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A one locus, biased mutation model and its equivalence to an unbiased model

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Abstract

Experimental data suggests that for some continuously-varying characters under stabilising selection, mutation may cause a mean change in the value of the character. A one locus, mathematical model of a continuously-varying biological character with this property of biased mutation is investigated. Via a mathematical transformation, the equilibrium equation describing a large population of individuals is reduced to the equilibrium equation describing a mutationally unbiased problem. Knowledge of an unbiased problem is thus sufficient to determine all equilibrium properties of the corresponding biased problem. In the biased mutation problem, the dependence of the mean equilibrium value of the character, as a function of the mutational bias, is non-monotonic and remains small, for all levels of mutational bias. The analysis presented in this work sheds new light on Turelli's House of Cards Approximation.

Keywords: Biased mutation; Quantitative trait; One locus; Theory

1. Introduction

When genetic material of living organisms is duplicated, during the act of reproduction, there is the possibility of copying errors (mutations). Here, we concentrate on mutations that affect characters possessing the feature of continuous variation, such as the height of an individual (Lynch and Walsh, 1998). Mutation is not solely characterised by its probability of occurrence; amongst other things, it is characterised by the distribution of changes it induces. While some mutations tend to increase the value of a character, others decrease it and in the recent past it has typically been assumed that, over the population as a whole, the mean mutational change in the character is zero (see e.g. Lande, 1976; Bulmer, 1980; Turelli, 1984). There is no a priori reason for this assumption of mutation causing zero mean genotypic change and there is some experimental data to the contrary (Santiago et al., 1992; Lyman et al., 1996; Mackay, 1996; Keightley and Ohnishi, 1998). Here, we consider a simple (possibly the simplest) model of a continuously-varying character of a sexual population, that incorporates the possibility of mutation causing a mean change in the

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value of the character. We note that a one locus model may, at the level of alleles controlling the trait, differ significantly from a mutationally biased multilocus model, the latter having been investigated elsewhere (Waxman and Peck, 2003). In particular, in the multilocus model, it has been found that there is generally a persistent turnover—and hence lack of equilibration—of alleles at loci affecting the trait—unless genetic constraint (Zeng and Cockerham, 1993) is incorporated into the model. No such allelic turnover occurs in a one locus model and in the present work no form of genetic constraint is included. By contrast to the behaviour at the allelic level, the trait itself rapidly equilibrates (Waxman and Peck, 2003). The present work provides an explicit example of the behaviour of a trait when mutation causes a mean change in its value. We also provide a novel calculational scheme that may have applications elsewhere.

2. Model

Consider a very large, effectively infinite population of individuals that possess non-overlapping generations. The effect of genetic drift is negligible, in such a population, and the model can be treated as entirely deterministic. Individuals are characterised by a single continuously-varying character and the probability that individuals survive from birth to reproductive maturity—their viability—is determined by the value of the character they possess. Individuals are taken to be diploid and reproduce sexually, with two genes within an individual determining the value of the character. There are negligible differences in the viability of individuals of the two sexes of common character value. This is thus a one locus, sexual model with discrete generations.

To proceed, let $x(y)$ label the allele of maternal (paternal) origin in an individual. Let the distribution of maternal origin alleles in one generation, immediately after formation of zygotes, be denoted by $\phi(x)$. Besides, possibly, the initial generation, the distribution of alleles of paternal origin is identical to that of maternal origin. Assuming random mating, the distribution of the alleles in zygotes is given by $\phi(x)\phi(y)$. To proceed further, we assume the value of the character of an organism is additively determined from their two genes. The genotypic value of the character, G, is thus taken as $G = x + y$, with the contribution (or effect) of an allele, to the character (x or y), having been taken to coincide with the label of the allele. Following Crow and Kimura (1964), we assume that x's and y's can take continuous values in the range $-\infty$ to ∞. Since individuals with different genotypic values, i.e. with different G's, generally have a different viabilities, the distribution of alleles in adults generally differs from $\phi(x)\phi(y)$ and is given by $w(x+y)\phi(x)\phi(y)/\overline{w}$, where $w(G)$ is proportional to the viability of individuals with character value G and the presence of $\overline{w} = \int w(x+y)\phi(x)\phi(y)\,\mathrm{d}x\,\mathrm{d}y$ (the mean fitness of the population), ensures normalisation of the distribution. Here and elsewhere, integrals with unspecified limits range from $-\infty$ to ∞. We take $w(G) = 1 - s(G - G_{\mathrm{opt}})^2$ where s is a positive constant that characterises the intensity of selection. The quantity G_{opt} is another constant and we work under the assumption that all values of G of non-negligible frequency are sufficiently close to G_{opt} that $w(G)$ does not become negative. The adopted form of $w(G)$, in the absence of other evolutionary processes, tends to cause the value of the character, G, to approach its "optimal value", G_{opt}, over time, and a viability depending quadratically on G is a mathematically tractable form of stabilising selection with similar properties to a Gaussian function $\exp(-s(G - G_{\mathrm{opt}})^2)$ (Haldane, 1954).

