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Generation of variation and a modified mean fitness principle: Necessity is the mother of genetic invention

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ABSTRACT

Generation of variation may be detrimental in well-adapted populations evolving under constant selection. In a constant environment, genetic modifiers that reduce the rate at which variation is generated by processes such as mutation and migration, succeed. However, departures from this *reduction principle* have been demonstrated. Here we analyze a general model of evolution under constant selection where the rate at which variation is generated depends on the individual. We find that if a modifier allele increases the rate at which individuals of below-average fitness generate variation, then it will increase in frequency and increase the population mean fitness. This principle applies to phenomena such as stress-induced mutagenesis and condition-dependent dispersal, and exemplifies *"Necessity is the mother of genetic invention."*

1. Introduction

According to the *reduction principle*, in populations at a balance between natural selection and a process that generates variation (i.e. mutation, migration, or recombination), selection favors neutral modifiers that decrease the rate at which variation is generated. The *reduction principle* was demonstrated for modifiers of recombination (Feldman, 1972), mutation (Liberman and Feldman, 1986), and migration (Feldman and Liberman, 1986). These results were unified in a series of studies (Altenberg, 1984; Altenberg and Feldman, 1987; Altenberg, 2009, 2012a, b; Altenberg et al., 2017).

The latter studies have established the conditions for a *unified reduction principle* by neutral genetic modifiers: (i) effectively infinite population size, (ii) constant-viability selection, (iii) a population at an equilibrium, and (iv) *linear variation* — the equal scaling of transition probabilities by the modifier, i.e., the modifier has the same effect on all individuals. A departure from the latter assumption occurs if two variation-producing processes interact (Feldman et al., 1980; Otto and Feldman, 1997; Altenberg, 2012a). Departures from the *reduction principle* have also been demonstrated when conditions (i)–(iii) are not met, see for example Holsinger et al. (1986) and references therein.

Another departure from the *linear variation* assumption of the *reduction principle* for mutation rates involves a mechanism by which the mutation rate increases in individuals of low fitness — a mechanism first observed in stressed bacteria (Foster, 2007), although not in a constant environment. A modifier gene that changes transition rates in only a subset of types exemplifies the *principle of partial control* (Altenberg, 1984, 2012a) a general statement about non-linear variation, which proposes that, "When the modifier gene has only partial control over the transformations occurring at loci under selection, then it may be possible for the part which it controls to evolve an increase in rates".

Ram and Hadany (2012) demonstrated that even in a constant environment, increasing the mutation rate of individuals with below-average fitness increases the population mean fitness, rather than decreases it. Their analysis assumed effectively infinite population size and fitness determined by the number of mutant alleles accumulated in the genotype. In their models, the only departure from the *reduction principle* conditions was the unequal scaling of mutation probabilities between different genotypes introduced by the correlation between the mutation rate and fitness. A similar result has been demonstrated for conditional dispersal (Altenberg, 2012a Th. 39), fitness-associated recombination (Hadany and Beker, 2003b) and for condition-dependent sexual reproduction (Hadany and Otto, 2007), and empirical evidence suggests these mechanisms are common in nature (Ram and Hadany, 2016).

Ram and Hadany (2012) stated that their result represents a departure from the *reduction principle*, but did not explain this departure. Their analysis was specific to a model that classified individuals by the number of mutant alleles in their genotype,

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similar to models studied by Kimura and Maruyama (1966) and Haigh (1978). Moreover, their argument was based on the expected increase of the stable population mean fitness, rather than on the invasion success of modifier alleles that modify the mutation rate (i.e., analysis of *evolutionary genetic stability*, see Eshel and Feldman, 1982; Lessard, 1990).

Here, we present an evolutionary model in which the type of the individual determines both its fitness and the rate at which it generates variation. Our results show that the population mean fitness increases if individuals with below-average fitness produce more variation than individuals with above-average fitness, and that modifier alleles that induce below-average individuals to produce more variation are favored by natural selection.

2. Models

2.1. General model

Consider a large population with an arbitrary set of types $A_1, A_2, \ldots, A_n$. The frequency and fitness of individuals of type A_k are f_k and w_k, respectively. The probability that an individual of type A_k will transition to some other type is C_k, and given a transition occurs, the probability that it will transition to type A_j is $M_{j,k}$. Therefore, the change in the frequencies of type A_k is described by the transformation $f \to f'$

$$\bar{w}f'_k = (1 - C_k)w_k f_k + \sum_{j=1}^{n} C_j M_{k,j} w_j f_j, \tag{1}$$

or in matrix form

$$\bar{w}f' = (I - C + MC)Df, \tag{2}$$

(Kirkland et al., 2006; Altenberg, 2012a) where $f = (f_1, f_2, \ldots, f_n)$ is a frequency vector with $f_k \geq 0$ and $\sum_{k=1}^{n} f_k = 1$; D is a positive diagonal matrix with entries w_k such that $w_k \neq w_j$ for some $k \neq j$; C is a positive diagonal matrix with entries C_k, where $C_k < 1$ for at least one k; M is an irreducible column-stochastic matrix: $M_{j,k} \geq 0$ for all j, k, $\sum_{j=1}^{n} M_{j,k} = 1$ for all k, hence $[(I - C + MC)^{\ell}]_{j,k} > 0$ for all j, k for some positive integer ℓ (the latter is the condition for primitivity, see Otto and Day, 2007, Appendix 3); I is the $n \times n$ identity matrix; and $\bar{w}$ is the normalizing factor such that $\sum_{k=1}^{n} f'_k = 1$ and is equal to the population mean fitness $\bar{w} = \sum_{k=1}^{n} f_k w_k$.

