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## Bet-hedging in stochastically switching environments

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#### HIGHLIGHTS

• Bet-hedging in stochastically switching environments is analzed via adaptive dynamics.

• Expansions of Lyapunoc exponents for linear 2-dim. systems and different time scales are derived.

• Fast time-scale: homogeneous phenotype, adapted to the average environment is optimal.

• Middle range time scale: bet-hedging is optimal.

• Slow time scale: phenotype adapted to one environment only is optimal.

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#### ABSTRACT

We investigate the evolution of bet-hedging in a population that experiences a stochastically switching environment by means of adaptive dynamics. The aim is to extend known results to the situation at hand, and to deepen the understanding of the range of validity of these results. We find three different types of evolutionarily stable strategies (ESSs) depending on the frequency at which the environment changes: for a rapid change, a monomorphic phenotype adapted to the mean environment; for an intermediate range, a bimorphic bet-hedging phenotype; for slowly changing environments, a monomorphic phenotype adapted to the current environment. While the last result is only obtained by means of heuristic arguments and simulations, the first two results are based on the analysis of Lyapunov exponents for stochastically switching systems.

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#### 1. Introduction

In recent years, it has become more and more evident that isogenic bacterial populations show different phenotypes. This phenomenon is also known as phenotypic heterogeneity and is often connected to bistability in regulatory pathways. A textbook example is persister cells in *Escherichia coli*: a certain fraction of the population largely deactivates their metabolism and rest. These cells do not divide and so stop contributing to the population growth, but they survive antibiotic attacks while active cells are

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killed. At the time the antibiotics are removed from the environment, some persisters can wake up again and form the nucleus of a re-appearing population (Balaban et al., 2004). Another example is the lactose metabolism of *E. coli*: if a gratuitous inducer (an inducer that is not metabolized but is able to bind to the repressor of the lac operon) is present, a part of the bacteria does and a part does not express *lac* (Smits et al., 2006). Obviously, the rational of this effect is related to the changing lactose densities in the environment. A third example is *Vibrio harveyi* that communicates by a quorumsensing system. It has been shown that only a fraction of the cells respond to the signaling molecules in this communication, though the population is clonal and all cells maintain the ability to produce and to sense the signals. The deeper reason for this observation is still unclear (Anetzberger et al., 2009). More examples can be found in the review paper of Smits et al. (2006).

These observations trigger two different questions. (i) What are the molecular mechanisms of the regulatory networks utilized to create heterogeneity? (ii) What is the purpose of this strategy in the light of evolution?

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The answer to the first question, which is not the focus of the present work, has been a major research topic in recent years: bacteria often make use of bistable pathways in combination with stochasticity due to small molecule numbers (Balaban et al., 2004; Elowitz et al., 2002; Ribeiro, 2008; Satory et al., 2011; Müller et al., 2008) in order to create heterogeneity. The regulatory systems are designed to switch stochastically between different states; the rate at which a cell jumps between the states as well as the fraction of the population that is in a certain state can be adapted to the environmental statistics very precisely over a wide range.

The present work primarily deals with the second question raised above: why, under which conditions, are observed bimorphic phenotypes evolutionarily stable? Bimorphism should provide a selective growth advantage over monomorphism, otherwise we do not expect this strategy to be evolutionarily stable. This point is of major interest as the two-type strategy may be considered as the beginning of a differentiation between different types of cells. It could be interpreted as a first step toward a system of specialized cells acting as a unit, perhaps even as an early form from which multicellular organisms evolved. Fluctuations of environmental conditions seem to be one of the main reasons for bimorphic strategies (Gaal et al., 2012) and bet-hedging in the sense of risk minimization (de Jong et al., 2011), though not the only scenario that promotes heterogeneity (Ackermann et al., 2008). We take up the basic ideas of Gaal et al. (2012) and consider an environment that assumes two different states (cold and hot, rainy and dry, etc.). We assume that no monomorphic phenotype can be optimal to cope with both environments in that different properties are required for adaptation. We furthermore assume that it is not possible or too expensive to maintain the properties of both phenotypes within one cell and that an active switching in response to the environment does not lead to desirable results, e.g. because the production of sensory molecules necessary to recognize the current environment is too expensive, or because active switching is too slow. Therefore, e.g. at the time of cell division, daughter cells decide about the type they become, or cells actively switch phenotype later in their life, but in the latter case not in response to the current environment but at a constant rate.