Mature adults duplicate their genetic material when they produce gametes and this entails copying errors—mutations, which occur to each allele independently. The probability of any allele mutating per generation is written as μ. Given a mutation does occur, we take the effect of the mutated allele, x, to have the distribution $f(x - x_{\mathrm{p}} - b)$ where x_{p} is the effect of the parental gene, of which the mutated gene is an imperfect copy, and the function $f(\bullet)$ is a Gaussian distribution with zero mean and a variance of m^2

$$f(x) = \sqrt{\frac{1}{2\pi m^2}}\,\exp\left(-\frac{x^2}{2m^2}\right) \tag{1}$$

The parameter b characterises the mean change in x caused by a mutation—the mutational bias. In a mutated individual, this mean change, relative to the (unmutated) parental value, is $\int (x - x_{\mathrm{p}}) f(x - x_{\mathrm{p}} - b)\,\mathrm{d}x = b$. If $b = 0$ we have the most conventional, unconstrained model of mutation (see e.g. Lande, 1976; Turelli, 1984).

The gametes produced by an individual contain a copy of only one of the individual's two alleles. With equal probability, only one of the two alleles of an individual is deposited into a gamete and this, and the perfect or imperfect transmission (mutation) of alleles between parent and gamete is taken into account by the function $K(x|y,z) = 1/2\sum_{\xi=y,z}[(1-\mu)\delta(x-\xi)+\mu f(x-\xi-b)]$. In terms of this function, the distribution of alleles in gametes in the next generation, written $\phi'(x)$, is given by

$$\phi'(x) = \bar{w}^{-1}\int K(x|y,z)w(y+z)\phi(y)\phi(z)\,\mathrm{d}y\,\mathrm{d}z,$$

$$\bar{w} = \int w(y+z)\phi(y)\phi(z)\,\mathrm{d}y\,\mathrm{d}z \tag{2}$$

As it stands, Eq. (2) is non-linear and, by virtue of the integration, non-local. To make progress, let us henceforth restrict all considerations to equilibrium, where $\phi'(x) = \phi(x)$. With no approximation, Eq. (2) can then be written as $[\bar{w} - w_1(x) + \mu w_1(x)]\phi(x) = \mu\int f(x-y-b)w_1(y)\phi(y)\,\mathrm{d}y$, where $w_1(x) = \int w(x+y)\phi(y)\,\mathrm{d}y$. Working on the assumption that μ and $1-w_1(x)$ are both small ($\ll 1$), we accurately neglect very small terms of order of the product of these terms, with the result

$$[s(x+\bar{x}-G_{\mathrm{opt}})^2 - s\overline{(x+\bar{x}-G_{\mathrm{opt}})^2} + \mu]\phi(x) - \mu\int f(x-y-b)\phi(y)\,\mathrm{d}y = 0 \tag{3}$$

where an overbar denotes an average with respect to $\phi(x)$: $\bar{x} = \int x\phi(x)\,\mathrm{d}x$, $\overline{(x+\bar{x}-G_{\mathrm{opt}})^2} = \int(x+\bar{x}-G_{\mathrm{opt}})^2\phi(x)\,\mathrm{d}x$. In the circumstance that $\bar{x} = 0$ (which is not generally the case of the present work), Eq. (3) coincides with the equilibrium equation describing a single haploid locus, with selection coefficient $s(x-G_{\mathrm{opt}})^2$ and a distribution of mutant effects of $f(x-y-b)$.

