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# Evolution of reduced mutation under frequency-dependent selection

Uri Liberman[a], Hilla Behar[b], Marcus W. Feldman[b,*]

[a] *School of Mathematical Sciences, Tel Aviv University, Tel Aviv, 69978, Israel*
[b] *Department of Biology, Stanford University, Stanford, CA 94305-5020, United States*

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ABSTRACT

Most models for the evolution of mutation under frequency-dependent selection involve some form of host–parasite interaction. These generally involve cyclic dynamics under which mutation may increase. Here we show that the reduction principle for the evolution of mutation, which is generally true for frequency-independent selection, also holds under frequency-dependent selection on haploids and diploids that does not involve cyclic dynamics.

## 1. Introduction

In large populations, when the selection on one or more genetic loci is constant over time (and hence frequency-independent), and there is mutation (or recombination) among the alleles at these loci, the Reduction Principle applies (Feldman and Liberman, 1986). The Reduction Principle states that a new allele introduced at a locus that controls the mutation (or recombination) rate among the alleles under selection at other (linked or unlinked) loci near a stable equilibrium of the mutation–selection system (or recombination–selection system with linkage disequilibrium) will invade the population if it reduces the mutation (or recombination) rate (Liberman and Feldman, 1986a,b). The same reduction result holds for a gene that modifies migration in a migration–selection system (Liberman and Feldman, 1989). The gene or genes on which selection occurs are usually called "major", while the locus controlling the parameter of interest (rate of mutation, recombination, or migration) is called the "modifier" locus (Feldman et al., 1997). The Reduction Principle applies to alleles that reduce mutation, recombination, and migration rates under any constant selection regime that allows an appropriate stable equilibrium at which the modifier allele is introduced.

These evolutionary genetic models suggest an alternative to the phenotypic dynamic approach, usually called "evolutionarily stable strategy" (ESS), that Eshel and Feldman (1982) termed "evolutionary genetic stability" (EGS). The latter applies to both haploid and diploid evolutionary dynamics. In the cases of mutation, recombination, and migration rates, the value zero has the property of EGS. For the case of mutation rate, Rosenbloom and Allen (2014) use the terminology "evolutionary stable mutation rate" (ESMR) to mean exactly the same thing. That the value zero has the property of EGS also entails that when the relevant rate is zero, a new modifier allele that increases the rate to a positive value cannot increase in frequency at a geometric rate.

Violations of the Reduction Principle have been demonstrated under a number of model scenarios that violate the conditions stated above. For example, increased recombination may evolve if the recombination-increasing allele arises while the major loci are proceeding towards fixation (Maynard Smith, 1980, 1988; Bergman and Feldman, 1990). Increased recombination may also evolve when the major loci are under cyclically fluctuating selection, either exogenously caused (Charlesworth, 1976) or induced by host–parasite dynamics (Hamilton, 1980; Nee, 1989; Gandon and Otto, 2007).

Mutation rates may also increase under some patterns of fluctuating selection. This is often studied in the context of phenotypic switching between phenotypes, represented in population genetic models as different haploid genotypes. Experimental (Acar et al., 2005, 2008) and theoretical analyses (Leigh, 1970; Ishii et al., 1989; Lachmann and Jablonka, 1996; Thattai and van Oudenaarden, 2004; Kussell and Leibler, 2005; Gaal et al., 2010; Liberman et al., 2011) have shown that cyclically (and some forms of stochastically) fluctuating selection can select for alleles that increase mutation rates. However, the direction of change in mutation rates can be very sensitive to the form of selection on the major loci, for example, whether it is symmetric (Salathe et al., 2009; Liberman et al., 2011; Carja et al., 2014). The fluctuations in the selection regime assumed in these studies are exogenous.

Most studies of mutation rate evolution with endogenously changing selection have involved some form of host–parasite (or

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[*] Corresponding author.
*E-mail addresses:* uril@tauex.tau.ac.il (U. Liberman), hilla.behar2@gmail.com (H. Behar), mfeldman@stanford.edu (M.W. Feldman).

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host–virus) interaction (Haraguchi and Sasaki, 1996; Kamp et al., 2003; Pal et al., 2007; M'Gonigle et al., 2009). Mutation rates can increase under host–parasite cycling. However, M'Gonigle et al. show that the stable mutation rate decreases as the recombination between the modifier and major genes increases. A different kind of cyclical trait dynamics was used by Rosenbloom and Allen (2014) in their analysis of the effect of frequency-dependent selection on the evolution of the mutation rate. In their model, the cycling was generated by "rock–paper–scissors" competition. The analysis of the invasion process for this model was carried out using adaptive dynamics, namely comparison of the marginal fitnesses of different mutation-modifying alleles. This analysis must be distinguished from the formal multi-dimensional analysis of modifier evolution that has become standard in population genetics (Feldman et al., 1997). Rosenbloom and Allen (loc. cit.) found an evolutionarily stable mutation rate (ESMR) that was non-zero. They also found, as did M'Gonigle et al. in the host–parasite case, that recombination (as modeled in their scheme, which is somewhat different from the way recombination is incorporated into population genetic models) reduced the stable mutation rate.

Although the model of Rosenbloom and Allen (2014) and its predecessor Allen and Rosenbloom (2012) were developed in terms of continuous time, the stability analyses that determined invasion made use of the Perron–Frobenius structure of the local stability matrix near the invaded equilibrium. This structure of the positive matrix whose leading eigenvalue determined whether or not a new modifier allele would invade also formed the basis of the analyses by Liberman and Feldman (1986a,b) of the evolution of mutation and recombination.

