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Numerical and exact solutions for continuum of alleles models

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Abstract. Two results are presented for problems involving alleles with a continuous range of effects. The first result is a simple yet highly accurate numerical method that determines the equilibrium distribution of allelic effects, moments of this distribution, and the mutational load. The numerical method is explicitly applied to the mutation-selection balance problem of stabilising selection. The second result is an exact solution for the distribution of allelic effects under weak stabilising selection for a particular distribution of mutant effects. The exact solution is shown to yield a distribution of allelic effects that, depending on the mutation rate, interpolates between the "House of Cards" approximation and the Gaussian approximation. The exact solution is also used to test the accuracy of the numerical method.

1. Introduction

In 1964 Crow and Kimura introduced a scheme of mutation where the effect of a mutant allele is randomly chosen from a continuous distribution. This corresponds to an infinite number of possible alleles with a continuum of possible effects.

Such a mutation scheme applies to situations where there are many possible alleles and mutations lead to new alleles that are essentially unique and have a negligible chance of being reversed by a subsequent mutation. While this can be applied to a locus controlled by many codons, the reality here is that all alleles are, fundamentally, discrete in character. In this case, however, mutations will typically arise in different genetic and possibly environmental backgrounds with uncontrolled (or unknown) epistasis and dominance effects. These may lead to a smoothed out behaviour that mimics a continuum of alleles model. An alternative viewpoint is that selection acts on more subtle aspects of variation as, for example, arises in non-coding regulatory sequences. These possess a great number of possible states and their variation may lead to a situation that closely corresponds to a model with a continuum of alleles.

There has been a considerable amount of work involving such models and we should mention contributions on the maintenance of genetic variability (Lande 1976), investigations into Gaussian (Karlin 1979) and non Gaussian models (Eshel

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1971; Karlin 1988) as well as investigations into mutation selection balance (Bürger 1988, 2000).

While a mutant allele is an imperfect copy of a parental allele, it is reasonable to assume that there is a correlation between the allelic effects of offspring and parental alleles. This correlation can be incorporated into the mutation scheme by assuming allelic effects of offspring are distributed around the allelic effect of parents (Crow and Kimura 1964; Kimura 1965). Alternative schemes of mutation, that are not considered here, include the House-of-Cards scheme (Kingman 1978 and, for recent work, Mahdi and Lessard 2000; Bürger 2000) that has zero correlation between parental and mutant offspring alleles and a regression mutation model (Zeng and Cockerham 1993) that interpolates between the Crow-Kimura and Kingman schemes.

Mathematical models of genetics involving a continuum of alleles have been used extensively in the literature when it is believed that many alleles, possibly of small effect, may be important. Such models have the advantage that the characterisation of mutation requires a small number of parameters, namely the mutation rate and the parameters needed to characterise the distribution of mutant effects. There is the other advantage that a continuum of alleles model may be subject to a mathematical analysis which may be not possible in the case of a models with a finite number of alleles. Analysis of simple, non-pleiotropic, discrete allele models, yields results that are close to the results of continuum of alleles models (Turelli 1984; Slatkin 1987) indicating an approximate independence of observable predictions on the precise genetics underlying the problem. In discrete allele models with pleiotropy, the situation may be more complex (Turelli 1985; Wagner 1989).

In this work two results are presented for problems involving alleles with a continuous range of effects.

(i) The first result is a robust, simple, yet highly accurate numerical method that is able to determine moments of the equilibrium distribution of allelic effects, the mutational load and the equilibrium distribution of allelic effects itself. The method is applied to the standard mutation selection balance problem associated with stabilising selection (Kimura 1965; Turelli 1984; Bürger 2000, pp 232–244) and a positive feature of the method is that it is not restricted to any lower limit on the size of the mutation rate (for earlier numerical approaches see e.g. Turelli 1984; Bürger 1986).

(ii) The second result is an exact solution of the weak-selection distribution of allelic effects under stabilising selection. The solution applies for a specific distribution of mutant effects. The exact solution provides a test of the numerical method introduced here and also stands in its own right as a useful and interesting result.

Throughout this work, let us use the convention that integrals with unspecified limits correspond to the integration variable covering the range $-\infty$ to ∞.

2. Standard problem

The theoretical investigations in this work are restricted to characterising a population of one locus haploid asexual individuals. The results obtained, however, have a wider applicability than just this simple model and are relevant, for example, to

a sexual population under the approximation of linkage equilibrium. In this case each member of the sexual population may be treated as a collection of alleles at haploid asexual loci and the selection coefficient of each haploid locus is derived from an average over the genetic background of the remaining alleles (see e.g. Kimura 1965).

The haploid asexual population under consideration is assumed to be sufficiently large that stochastic effects can be neglected. Generations are non-overlapping and censused in the offspring, prior to selection. One generation of the lifecycle is as follows: (i) Newly produced offspring undergo viability selection and the surviving individuals are termed adults. (ii) All adults produce offspring during a relatively narrow time interval and die shortly afterwards. (iii) Mutations occur at the production of offspring.

