}$ and spends a period of time in this group where it does not reproduce. The bacterium then moves from the group $\tilde{z}$ to the phenotype $\tilde{y}$. The group $\tilde{w}$ works in a similar manner for transitions from the phenotype

$\tilde{y}$ to the phenotype $\tilde{x}$. This gives the new model

$$\tilde{x}' = \Gamma_1(E)\tilde{x} - \kappa_1(E)\tilde{x} + \delta_2\tilde{w}, \tag{4a}$$
$$\tilde{y}' = \Gamma_2(E)\tilde{y} - \kappa_2(E)\tilde{y} + \delta_1\tilde{z}, \tag{4b}$$
$$\tilde{z}' = \kappa_1(E)\tilde{x} - \delta_1\tilde{z}, \tag{4c}$$
$$\tilde{w}' = \kappa_2(E)\tilde{y} - \delta_2\tilde{w}, \tag{4d}$$

where $\Gamma_1(E)$ and $\Gamma_2(E)$ are given by equation (2); κ_1 and κ_2 are step functions (3) with the jumps occurring at $E = E_T + \alpha$ and $E = E_T - \alpha$, repectively; and, the parameters δ_1 and δ_2 represent the inverse of the average shock period that the bacteria undergo for changing phenotypes. In order to simulate this model numerically, we perform a change of variables and consider the population of the bacteria in each group in terms of its fraction of the total population. With the change of variables $x = \frac{\tilde{x}}{N}$, $y = \frac{\tilde{y}}{N}$, $z = \frac{\tilde{z}}{N}$ and $w = \frac{\tilde{w}}{N}$ where $N = \tilde{x} + \tilde{y} + \tilde{z} + \tilde{w}$, we obtain

$$x' = \Gamma_1(E)(1-x)x - \kappa_1 x + \delta_2 w - \Gamma_2(E)xy, \tag{5a}$$
$$y' = \Gamma_2(E)(1-y)y - \kappa_2 y + \delta_1 z - \Gamma_1(E)xy, \tag{5b}$$
$$z' = \kappa_1 x - \delta_1 z - \Gamma_1(E)zx - \Gamma_2(E)zy, \tag{5c}$$
$$w' = \kappa_2 y - \delta_2 w - \Gamma_1(E)wx - \Gamma_2(E)wy \tag{5d}$$

for the set of equations (4).

2.2. Analysis and results

The average growth rate, λ, for the system (5) is

$$\lambda = \lim_{t\to\infty} \frac{1}{t} \int_0^t (\Gamma_1(E)x + \Gamma_2(E)y)\,\mathrm{d}\tau, \tag{6}$$

where x and y are the fractional populations of the phenotypes $\tilde{x}$ and $\tilde{y}$ and $\Gamma_1(E)$ and $\Gamma_2(E)$ are the growth rates of those phenotypes. Our interest is to see the effect on the average growth rate of the system when we make changes to the thresholds at which the functions κ_1 and κ_2 change value. We only consider the case of symmetric shifts in the switching thresholds, that is if we change the threshold value by an amount α then the switching threshold of κ_1 is $E_T + \alpha$ and the threshold of κ_2 becomes $E_T - \alpha$. The value of α varies over the range $(-3, 3)$. A negative value of α means that the bacteria begin to change before the environment has stopped favouring their phenotype. Switching in this region we call *predictive* switching as the bacteria attempt to predict changes in the environment before they occur. A zero value of α means that the bacteria switch phenotype when the environment starts to favour the other phenotype marginally stronger. We call switching at this value *environmental* switching, or *memoryless* switching, as the bacteria switch each time the environment passes the point $E = E_T$. A positive value of α means that the bacteria do not switch until a sufficient bias for the other phenotype has been created in the environment. We call this switching *delayed* switching as the bacteria delay changing phenotypes until there is a strong favouring of the other phenotype. A positive α introduces memory into the system as the response of bacteria to variations of the environment depends on their state (phenotype).

