Theoretical Population Biology 86 (2013) 29–42

Contents lists available at SciVerse ScienceDirect

Theoretical Population Biology

journal homepage: www.elsevier.com/locate/tpb

Evolution with stochastic fitnesses: A role for recombination

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HIGHLIGHTS

- We investigate the effect of recombination on the geometric mean principle under different environmental regimens and fitness landscapes.
- We determine invisibility conditions for modifiers of fitness variance.
- We show that only alleles that reduce variance in fitness can invade a population and this invasion threshold is an increasing function of the recombination rate.
- Under some conditions, an allele with a lower geometric mean fitness can achieve highest frequency in the population.

ARTICLE INFO

Article history:
Received 4 October 2012
Available online 18 March 2013

Keywords:
Fluctuating environments
Stochastic fitness
Recombination
Variance modifiers
Adaptive evolution

ABSTRACT

Phenotypic adaptation to fluctuating environments has been an important focus in the population genetic literature. Previous studies have shown that evolution under temporal variation is determined not only by expected fitness in a given generation, but also by the degree of variation in fitness over generations; in an uncertain environment, alleles that increase the geometric mean fitness can invade a randomly mating population at equilibrium. This geometric mean principle governs the evolutionary interplay of genes controlling mean phenotype and genes controlling phenotypic variation, such as genetic regulators of the epigenetic machinery. Thus, it establishes an important role for stochastic epigenetic variation in adaptation to fluctuating environments: by modifying the geometric mean fitness, variance-modifying genes can change the course of evolution and determine the long-term trajectory of the evolving system. The role of phenotypic variance has previously been studied in systems in which the only driving force is natural selection, and there is no recombination between mean- and variance-modifying genes. Here, we develop a population genetic model to investigate the effect of recombination between mean- and variance-modifiers of phenotype on the geometric mean principle under different environmental regimes and fitness landscapes. We show that interactions of recombination with stochastic epigenetic variation and environmental fluctuations can give rise to complex evolutionary dynamics that differ from those in systems with no recombination.

1. Introduction

Organismal response to environmental variability is viewed as one of the major forces driving evolution. Fluctuating environments can have important effects on genetic systems; for example, on robustness (Wagner, 2007; Lenski et al., 2006; Ciliberti et al., 2007; Wagner, 2008; Soyer and Pfeiffer, 2010), on evolvability (Draghi and Wagner, 2009; Earl and Deem, 2004), on genotype–phenotype mapping (Wagner and Altenberg, 1996), and on diversity and survival (Wolf et al., 2005; Kussell and Leibler, 2005; Acar et al., 2008). Environmental uncertainty is also hypothesized to expedite evolution (Kashtan et al., 2007) and the emergence of complex traits (Wakano and Aoki, 2006).

Since the early work of Haldane and Jayakar (1963), Kimura (1965), Ewens (1967), Levins (1968) and Lewontin and Cohen (1969), it has become clear that the ability to respond to environmental variability has a selective advantage and models incorporating stochastic fluctuations in fitness are an important part of the population genetic literature (Felsenstein, 1976; Dempster, 1955; Jablonka et al., 1995; Ancel and Fontana, 2000; Lachmann and Jablonka, 1996; Frank and Slatkin, 1990). Gillespie (1973a,b), Hartl and Cook (1973) and Karlin and Liberman (1974, 1975) first showed that the evolution of a system under temporal fluctuations is determined not only by expected fitness in a given generation, but also by the degree of variation in fitness over time, and established the geometric mean fitness principle (Frank, 2011; Lande, 2008), which states that in a random environment, alleles that

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http://dx.doi.org/10.1016/j.tpb.2013.02.005

increase the geometric mean fitness can invade a randomly mating population at equilibrium. It follows that an allele with higher mean fitness can be outcompeted by one with lower mean fitness if the variance of the latter's fitness is sufficiently lower than that of the former.

It is only recently that the question of how different alleles can regulate phenotypic variance has started to receive more attention. Recent empirical and theoretical analyses have looked at variation in phenotypic stochasticity (Jimenez-Gomez et al., 2011), in developmental stability (Ordas et al., 2008) and have found variance-controlling alleles in chickens (Rowe et al., 2006), snails (Ros, 2004) and pigs (Sorensen and Waagepetersen, 2003). In addition, genome wide association studies have been performed with the goal of identifying variance-heterogeneity GWAS, or vGWAS, loci that affect phenotypic variability (Shen et al., 2012; Ronnegard and Valdar, 2011, 2012; Hulse and Cai, 2012). These studies have found that variance-modifying loci (referred to as v- or ev-QTLs) can be as common as mean-modifying loci and can, in some cases, explain more than 20% of the phenotypic variance (Shen et al., 2012).

The exact biological mechanisms behind these variance-controlling alleles are still unclear. Recent analyses of the role of stochastic epigenetic/non-genetic variation in short- and long-term evolution (Johannes et al., 2009; Cubas et al., 1999; Bonduriansky and Day, 2009; Danchin et al., 2011; Thattai and van Oudenaarden, 2004; Salathe et al., 2009; Bjornsson et al., 2004; Youngson and Whitelaw, 2008; Johnson and Tricker, 2010) have added a new dimension to the qualitative importance of these models and could help shed light on the processes involved. We propose that interpreting variation in fitness as epigenetically-determined noise that results in phenotypic variation can help to elucidate the evolutionary significance of epigenetic variation, and provide new insights into how genetic and epigenetic patterns of diversity interact in constant or fluctuating environments. For example, in a system with two loci, one controlling mean phenotype (the mean locus) and one "epilocus" controlling the variability of the phenotype (Feinberg and Irizarry, 2010; Carja and Feldman, 2012), the geometric mean principle entails that the interaction between these loci will determine the evolution of the system. Thus variance-modifying epigenes could change the course of evolution at mean-modifying genes and determine the long-term trajectory of the evolving system.