Our objective in this note is to explore how the evolution of mutation rate is affected by frequency-dependent selection. We use classical models of haploid and diploid selection on a single (major) diallelic locus. The modifier locus affects the symmetric (i.e., equal in both directions) mutation rate between the alleles at the major gene. Our model of frequency-dependent selection is classical—in the sense that the fitness is a function of the allele frequency at the major locus (see, e.g., Wright, 1969, Chapter 2). We show that if there is a stable mutation–selection equilibrium then a new mutation-modifying allele introduced near this equilibrium will invade if it reduces the mutation rate. As a result, zero mutation has the property of evolutionary genetic stability (Eshel and Feldman, 1982). We also show that this result does not depend on the rate of recombination between the major and modifier loci and that the zero mutation rate cannot be invaded at a geometric rate.

## 2. The model

Consider a large population of haploids evolving under the influence of selection, recombination, and mutation. The fitness of an individual is determined by its genotype at one locus, with alleles $A$ and $a$, which is linked to a modifier locus with alleles $M$ and $m$ that produce mutation rates $\mu_M$ and $\mu_m$, respectively. The mutation rates from $A$ to $a$ and from $a$ to $A$ at the major locus are the same, and the modifier locus is selectively neutral so it does not affect the fitness parameters for the major locus. Thus there are four genotypes:

$$\begin{array}{lllll} \text{genotype} & AM & Am & aM & am \\ \text{fitness} & w_1 & w_2 & w_3 & w_4 \\ \text{frequency} & x_1 & x_2 & x_3 & x_4 \end{array} \tag{1}$$

with $\sum_{i=1}^{4} x_i = 1$. As the modifier locus is selectively neutral, we have

$$w_1 = w_2 \qquad w_3 = w_4. \tag{2}$$

In the next generation, after selection, random union of gametes, recombination, and segregation (in that order), the new genotypic frequencies are $x_1', x_2', x_3', x_4'$:

$$\begin{aligned} x_1' &= (1-\mu_M)\left[\frac{w_1x_1}{w} - r\frac{w_1w_4}{w^2}D\right] \\ &\quad + \mu_M\left[\frac{w_3x_3}{w} + r\frac{w_1w_4}{w^2}D\right] \\ x_2' &= (1-\mu_m)\left[\frac{w_2x_2}{w} + r\frac{w_1w_4}{w^2}D\right] \\ &\quad + \mu_m\left[\frac{w_4x_4}{w} - r\frac{w_1w_4}{w^2}D\right] \\ x_3' &= (1-\mu_M)\left[\frac{w_3x_3}{w} + r\frac{w_1w_4}{w^2}D\right] \\ &\quad + \mu_M\left[\frac{w_1x_1}{w} - r\frac{w_1w_4}{w^2}D\right] \\ x_4' &= (1-\mu_m)\left[\frac{w_4x_4}{w} - r\frac{w_1w_4}{w^2}D\right] \\ &\quad + \mu_m\left[\frac{w_2x_2}{w} + r\frac{w_1w_4}{w^2}D\right], \end{aligned} \tag{3}$$

where $r$ is the recombination fraction between the major and modifier loci, $D$ the linkage disequilibrium:

$$D = x_1x_4 - x_2x_3, \tag{4}$$

and $w$ is the mean fitness

$$w = \sum_{i=1}^{4} w_ix_i. \tag{5}$$

In what follows we will assume that the selection is *frequency-dependent*; that is, $w_i = w_i(\mathbf{x})$ for $i = 1, 2, 3, 4$ where $\mathbf{x} = (x_1, x_2, x_3, x_4)$ is the frequency vector. We proceed to evaluate the effect of the frequency-dependent selection on the evolution of mutation. Specifically, our goal is to determine whether the Reduction Principle for mutation rates seen in the case of constant selection (Feldman and Liberman, 1986) holds when selection is frequency-dependent.

## 3. Equilibria

In the absence of the modifier allele $m$ (in which case recombination is irrelevant) $x_2 = x_4 = 0$, and the transformation (3) reduces to

$$\begin{aligned} wx_1' &= (1-\mu_M)\, w_1x_1 + \mu_M w_3x_3 \\ wx_3' &= (1-\mu_M)\, w_3x_3 + \mu_M w_1x_1, \end{aligned} \tag{6}$$

with $x_1 + x_3 = x_1' + x_3' = 1$. Let $u = x_1/x_3$, $u' = x_1'/x_3'$ and write the frequency dependent fitness parameters as

$$w_1 = w_1(u), \qquad w_3 = w_3(u). \tag{7}$$

Then in terms of $u$, the transformation (6) is equivalent to

$$u' = f(u) = \frac{(1-\mu_M)\, w_1u + \mu_M w_3}{\mu_M w_1 u + (1-\mu_M)\, w_3}. \tag{8}$$

At equilibrium, $f(u) = u$ and the equilibria are the solutions of $Q(u) = 0$, where

$$Q(u) = \mu_M w_1 u^2 + (1-\mu_M)\,(w_3 - w_1)\, u - \mu_M w_3 \tag{9}$$

with $w_1 = w_1(u)$, $w_3 = w_3(u)$.

We will assume that $Q(u) = 0$ has a root $u^*$ that determines a unique equilibrium $\mathbf{x}^* = (x_1^*, 0, x_3^*, 0)$ with $x_1^* = u^*/(1+u^*)$, $x_3^* = 1/(1+u^*)$ while $x_2 = x_4 = 0$.

**Remark 1.** The kind of frequency-dependent selection on the major loci included here precludes the kind of cycling in the absence of mutation that is treated in Rosenbloom and Allen (2014). That kind of cycling requires an analysis different from