3. Transformation of the distribution

The presence of averaged quantities, such as $\bar{x}$, in Eq. (3), means the problem is still non-linear and non-local. Changing description in Eq. (3) from x and $\phi(x)$ to a new variable X and its distribution $\psi(X;b,\mu)$, as defined by

$$X = x + \bar{x} - G_{\mathrm{opt}}, \qquad \psi(X;b,\mu) = \varphi(x) \tag{4}$$

yields

$$sX^2\psi(X;b,\mu) - \mu\int f(X-Y-b)\psi(Y;b,\mu)\,\mathrm{d}Y = -s\alpha^2\psi(X;b,\mu) \tag{5}$$

where $\alpha^2 = \mu/s - \int X^2\psi(X;b,\mu)\,\mathrm{d}X$. Eq. (5), which now coincides exactly with the equilibrium equation describing a single haploid locus, may be interpreted as an eigenvalue equation where $-s\alpha^2$ plays the role of an eigenvalue and $\psi(X;b,\mu)$ the eigenfunction. Thus, underlying the equilibrium distribution of the biological problem is, to high accuracy, a *linear* eigenvalue problem. The eigenfunction, since it represents a probability density, is subject to the conditions $\psi(X;b,\mu) \geq 0$ and $\int\psi(X;b,\mu)\,\mathrm{d}X = 1$ and these uniquely determine α^2.

Using the form of $f(\bullet)$ of Eq. (1), it directly follows that $f(X-Y-b) = \mathrm{e}^{-b^2/(2m^2)} \times \mathrm{e}^{b(X-Y)/m^2} f(X-Y)$. Using this in Eq. (5) along with a new function, $\sigma(X)$, defined by

$$\sigma(X) = \frac{\mathrm{e}^{-bX/m^2}\psi(X;b,\mu)}{\int \mathrm{e}^{-bX/m^2}\psi(X;b,\mu)\,\mathrm{d}X} \tag{6}$$

leads to $\sigma(X)$ satisfying

$$sX^2\sigma(X) - U(b)\int f(X-Y)\sigma(Y)\,\mathrm{d}Y = -s\alpha^2\sigma(X) \tag{7}$$

$$U(b) = \mu\mathrm{e}^{-b^2/(2m^2)} \tag{8}$$

We observe that in Eq. (7),

(i) b is not present in the argument of $f(\bullet)$,
(ii) the mutation rate in Eq. (5), μ, is replaced by $U(b)$,
(iii) $\sigma(X)$ is non-negative and normalised to unity: $\sigma(X) \geq 0$, $\int\sigma(X)\,\mathrm{d}X = 1$.

Accordingly, $\sigma(X)$ corresponds with the equilibrium distribution in an unbiased ($b = 0$) problem where the mutation rate is $U(b)$. Thus, a direct comparison of Eqs. (5) and (7) allows us to make the identification $\sigma(X) = \psi(X;0,U(b))$. Using this result in Eq. (6) and solving the resulting equation for $\psi(X;b,\mu)$ yields

$$\psi(X;b,\mu) = \frac{\mathrm{e}^{bX/m^2}\psi(X;0,U(b))}{\int \mathrm{e}^{bX/m^2}\psi(X;0,U(b))\,\mathrm{d}X} \tag{9}$$

This equation indicates that knowledge of the equilibrium distribution of a single symmetric (i.e. $b = 0$) problem, $\psi(X; 0, U)$, for a range of mutation rates, U, that are $\leq \mu$, is sufficient to determine the equilibrium distribution, $\psi(X; b, \mu)$, for all b, of a biased problem. Eq. (9) is a statement of the *exact relation* between the solution $\psi(X; b, \mu)$ of Eq. (5) and $\psi(X; 0, U(b))$.