The types A_k can represent a single or multiple haploid genetic loci or non-genetic traits. Importantly, type transmission is vertical and uni-parental (the type is transmitted from a single parent to the offspring) and is independent of the frequencies of the other types. This model precludes processes such as recombination, social learning, sexual outcrossing, and horizontal or oblique transmission, as these processes are frequency-dependent (Cavalli-Sforza and Feldman, 1981, pg. 54).

Transition between types is determined by a combination of two effects: (i) the probability of transitioning *out* of type A_k is determined by C_k; (ii) given a transition out of type A_k, the distribution of the destination types A_i is given by $M_{i,k}$ (note the index order). Importantly, different types can have different rates. That is, $C_i \neq C_j$ for some i, j. The case $C_i = C_j$ for all i, j is covered by the *reduction principle* (see Altenberg et al., 2017).

In the following section we present four examples of the model (Eq. (2)) that apply to mutation, migration, and learning.

2.2. Mutation model 1

Here we consider a large population of haploids and a trait determined by a single genetic locus with n possible alleles $A_1, A_2, \ldots, A_n$ and corresponding fitness values $w_1, w_2, \ldots, w_n$. The mutation rates C_k of individuals with allele A_k are potentially different; specifically, with probability $1 - C_k$, the allele A_k does not mutate, and with probability $\frac{C_k}{n-1}$, the allele A_k mutates to A_j for any $j \neq k$. This is an extension of a model studied by Altenberg et al. (2017) that allows for C_k, the mutation rate of A_k, to depend on properties of the allele A_k.

Let the frequency of A_k in the present generation be f_k with $f_k \geq 0$ and $\sum_{k=1}^{n} f_k = 1$. Then after selection and mutation, f'_k in the next generation is given by

$$f'_k = (1 - C_k)\frac{w_k}{\bar{w}} f_k + \frac{1}{n-1}\sum_{j \neq k} C_j \frac{w_j}{\bar{w}} f_j, \tag{3}$$

for $k = 1, 2, \ldots, n$, where $\bar{w} = \sum_{k=1}^{n} f_k w_k$ is the population mean fitness.

This model is a special case of the general model (Eq. (2)) where

$$M = \frac{1}{n-1}\begin{bmatrix} 0 & 1 & 1 & \ldots & 1 \\ 1 & 0 & 1 & \ldots & \vdots \\ 1 & 1 & 0 & \ldots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & \ldots & \ldots & \ldots & 0 \end{bmatrix}, \tag{4}$$

with zeros on the diagonal and $\frac{1}{n-1}$ elsewhere. Note that here M is primitive (i.e., irreducible and aperiodic).

2.3. Mutation model 2

Again, we consider a large population of haploids, but here individuals with genotype A_k are characterized by the number k of deleterious or mutant alleles in their genotype, where $0 \leq k \leq n$. Specifically, the fitness of individuals with k mutant alleles is w_k ($w_0 > w_1 > \cdots > w_n$), and the probability C_k that a mutation occurs in individuals with k mutant alleles depends on k. When a mutation occurs it is *deleterious* with probability δ, generating a mutant allele and converting the individual from A_k to A_{k+1}, or it is *beneficial* with probability β, converting the individual from A_k to A_{k-1}. Note that such beneficial mutations can be either compensatory or back-mutations, and that mutations are neutral with probability $1-\delta-\beta$. We assume that both the deleterious and the beneficial mutation rates are low enough that two mutations are unlikely to occur in the same individual in one generation: $C_k(\delta + \beta) \ll 1$ for all $k = 1, \ldots, n$. This model has been analyzed by Ram and Hadany (2012).

Let the frequency of A_k in the present generation be f_k with $f_k \geq 0$ and $\sum_{k=0}^{n} f_k = 1$. Then after selection and mutation f'_k in the next generation is given by

$$\begin{aligned} f'_0 &= (1 - \delta C_0)\frac{w_0}{\bar{w}} f_0 + \beta C_1 \frac{w_1}{\bar{w}} f_1, \\ f'_k &= (1 - (\delta + \beta)C_k)\frac{w_k}{\bar{w}} f_k + \\ &\quad \delta C_{k-1}\frac{w_{k-1}}{\bar{w}} f_{k-1} + \beta C_{k+1}\frac{w_{k+1}}{\bar{w}} f_{k+1}, \\ f'_n &= (1 - \beta C_n)\frac{w_n}{\bar{w}} f_n + \delta C_{n-1}\frac{w_{n-1}}{\bar{w}} f_{n-1}, \end{aligned} \tag{5}$$

for $k = 1, 2, \ldots, n-1$. Here $\bar{w} = \sum_{k=0}^{n} f_k w_k$ is the population mean fitness.

Therefore, setting

$$M = \begin{bmatrix} 1-\delta & \beta & 0 & \cdots & 0 \\ \delta & 1-\delta-\beta & \beta & \ddots & 0 \\ 0 & \delta & 1-\delta-\beta & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & \beta \\ 0 & 0 & 0 & \delta & 1-\beta \end{bmatrix}, \tag{6}$$