The role of adaptation in response to fluctuating environments has been discussed for a long time in theoretical population genetics; the first papers have been concerned with obtaining some idea of which mutation rates in slowly changing environments would be optimal in the sense that they keep the balance between adaptedness and adaptability in an optimal way (Kimura, 1967; Leigh, 1970). A number of papers (see e.g. Cohen, 1966; Ellner and Hairston, 1994; Sasaki and Ellner, 1995; Svardal et al., 2011 and references therein) focussed on a classical model for seed that either germinate soon or hibernate (or assume other inactive, long-living phenotypes) for time-discrete models with variable environments. In these papers it is proven that genotypic variations are stable that evolutionary branching points in the sense of Metz et al. (1995) and Geritz et al. (1998) do occur. These papers focussed on the consideration of genotypes; given a genotype, an individual selects its phenotype from a given distribution. The phenotype is neither changed during life nor depends on the mother's phenotype. In these models, strategies interpreted as bet-hedging appeared to be optimal in varying environment: if some offspring hibernates for years, there will be germinating offspring in favorable years, even if they are relatively seldom and randomly distributed. The seeds of a plant "test" each year, and the successful seed is able to produce a lot of offspring, compensating for the less lucky seeds that fail to reproduce.

Only recently, bacteria became model organisms to investigate not a genotypic but a certain phenotypic heterogeneity known as bet-hedging (Acar et al., 2007). This model and its successors differ from those mentioned above in that these new models allow individuals to change their phenotype during live, resp. to allow the daughter cell's phenotype to depend on that of their mothers. Based on numerical simulations, a link between the rate at which the environment switches and the rate at which a bimorphic phenotype of bacteria changes its subtype has been conjectured already in that paper (Acar et al., 2007). This conjecture has been confirmed in a time-discrete setup considering models with a finite number of individuals (King and Masel, 2007; Fudenberg and Imgof, 2012). The implications of periodic environments have been analyzed by Pang and Tzeng (2008) and Gaal et al. (2012). In the present work, we extend these considerations to a stochastically fluctuating environment. Stochastic environments have been considered in Salathe et al. (2009) and Thattai and van Oudenaarden (2004), mainly by means of Monte Carlo simulations. Kussell and Leibler (2005) proposed a heuristic approximation of the Lyapunov exponent based on a separation of time scales, while Jablonka et al. (1995) focus on upper and lower estimates for the Lyapunov exponent. Here, we were able to extend the results of Gaal et al.: for rapidly switching environments, a monomorphic type, adapted to the averaged conditions, is optimal; if the environment switches on an intermediate timescale, a bimorphic bet-hedger strategy is optimal; the rates at which the types are changed are - up to higher order terms - one over the average time the corresponding environment is present. However, if the time scale of the environmental change becomes even slower, then a monomorphic type adapted to the current environment will outcompete the bet-hedger. This is, for very rapidly and very slowly changing environments, we find one monomorphic type; the difference is that this type is adapted to the average environment in the first case, and to the current environment in the second type.

The paper is structured as follows: In Section 2.1, we develop a model for large populations in stochastically changing environments: the population dynamics itself can be formulated in a deterministic manner, and the environment switches stochastically between two different states. The results of the model analysis are summarized in Section 2.2. The proofs of the results, which are rather technical, can be found in the appendix. Section 2.3 is devoted to a heuristic discussion of a completely stochastic model, where also the populations themselves follow a stochastic birth-death process. These considerations illuminate the range of validity of the results derived in the first two subsections, and give some hint from which effects are to be expected in completely stochastic models. In contrast to the deterministic setup, in the case of a slowly changing environment, the completely stochastic model predicts that cells exhibiting a monomorphic phenotype, adapted to one environment only, will perform best. However, it is out of scope for the present work to perform a strict analysis of this completely stochastic case. In Section 3 we discuss the results obtained so far and their relevance for biological systems.

The appendix is split into two parts: in Appendix A the Lyapunov exponent of a stochastically switching system, that jumps between two linear, two-dimensional ordinary differential equations (ODEs), is determined. In particular, the asymptotics of the Lyapunov exponent for switching on a rapid respectively very slow time scale is discussed. These formulas are applied to our model in Appendix B in order to prove the theorems stated in Section 2.2.

#### 2. Bet-hedging in a stochastic environment

#### 2.1. Model

We develop a model for a population with two phenotypes in a stochastically switching environment. Adaptive dynamics will be Download English Version:

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