Individuals are subject to Gaussian stabilising selection on a phenotypic value controlled by a single locus. Without loss of generality, the optimal phenotypic value is taken to be zero, so the probability of an individual with phenotypic value z surviving to reproductive age is given by $\exp\left(-z^2/(2V)\right)$ where $V > 0$ (Haldane 1954). The phenotypic value decomposes into an allelic effect x and an environmental effect, ε, thus $z = x + \varepsilon$ and ε is taken to be a Gaussian random variable with zero mean and variance V_E. Let $w(x)$ be proportional to the probability of surviving to reproductive age for an individual with a particular allelic effect x. We obtain $w(x)$ by averaging, over all possible environmental effects ε, the probability that this individual survives viability selection (a similar approach is used to average over other loci in a multi-locus sexual problem, thereby taking their genetic variation into account). By convention, $w(x)$ is scaled so its value is unity for an individual with the optimal allelic effect, $x = 0$. This yields $w(x) = \exp\left(-x^2/(2V_s)\right)$ where $V_s = V + V_E$. In the following sections, we adopt the standard convention that quantities are scaled in such a way that the environmental variance is set to unity: $V_E = 1$.

Mutations occur with probability u per generation and the result of a mutation results in the allelic effect of an offspring being different to that of the parental allele of which it is an imperfect copy. The allelic effect of a mutated offspring is taken to be a random variable that is continuously distributed over $(-\infty, \infty)$ around the parental value. A mutant offspring of a parent with allelic effect y will have an allelic effect in the infinitesimal interval $(x, x + dx)$ with probability $f(x - y)dx$, where $f(x)$ is the distribution of mutant effects – a function whose variance we denote by m^2. Different forms for $f(x)$ have been adopted in the literature and we shall consider a specific form of $f(x)$ later in this work. As pointed out in the Introduction, a mutational distribution that depends on parental allelic effects, y, and mutant offspring effects, x, in the form $f(x - y)$, is not the most general distribution, although it is one that has received considerable attention in the literature (see e.g. Bürger 2000 Chapter IV).

From the preceding paragraphs, it follows that the distribution (probability density) of allelic effects in offspring in generation t, which we denote by $\Phi(x, t)$, obeys

$$\Phi(x, t+1) = \frac{(1-u)w(x)\Phi(x,t) + u\int f(x-y)w(y)\Phi(y,t)dy}{\overline{w}(t)} \qquad (1)$$

where $t = 0, 1, 2, ...$ and $\overline{w}(t) = \int w(y)\Phi(y,t)dy$. Only equilibrium solutions of Eq. (1), where all quantities are independent of t, will be considered here.

Let us restrict our analysis to weak selection. Thus for all x of appreciable frequency, $1 - w(x) \ll 1$, hence $w(x) \simeq 1 - s(x)$ where

$$s(x) \stackrel{\text{def}}{\equiv} \frac{x^2}{2V_s}. \tag{2}$$

This approximation applies when V_s is sufficiently large that on expanding $w(x)$ in powers of x, the term in x^4 is, on average, much smaller than the quadratic term, $s(x)$. We estimate, from results taken from the House of Cards approximation and the Gaussian approximation (Turelli 1984; Kimura 1965; Bürger 2000, pp120–123) that the quartic term can always be neglected when $u \ll 1$ and $m^2/V_s \ll 1$. Assuming these conditions apply, we can then approximate Eq. (1) by neglecting very small terms of order $s \times s$ and $s \times u$ to obtain the equilibrium equation

$$[s(x) - \overline{s} + u]\,\Phi(x) = u \int f(x-y)\Phi(y)dy \tag{3}$$

with $\overline{s} = \int s(x)\Phi(x)dx$.

Note that by virtue of its interpretation as a probability density, $\Phi(x)$ is non-negative and normalised to unity: $\int \Phi(x)dx = 1$, and we must solve Eq. (3) subject to these conditions.

Note also that there is an alternative interpretation of Eq. (3).This is as the equilibrium equation describing a population that evolves in continuous time (Kimura 1965; Bürger 2000, p119), when subject to a death rate that depends quadratically on x. The equivalence of Eq. (3) and the continuous time problem may or may not be exact, depending on the precise way population number is regulated. Further discussion of this point is given in Appendix A.

3. Numerical method

We can determine a robust iterative numerical scheme for determining the equilibrium distribution $\Phi(x)$ by a suitable rewriting of Eq. (3). To proceed, let us define

$$a = u - \overline{s} \tag{4}$$

and use this equation and Eq. (3) to write

$$\Phi(x) = \frac{u \int f(x-y)\Phi(y)dy}{s(x) + a}. \tag{5}$$

Normalisation of $\Phi(x)$ entails $\int \Phi(x)dx = 1$ and from Eq. (5) this yields

$$u = \left(\int \frac{\int f(x-y)\Phi(y)dy}{s(x)+a} dx \right)^{-1}. \tag{6}$$

Note that the parameter a is not an independently specified quantity but one that is determined by the requirements on $\Phi(x)$ of being non-negative and normalised to unity. Satisfying these requirements ultimately leads to a depending on u, V_s and

parameters in $f(x)$, such as its variance, which we denote by m^2. Let us make a shift in emphasis, however, and regard a as a quantity we specify and u as a quantity that is determined (V_s and m remaining fixed). Since inconsistencies arise if $a \leq 0$, we only consider positive a.