The environmental state is chosen to vary as a stochastic single well potential centered at the value E_T. The environmental input to the system of equations (5) is thus given by

$$\mathrm{d}E = -(E - E_T)\mathrm{d}t + \mathrm{d}W_t, \tag{7}$$

where W_t is the Weiner process. As the mean value of E equals $E_T = 0.5$, in the absence of any stochastic fluctuations both phenotypes grow at the same rate.

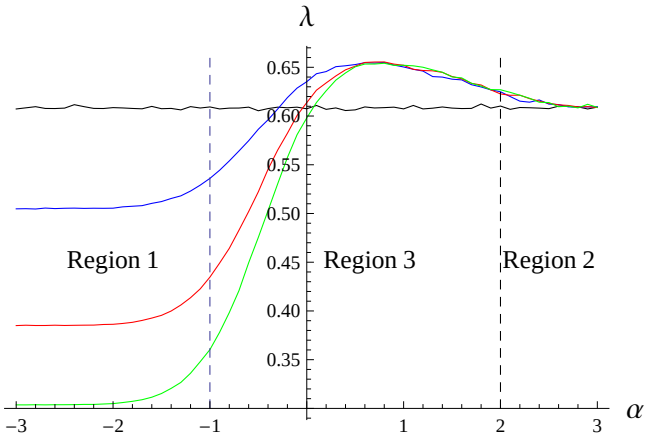


Figure 2: Plot of the average growth rate λ for various α obtained by averaging 20 simulations of the system of equations (5). The black line is for a transition rate $\kappa = 0.0$, the blue line is for $\kappa = 0.5$, the red line is for $\kappa = 1.0$, and the green line is for $\kappa = 1.5$. The other parameters used in the simulations were $\gamma_{unfit} = 0.1$, $\sigma = 1$ and $\delta_{1,2} = 1$. The initial populations of the groups were $x_0 = 0.5$, $y_0 = 0.5$, $z_0 = 0$ and $w_0 = 0$, the environment started from the state $E_0 = 0$.

Figure 2 presents results of numerical integration of system (5) with the input (7). We divide the plot into three regions. We take $\alpha \leq -1$ as region 1, $\alpha \geq 2$ as region 2 and $-1 < \alpha < 2$ as region 3. The black line gives the results for $\kappa = 0$, the case where there is no transitions between phenotypes. Here the average growth rate λ for all the values of α is nearly constant and close to the value $\gamma_{unfit} + 0.5\sigma = 0.6$, which corresponds to the growth rate at $E = E_T$ of both phenotypes. The variability of the line is a result of the stochastic nature of the input to the system and should be eliminated by the inclusion of more simulations.

In region 1, by increasing the value of κ we rapidly decrease the average growth obtained. For red, blue and green lines, the value of α is sufficient so that the environment input rarely reaches the thresholds of κ_1 and κ_2. Since α is negative and the thresholds of the functions κ_1 and κ_2 are rarely reached, the majority of bacteria are nearly always in a transition state. The higher the transition rate κ becomes the higher the percentage of the total population that gets stuck in the groups z and w which do not add to the growth rate of the system, hence lower λ.

In region 2, the value of α is also sufficient so that the environmental input rarely alters the value of the functions κ_1 and κ_2. Since in this region α is positive, both $\kappa_{1,2}$ are nearly always zero and the majority of bacteria are in the non-transition states x, y. In this region, the plots of λ for the non-zero values of κ tend to that obtained for $\kappa = 0$ as α increases.

In region 3, we see that each of the lines corresponding to a non-zero value of κ has a distinct peak average growth rate for some value of $\alpha > 0$. This means that the bacteria modelled by the system of equations (5) with the environment given by equation (7) achieve the maximum average growth rate by the phenotypes behaving under the delayed switching method. That is, they delay switching phenotypes until the environment has a strong favouring of the other phenotype. This delayed switching behaviour is beneficial to the system as a whole as it eliminates any unnecessary switching that may occur as the environment varies stochastically. The unnecessary switching is a result of the environmental input crossing the environmental threshold E_T and then quickly changing back.