Note that (i) since $\psi(X; 0, U(b))$ is non-negative, it must be a function of X that has no zeros. (ii) Taking $X \to 0$ in Eq. (7), yields $-U(b) \int f(Y)\psi(Y; 0, U(b))\,\mathrm{d}Y = -s\,\alpha^2\psi(0; 0, U(b))$. The left side of this equation is negative definite and $\psi(0; 0, U(b))$ is non-negative, so the eigenvalue must be negative: $-\alpha^2 < 0$. (iii) The smallness of the allelic mutation rate, μ, means that typically, there will only be a single negative eigenvalue.

4. House of cards approximation

We can rewrite Eq. (7) for $\sigma(X) \equiv \psi(X; 0, U(b))$ as $\sigma(X) = [U(b)/s] \int f(X - Y)\sigma(Y)\,\mathrm{d}Y/(X^2 + \alpha^2)$ and an approximation for $\psi(X; 0, U(b))$ is given by

$$\psi(X; 0, U(b)) \simeq \frac{U(b)}{s}\,\frac{f(X)}{X^2 + \alpha^2} \tag{10}$$

where α^2 is determined from the requirement of normalisation, $\int \psi(X; 0, U(b))\,\mathrm{d}X = 1$.

The above approximation is valid when α is small compared with the "range" over which $f(\bullet)$ is appreciable, which is of order m, i.e. when $\alpha \ll m$. When this applies, $\alpha \simeq \pi U(b) f(0)/s$, hence the approximation is applicable when $\pi U(b) f(0)/s \ll m$. An alternative way of viewing this approximation is to note that it corresponds to the range of mutations, m, being large compared with the range of $\psi(X; 0, U(b))$, which is of order α. When this occurs there is little relation between the pre and post-mutated state of an individual and this is close to the exact behaviour of the House of Cards *model* of mutation (Kingman, 1978). Thus, Eq. (10) is called the House of Cards Approximation (Turelli, 1984).

It is of interest to know the properties of the quantity $\alpha^2 \equiv \alpha^2(b, \mu)$, which is proportional to the eigenvalue of Eq. (5), as a function of the bias parameter, b. We can determine a property of α^2 from the observation that the same eigenvalue, $-s\alpha^2$, appears in the original eigenvalue equation, Eq. (5), and the transformed equation, Eq. (7). An eigenvalue of an operator can only depend on parameters present in the operator, thus on comparison of Eqs. (5) and (7), it follows that we have the exact relation $\alpha(b, \mu) = \alpha(0, U(b))$ where $-s\alpha^2(0, U)$ is the negative eigenvalue of an unbiased problem, with a mutation rate U. The approximation $\alpha \simeq \pi U(b) f(0)/s$ depends on μ and b only in the combination $U(b) \equiv \mu \exp[-b^2/(2m^2)]$ and this form is compatible with the general relation $\alpha(b, \mu) = \alpha(0, U(b))$.

We have noted above that the smallness of α provides the justification of the House of Cards Approximation. We have that $\alpha(b, \mu) \simeq \pi\mu \exp[-b^2/(2m^2)]\, f(0)/s$, hence for $b \neq 0$, $\alpha(b, \mu) < \alpha(0, \mu)$. As a consequence, the House of Cards Approximation, as applied to Eq. (7) and resulting in Eq. (10), applies with higher accuracy in a biased mutation problem than it does in its application in a standard unbiased problem.

4.1. Mean character value

The equilibrium mean value of the character is $\bar{G} = \int (x + y)\phi(x)\phi(y)\,\mathrm{d}x\,\mathrm{d}y = 2\int x\phi(x)\,\mathrm{d}x \equiv 2\bar{x}$. Using Eq. (4) we have $\int X\psi(X; b, \mu)\,\mathrm{d}X = 2\bar{x} - G_{\mathrm{opt}} = \bar{G} - G_{\mathrm{opt}}$ and using Eq. (9) and the approximation of Eq. (10) yields $\bar{G} - G_{\mathrm{opt}} \simeq (U(b)/s) \int \mathrm{d}X\, X\, \mathrm{e}^{bX/m^2} f(X)/(X^2 + \alpha^2)$ neglecting the denominator in Eq. (9), which is very close to unity. We can rewrite the integral as $\int \mathrm{d}X\, X \sinh(bX/m^2) f(X)/(X^2 + \alpha^2)$ and in this form, it can be verified that neglecting α, since it is $\ll m$, is an accurate approximation. Following from this, we obtain