Most theoretical treatments of temporal variation in fitness do not specifically include recombination in their evolutionary dynamics. However, a trans-acting, variance-modifying regulatory epiallele as discussed above is likely to recombine with the mean-modifying loci that it regulates. How does recombination affect the geometric mean principle? Work on the evolution of recombination rates in heterogeneous environments suggests that fluctuating selection may favor increased recombination when the direction of selection changes appropriately over time; thus the reduction principle (Liberman and Feldman, 1986; Feldman and Liberman, 1986), which holds at equilibrium in constant environments, does not always apply in changing environments (Otto and Michalakis, 2007; Lenormand and Otto, 2000; Charlesworth, 1976, 1993). This is hypothesized to be due to recombination, which may allow a population to keep up with environmental changes by producing appropriate novel allelic combinations (Robson et al., 1999; Manos et al., 2000). Recombination also plays important roles in determining equilibria and stability in constant fitness regimes (Karlin and Feldman, 1970). All these point to the importance of studying the effect of recombination on the geometric mean fitness principle in genetic systems experiencing fluctuating selection.

In this paper, we investigate conditions under which variance-modifying genes can change the course of evolution at mean-modifying genes and how recombination affects these conditions. Motivated by the observations that genetic and/or epigenetic control of phenotypic variance appears to be widespread, we develop a population genetic model for the evolution of variance-modifying genes; genes that are drivers of the epigenetic machinery could represent a possible mechanism for this variance modification. Epigenetic plasticity across a diverse array of developmental stages, tissue types and environmental conditions can produce phenotypic variance whose evolution could be subject to the interaction between the form of natural selection and the rate of recombination. We investigate the geometric mean fitness principle for systems with recombination and address how recombination and the moments of randomly varying selection parameters affect their evolutionary dynamics.

2. The model: one single random environment

Consider a random mating haploid population large enough that genetic drift can be ignored. Each individual in this population is defined by two bi-allelic loci, A/a and M/m, and the four genotypes AM, aM, Am and am have frequencies denoted by x_1, x_2, x_3 and x_4, respectively.

We assume that the locus A/a controls the mean phenotype and the locus M/m controls the variance of this phenotype; that is, M/m controls the expression of statistical variance in the phenotype without affecting its expectation. M/m could represent a locus that regulates the epigenetic machinery that affects epigenetic plasticity during development. We study the co-evolutionary dynamics of these four genotypes and in particular how the M/m locus affects invasion at the A/a locus and its subsequent evolution. The phenotype here is fitness, which may fluctuate over time:

$$\begin{array}{ll} \text{Genotype} & AM \quad aM \quad Am \quad am \\ \text{Fitness} & \sigma_{AM} \quad \sigma_{aM} \quad \sigma_{Am} \quad \sigma_{am}. \end{array}$$

Here $\sigma = (\sigma_{AM}, \sigma_{aM}, \sigma_{Am}, \sigma_{am})$ is a vector of random variables independent and identically distributed over generations. In the particular case where M/m affects only the variance in fitness, we would have $E(\sigma_{AM}) = E(\sigma_{Am})$ and $E(\sigma_{aM}) = E(\sigma_{am})$, while $\mathrm{Var}(\sigma_{AM}) = \mathrm{Var}(\sigma_{aM})$ and $\mathrm{Var}(\sigma_{Am}) = \mathrm{Var}(\sigma_{am})$. In most of the subsequent analysis, we will focus on the case in which the alternative allele at the mean modifying A/a locus can invade and spread in a population only in association with a variance-modifying allele. Therefore, if we are assuming AM fixed in the population, we will study the case in which an initial small frequency of m allele can lead to invasion and spread of am genotype in the system.

The baseline for comparison in such a system is a constant environment, where σ_i are fixed numerical values that do not change over time. The forces acting on the population are recombination and selection, in that order. The evolution of the four genotypes over time is determined by the recursions

$$\begin{aligned} \overline{\omega} x_1' &= \sigma_{AM}(x_1 - rD) \\ \overline{\omega} x_2' &= \sigma_{aM}(x_2 + rD) \\ \overline{\omega} x_3' &= \sigma_{Am}(x_3 + rD) \\ \overline{\omega} x_4' &= \sigma_{am}(x_4 - rD), \end{aligned} \tag{1}$$

where r is the recombination rate, $D = x_1x_4 - x_2x_3$ is the linkage disequilibrium and $\overline{\omega} = \sigma_{AM}x_1 + \sigma_{aM}x_2 + \sigma_{Am}x_3 + \sigma_{am}x_4 - rD(\sigma_{AM} - \sigma_{aM} - \sigma_{Am} + \sigma_{am})$ is a normalizing factor and the sum of the right-hand sides.

Near fixation of AM, which is represented as $\hat{\mathbf{e}}_1 = (1, 0, 0, 0)$, the fate of an initially small frequency of the m allele, namely the local stability of $\hat{\mathbf{e}}_1$, is determined by the matrix

$$\mathbf{S} = \begin{pmatrix} \frac{\sigma_{aM}}{\sigma_{AM}} & 0 & r\frac{\sigma_{aM}}{\sigma_{AM}} \\ 0 & \frac{\sigma_{Am}}{\sigma_{AM}} & r\frac{\sigma_{Am}}{\sigma_{AM}} \\ 0 & 0 & (1-r)\frac{\sigma_{am}}{\sigma_{AM}} \end{pmatrix}, \tag{2}$$