3. Multi-species model

3.1. Model equations

We have shown that delaying switching between phenotypes helps bacteria to achieve a higher average growth rate in a stochastic environment in model (5). If bacteria maximise the average growth rate by having a delay of α on the environmental threshold, then, in the case of high transition rate κ, the dynamics of the state that bacteria are in can be modelled by the non-ideal relay, R_α, with thresholds $-\alpha$, α, values ± 1, and input E; for a discussion of the dynamics of the non-ideal relay see, for example, [21]. When $R_\alpha = 1$, the bacteria is in the state (phenotype) which favours the nutrient F_1; if $R_\alpha = -1$, then the bacteria favours the nutrient F_2. Adopting this model for the states of the bacteria, we consider a collection of populations of bacteria with different thresholds α sharing the same food supply. The density of bacteria with the threshold α at a moment t is denoted by $n(t, \alpha)$. We assume that a bacterium can sporadically change its threshold α. We model the resulting variability in α by a diffusion process[2]. With these assumptions, we consider the following model of evolution of bacteria and food,

$$\frac{\partial n}{\partial t} = k\Delta n + \frac{1}{2}(1 + R_\alpha(p; R_\alpha^0))nF_1 + \frac{1}{2}(1 - R_\alpha(p; R_\alpha^0))nF_2, \tag{8a}$$

$$\frac{\mathrm{d}F_1}{\mathrm{d}t} = -\frac{1}{2}F_1 \int_{\underline{\alpha}}^{\overline{\alpha}} (1 + R_\alpha(p; R_\alpha^0))n \,\mathrm{d}\alpha, \tag{8b}$$

$$\frac{\mathrm{d}F_2}{\mathrm{d}t} = -\frac{1}{2}F_2 \int_{\underline{\alpha}}^{\overline{\alpha}} (1 - R_\alpha(p; R_\alpha^0))n \,\mathrm{d}\alpha. \tag{8c}$$

Here all the non-ideal relays have the same input $p = E - E_T$ where $E = F_1/(F_1 + F_2)$, $E_T = 0.5$; the state $R_\alpha(p; R_\alpha^0)$ of the non-ideal relay R_α is a binary function of time; R_α^0 denotes the initial state of this relay; k is the rate at which the diffusion of the thresholds in the birth process occurs; $\frac{1}{2}(1 + R_\alpha)F_1 n$ is the growth rate for bacteria in the state 1; and, $\frac{1}{2}(1 - R_\alpha)F_2 n$ is the growth rate for bacteria in the state -1. Both growth rates are proportional to the population density with the coefficient of proportionality scaled to unity. The rate of consumption of food in the equation for $F_i = F_i(t)$ is proportional to the total number of bacteria in the phenotype eating this type of food, hence the integral (the coefficient of proportionality is also set to unity for simplicity); $\underline{\alpha}$ and $\overline{\alpha}$ are the lower and upper bounds on available threshold values, respectively. A certain amount of food is available at the initial moment; the food is not supplied after that moment. Bacteria do not die but stop growing when all the food has been consumed.

In model (8), we make the assumption that for a given α all the bacteria with this α value are in the same state at a particular time moment. That is, $n(t, \alpha)$ is the total population of bacteria with the threshold α at the moment t and they are all in the same state. It means that when a bacterium with a threshold α' sporadically changes its threshold to a different value α, it simultaneously copies the state from other bacteria which have the threshold α. In particular, this may require a bacterium to change the state when its threshold changes. Models where the state of a bacterium remains unchanged after a change of the threshold will be considered in a different work.

To complete the model, we assume that α values of bacteria are restricted to a selected region $\underline{\alpha} \le \alpha \le \overline{\alpha}$ and so apply the Neumann boundary conditions

$$\frac{\partial n}{\partial \alpha} = 0, \quad \alpha = \underline{\alpha}, \overline{\alpha}$$

to system (8). Replacing the variables F_1, F_2 with the new variables $F = F_1 + F_2$, the total food, and $p = E - E_T = F_1/(F_1 + F_2) - 0.5$, the deviation of the fraction of the food F_1 from

[2] Additional diffusion can occur in the birth process if we assume that a bacterium with a threshold α produces offsprings with different thresholds, for example, according to the Gaussian distribution centered at α