$$\begin{aligned}\bar{G} - G_{\mathrm{opt}} &\simeq \frac{\mu}{sm}\mathrm{e}^{-b^2/(2m^2)} \int_0^{b/m} \mathrm{e}^{v^2/2}\,\mathrm{d}v \\ &= \sqrt{\frac{\pi}{2}}\,\frac{\mu}{sm}\mathrm{e}^{-b^2/(2m^2)}\,\frac{1}{i}\,\mathrm{erf}\left(\frac{ib}{\sqrt{2}m}\right)\end{aligned} \tag{11}$$

where $i = \sqrt{-1}$ and $\mathrm{erf}(\bullet)$ denotes the error function (Abramowitz and Stegun, 1965).

The result above for $\bar{G} - G_{\mathrm{opt}}$ is an odd, non-monotonic function of b: for $|b/m| \ll 1$, $\bar{G} - G_{\mathrm{opt}} \simeq \mu b/(sm^2)$ i.e. proportional to b while for $|b/m| \gg 1$, $\bar{G} - G_{\mathrm{opt}} \simeq \mu/(sb)$ i.e. proportional to b^{-1}, see Fig. 1.

The non-monotonic behaviour of $\bar{G} - G_{\mathrm{opt}}$, as a function of b, indicates that although mutations may cause a non-zero mean change in the value of the character, there is only a *very limited* amount of change

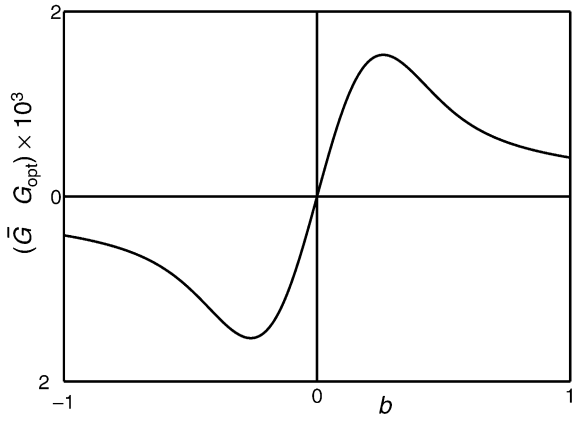

Fig. 1. The deviation of the equilibrium mean genotypic value, $\bar{G}$, from its optimal value, G_{opt}, namely $\bar{G} - G_{opt}$, is plotted as a function of mutational bias, b. Eq. (11) was used to produce the figure and the parameter values adopted were the "typical" values $\mu = 10^{-5}$, $m = 0.2$, and $s = 0.025$ of a sexual population (Lynch and Walsh, 1998).

they can bring about: $\max_b(\bar{G} - G_{opt}) \simeq 0.77\mu/(sm)$, with the maximum occurring at $b \simeq 1.3m$. This non-monotonic behaviour arises because of the detailed interplay between mutation and selection. In the absence of selection, the effect of any $b > 0$ would be to systematically increase the character value over time. Selection results in a decreased survival probability of individuals with large character-values and the combined outcome of mutation and selection is a non-monotonic equilibrium behaviour. It may be verified, using a similar approach to that used in the determination of $\bar{G}$, that when the House of Cards Approximation is applicable, there is negligible change in the genetic variance from its $b = 0$ value.

In the case of a single haploid locus, with mean allelic effect $\bar{x}$, it is possible to establish results that indicate that the deviation of $\bar{x}$ from the optimal value, $|\bar{x} - x_{opt}|$, vanishes faster than $\sqrt{\mu}$, as $\mu \to 0$ (see Eq. (6.10) of Bürger, 2000). We have already noted, in Section 2, that Eq. (3) is not identical to the equation of a single haploid locus thus this limiting result does not fulfil the conditions for it to be applicable in this case. However, inspection of Eq. (11) indicates that $|\bar{G} - \bar{G}_{opt}|$ is proportional to μ and consequently does vanish faster than $\sqrt{\mu}$, as $\mu \to 0$ (much faster, indeed). We note that while such limiting results, when applicable, do put some constraints on the size of $|\bar{x} - x_{opt}|$, they are fairly blunt instruments, in that they are unable to capture or predict the existence of the type of non-monotonic behaviour we have seen exhibited in $|\bar{G} - \bar{G}_{opt}|$ and which is also manifested in one locus haploid models.

5. Discussion

As formulated, the model presented applies only to organisms with a character controlled by a single genetic locus. The calculation may be directly extended to the case of a character controlled by more than one locus, and hence more than two genes, if, and only if, the mutational parameters b, μ, and m have no variation across loci. In this case, under the approximation of linkage equilibrium (Bulmer, 1989; Turelli and Barton, 1990), the value of $\bar{G} - G_{opt}$ is identical to the result of Eq. (11). Thus, in this multilocus case, the deviation of $\bar{G}$ from G_{opt} is proportional to (and limited by) the *allelic* mutation rate, and not, as one might guess, the mutation rate of the character itself. This alone, is somewhat strange, however, when b, μ and m do not have the same values at all loci, the situation is one with *substantially* more complicated behaviour. In particular, and as noted earlier, the distributions of alleles at different loci do not equilibrate, although the distribution of the character, and hence its mean value, $\bar{G}$, does equilibrate (Waxman and Peck, 2003). The situation is sufficiently complicated that at the present time, only numerical results for the value of $\bar{G}$ are available, in this case.

An alternative, to considering multilocus generalisations of the present work, is to consider if the mathematical results presented can be looked at from a more general viewpoint. The essence of the present work concerned a mathematical transformation of the equation that determined the equilibrium distribution of allelic effects. The transformation changed the equation into a related (simpler) equation. In particular, the distribution of mutant allelic effects had a parameter representing mutational bias transformed away, at the cost of a modified rate of mutation. In a general sense, this procedure can be viewed as a way of relating two models with different distributions of mutant allelic effects. Let us therefore return to Eq. (3), or equivalently Eq. (5), but now with a distribution of mutant effects $g(x - y)$ so it reads

$$sX^2\psi(X) - \mu \int g(X - Y)\psi(Y)\,\mathrm{d}Y = -s\alpha^2\psi(X) \tag{12}$$

At this stage, we do not make any assumptions about $g(x-y)$ apart from its non-negativity and normalisation to unity, (we do, however, note that Eq. (5) is a special case of Eq. (12), and follows from the choice $g(x-y)=f(x-y-b)$). We can then relate the solution $\psi(X)$ of Eq. (12), with the distribution of mutant effects $g(X-Y)$ to the solution with a different distribution of mutant effects by substituting $\psi(X)=\mathrm{e}^{-cX}\,\sigma(X)/\int \mathrm{e}^{-cX}\,\sigma(X)\,\mathrm{d}X$ for some new function $\sigma(X)$ and parameter c. Eliminating the factors e^{-cX} from Eq. (12), after the substitution has been carried out, yields

$$sX^2\sigma(X)-V(c)\int h(X-Y)\sigma(Y)\,\mathrm{d}Y=-s\,\alpha^2\sigma(X) \tag{13}$$

where

$$V(c)=\mu\int \mathrm{e}^{cX}g(X)\,\mathrm{d}X \tag{14}$$

$$h(X-Y)=\frac{\mathrm{e}^{c(X-Y)}\,g(X-Y)}{\int \mathrm{e}^{cX}g(X)\,\mathrm{d}X} \tag{15}$$

We thus see that proceeding in the above manner, we have gone from an equation describing the equilibrium behaviour of a model with mutation rate μ and distribution of mutant effects $g(X-Y)$, to a model with mutation rate $V(c)$, Eq. (14), and distribution of mutant effects $h(X-Y)$, Eq. (15). Of course, for these calculations to be meaningful, the integral appearing in Eqs. (14) and (15) must exist and this puts some restriction on the asymptotic form of $g(X)$.

From the above considerations, it follows that some models of the type considered here—involving mutation and selection of a continuous character, but with apparently different distributions of mutant effects, are, via a transformation, convertible into each other. The case of a Gaussian distribution of mutant effects—the main example of this work— was a particular example of this, where a transformation connected biased and unbiased problems.

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