0.5, we obtain the equivalent system

$$\frac{\partial n}{\partial t} = k\Delta n + \frac{1}{2}Fn + pFnR_\alpha(p; R^0_\alpha), \tag{9a}$$

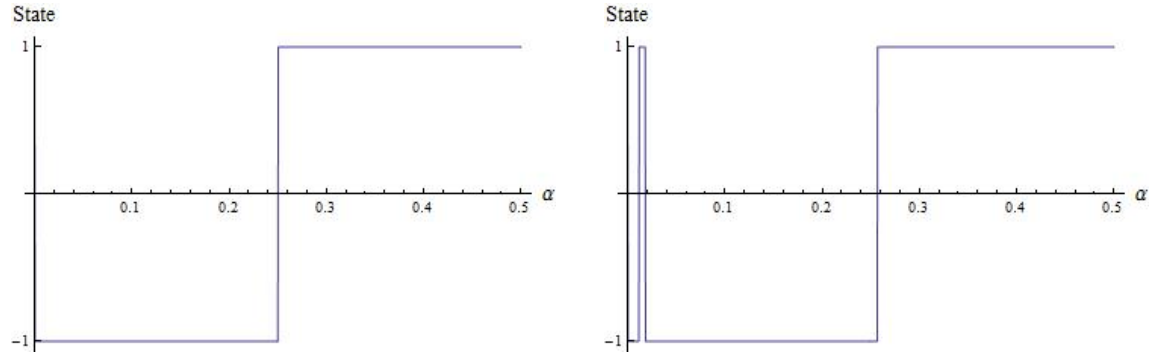
$$\frac{\mathrm{d}F}{\mathrm{d}t} = -\frac{1}{2}F\int_{\underline{\alpha}}^{\overline{\alpha}} n\,\mathrm{d}\alpha - pF\int_{\underline{\alpha}}^{\overline{\alpha}} nR_\alpha(p; R^0_\alpha)\,\mathrm{d}\alpha, \tag{9b}$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = (p^2 - \frac{1}{4})\int_{\underline{\alpha}}^{\overline{\alpha}} nR_\alpha(p; R^0_\alpha)\,\mathrm{d}\alpha. \tag{9c}$$

The last integral in the second equation and the integral term in the last equation are the Preisach operator with the input $p = p(t)$ and the time dependent density function $n(t, \alpha)$ concentrated on the bisector of the Preisach half-plane [21]. Well-posedness of this system has been established in [22].

3.2. Results for the multi-species model

The distribution of phenotypes for different threshold values after long time simulation of system (9) is shown in Figures 3 and 4. In each simulation, the distribution, which at any point in time is a binary function of α, stabilises to some stationary limit profile. Initially, all the non-ideal relays were set to be in the state $R^0_\alpha = 1$, $\underline{\alpha} \le \alpha \le \overline{\alpha}$. The initial population density $n(0, \alpha)$ was set to a non-zero value at the point $\alpha = \overline{\alpha}$ and to zero in all the other nodes of the α-mesh; that is, all the population initially consisted of bacteria with the largest threshold. The food supply was equally distributed between the food types F_1 and F_2, that is the initial value of p was $p(0) = 0$.



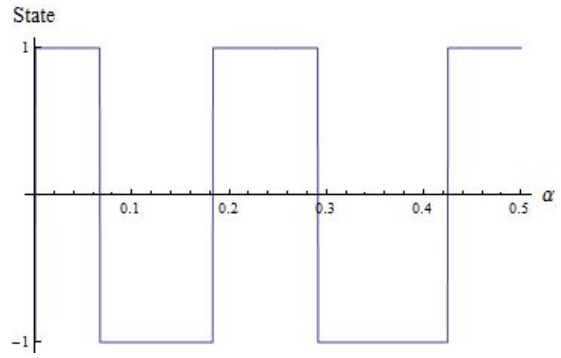
(a) The initial food supply $F(0) = 10$ and the diffusion rate $k = 0.1$.

(b) The initial food supply $F(0) = 100$ and the diffusion rate $k = 0.1$.

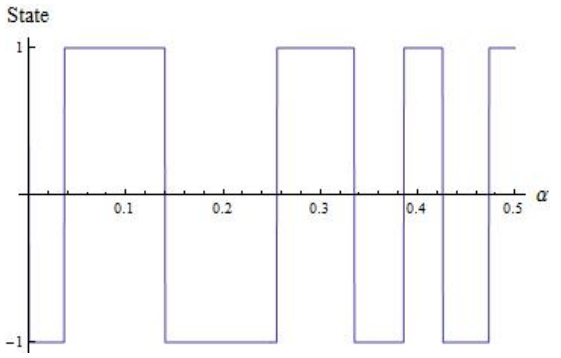
Figure 3: Stationary limit distribution of the states of the relays after long time simulation of the system (9) in case of faster diffusion. The range of available thresholds is $[\underline{\alpha}, \overline{\alpha}] = [0, 0.5]$.

By comparing Figures 3a and 4a, we see that with the decrease of the diffusion rate, k, the limit distribution takes on a different form. In the case of faster diffusion between populations with different α, the phenotypes split equally into two regions, those in the region $0 \le \alpha \le 0.25$ are in the state -1 and those in the region $0.25 < \alpha \le 0.5$ are in the state 1. In the case of slower diffusion, we observe a more oscillatory pattern in the limit distribution. In both cases, the density n converges to the same constant value.

Figures 3b and 4b show the changes in the distribution caused by increasing the initial food supply. Increasing the initial food supply increases the number of oscillations in the distribution of the relays. Decreasing the diffusion rate has a greater effect on causing the distribution to take on an oscillatory pattern.



(a) The initial food supply $F(0) = 10$ and the diffusion rate $k = 0.001$.



(b) The initial food supply $F(0) = 100$ and the diffusion rate $k = 0.001$.

Figure 4: Stationary limit distribution of the states of the relays after long time simulation of the system (9) in case of slower diffusion. The range of available thresholds is $[\underline{\alpha}, \overline{\alpha}] = [0, 0.5]$.

4. Conclusions

We developed a model for two phenotype bacteria with a cost for transitioning between phenotypes and saw that, in an environment that varies stochastically, the average growth rate of the system could be maximised by the bacteria delaying the phenotype switching until there was a stronger favouring of the other phenotype. Dynamics of the optimal system can be interpreted as a kind of a probabilistic memory switch, or relay, driven by a varying input (environment). The standard deterministic non-ideal relay R_α switches from state -1 to state 1 when the input reaches the threshold value α, and switches back when the input achieves the value $-\alpha$; transitions in both directions are instantaneous. We define the switching rules for the probabilistic relay as follows. The relay does not switch from state -1 to state 1 as long as the input satisfies $p < \alpha$. When $p > \alpha$, we assume a positive transition probability rate κ for transitioning from -1 to 1 (that is, the exponential distribution of the resident time in state -1 before switching, as in the Poisson process). Similarly, there is no switching from state 1 to -1 as long as $p > -\alpha$; and, the transition probability rate $\kappa > 0$ when $p < -\alpha$.

In model (5), we also have an intermediate state, so that when the relay departs from state -1 (or, 1) , it spends a period of time in the intermediate state before arriving in state 1 (state -1, respectively). A similar behaviour of the probabilistic relay can be achieved by adding two intermediate states A and B; assuming the transition probability rate $\kappa > 0$ from state -1 to A when $p > \alpha$ and zero probability rate from -1 to A for $p < \alpha$; assuming a positive probability rate δ_1 from A to 1 (independent of the value of p); and, similarly, assuming the transition probability rate κ from state 1 to B when $p < -\alpha$, zero probability rate from 1 to B for $p > -\alpha$, and a positive probability rate δ_2 from B to -1 independent of p. With this modification, the evolution of the probabilities to find the probabilistic non-ideal relay in states $-1, 1, A, B$ is described by deterministic equations similar to (5).

The above dynamics, which is achieved in model (5) for positive α, can maximise the growth rate of the population of bacteria in a stochastic environment if a typical time that bacteria spend in the intermediate states is comparable to the characteristic time of the input variation. A positive delay α prevents transitions from less to more favoured phenotype when favouring is not strong. A slight decrease in the growth rate due to small fluctuations of the environment from the point E_T can be less dramatic than a drop in the growth rate due to passing through the intermediate states where bacteria do not reproduce. This trade off between too much responsiveness (small α), with the associated cost of often transitions, and too much inertia (large α), which leaves too many bacteria in unfavoured states, shifts α_{opt} to the positive range

provided that the time bacteria have to spend in the intermediate states is significant.

If transitions between the states are fast compared to the time scale of input variations (large κ and $\delta_{1,2}$), then dynamics of system (5) can be approximated by the deterministic non-ideal relay R_α. For example, this is the case if we consider a population of bacteria which are best fit to some stochastic environmental input with $\alpha \approx \alpha_{opt}$ in model (5), and then change the input to a much slower, less variable, or more predictable environment (such as, for instance, in a lab). In the new environment E_{slow}, nearly all the population, at almost any given instant on the slow time scale, will have the same phenotype; transitions between the phenotypes will be almost instantaneous; and, switching between the two phenotypes will be described by the deterministic non-ideal relay R_α with the input E_{slow}; that is, the system will demonstrate persistent bistable (hysteretic) memory.

Assuming this simpler switching regime, we considered a reaction-diffusion model of multiple populations of bacteria competing for food. The switching rules for each population were modelled by the deterministic relay R_α; the populations were parametrised by the thresholds α varying over an interval of values. In our model, a finite amount of food is available, bacteria stop growing but do not die when all the food has been consumed, and the population density $n(t, \alpha)$ tends to a positive constant as t increases. We have shown numerically that a binary function describing the distribution of two phenotypes among bacteria with different α also converges to a stationary pattern. However, this sign changing pattern is different for different initial data. The limit stationary pattern becomes more oscillatory with the increase of the initial food supply. The limit pattern is sensitive to the diffusion rate between species with different thresholds. Lowering the diffusion rate leads to more oscillatory patterns.

It would be interesting to consider variations of the multi-species model (9) and their effect on the attractor and the pattern formation. Possible modifications might account for the death process and constant or variable food supply; testing the model with no diffusion process; the inclusion of relays $R_{\alpha,\beta}$ with asymmetric thresholds α, β, $\beta \neq -\alpha$; variations of the boundary conditions; replacing each deterministic relay with the differential model (5); or, modelling populations by a collection of probabilistic memory switches using stochastic differential equations. Systems of reaction-diffusion equations coupled to ordinary differential equations with bistable dynamics have been used in [23, 24] to model the formation of spatial patterns observed experimentally in a culture of bacteria grown in a Petri dish. An important assumption we made in multi-species model (9) was that bacteria, when sporadically changing their threshold α' to a new value α, simultaneously copy the state from their peers who have the same threshold α. It would be natural to explore a model where the state remains unchanged when the threshold changes. Such a model should have simultaneous nonzero populations of bacteria with the same threshold in two phenotypes. This is a subject of future work.

The nonlocal terms introduced by the integral $\int_{\underline{\alpha}}^{\overline{\alpha}} nR_\alpha(p; R^0_\alpha)\, \mathrm{d}\alpha$ in equations (9) is the Preisach operator with the input p and the time dependent density function $n(t, \alpha)$. The evolution of the Preisach density function is coupled to the evolution of other variables in the system. This contrasts to all the variety of known applications of the Preisach operator model, where one needs to know the Preisach density function *a priori* in order to parametrise the model [25] and analyze dynamics (see, for example, [26–37]). Identification of the Preisach density function is a daunting task requiring multiple experiments in applied physics and engineering [38]; measurements of the density function in applications to economics and finance are even less accessible. In model (9) and its modifications, the profile of the density function at any moment is defined by its initial profile $n(0, \alpha)$. However, if one is interested in long term behaviour, then no (or, little) information about the initial profile is needed provided that the attractor has a simple structure. That is, in this case, one does not need to solve the problem of identification of the Preisach operator density function. On the other hand, we have shown that the diffusive evolution of the Preisach density function leads to a new mechanism of pattern

formation, which is not observed in systems with the steady Preisach density functions.

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