A direct way of proceeding would be to iterate Eqs. (5) and (6), from an initial choice of $\Phi(x)$ and u. This has been observed to have numerical instabilities. We could, alternatively, eliminate u from Eqs. (5) and (6), and arrive at a self contained equation that could be iterated:

$$\Phi(x) = \frac{[s(x)+a]^{-1} \int f(x-y)\Phi(y)dy}{\int\int [s(x_1)+a]^{-1} f(x_1-y)\Phi(y)dydx_1}. \tag{7}$$

This is still problematic, since it requires numerical integration procedures that can deal with near singular integrals involving $[s(x)+a]^{-1}$ (e.g. for $u = 10^{-5}$, the parameter a is approximately 2×10^{-7}). This is not an impossible task but it is preferably avoided, especially in more general cases, where $s(x)$ is not simply quadratic in x.

An alternative approach is to work with the Fourier transform of Eq. (7). To derive this approach, we multiply Eq. (7) by e^{ikx} and integrate over all x. We define

$$G_a(k) = \int e^{ikx} \frac{1}{s(x)+a} \frac{dx}{2\pi} = \frac{V_s}{\sqrt{2V_s a}} \exp\left(-\sqrt{2V_s a}|k|\right) \tag{8}$$

and also

$$\phi(k) = \int e^{ikx}\Phi(x)dx, \qquad F(k) = \int e^{ikx} f(x)dx. \tag{9}$$

Since, in general, $f(x)$ is not symmetric, it follows that $F(k)$ is generally complex. Furthermore, even when $f(x)$ is symmetric and hence $F(k)$ is real, there is no requirement that ensures $F(k)$ is positive everywhere.

It follows, using standard properties of Fourier transforms, that the numerator of Eq. (7) is given by $\int G_a(k-q)F(q)\phi(q)dq$ while the denominator is simply $\int G_a(q)F(q)\phi(q)dq$. Thus

$$\phi(k) = \frac{\int G_a(k-q)F(q)\phi(q)dq}{\int G_a(q)F(q)\phi(q)dq}. \tag{10}$$

This is the equation that is suitable for numerical iteration and the steps in the iterative scheme that lead to the solution are:

1. Specify a positive numerical value of the parameter a.
2. Specify an initial distribution, $\phi_0(k)$.
3. Use Eq. (10) to determine
   $\phi_1(k) = \int G_a(k-q)F(q)\phi_0(q)dq / \int G_a(q)F(q)\phi_0(q)dq$. Similarly, determine $\phi_2(k)$, $\phi_3(k)$, ... where generally

$$\phi_{n+1}(k) = \frac{\int G_a(k-q)F(q)\phi_n(q)dq}{\int G_a(q)F(q)\phi_n(q)dq}. \tag{11}$$

   This equation is iterated until convergence is achieved, with the result termed $\phi_\infty(k)$.

To perform the integrations q is discretised – thereby turning integrals into sums. The discretised q adopted covers only a finite range, namely the region where $F(q)$ is appreciably different from zero. It is also efficient to not determine $\phi_{n+1}(k)$ for all k, but only for k in the same range as q. Thus we discretise k identically to q and determine $\phi_{n+1}(k)$, and ultimately $\phi_\infty(k)$, only for the finite range of k where $F(k)$ is appreciably different from zero.

4. The mutation rate u, corresponding to the value of a adopted, follows from the Fourier transform of Eq. (6) with $\phi(q)$ replaced by $\phi_\infty(k)$:

$$u = \left(\int G_a(q) F(q) \phi_\infty(q) dq \right)^{-1} . \tag{12}$$

The mutational load of the population ($1 - \overline{w} \simeq \overline{s}$) is given by $\overline{s} = u - a$, as follows from Eq. (4) and both u and a are known (u is known from Eq. (12) and a is known since it has been specified from the outset). Moments of $\Phi(x)$, i.e. $\overline{x^n} \stackrel{\text{def}}{\equiv} \int x^n \Phi(x) dx$ may be estimated by fitting a polynomial in k to $\phi(k)$ in the vicinity of $k = 0$ and since $\phi(k) = \sum_{n=0}^{\infty} i^n k^n \overline{x^n}/n!$ the coefficient of k^n is $i^n \overline{x^n}/n!$.

Steps $1 - 4$ above are repeated for a set of different a values and lead to new values of $u, \overline{s}$, moments of $\Phi(x)$ as well as $\phi_\infty(k)$. This is sufficient to numerically determine relations between quantities of interest. For example, the dependence of the load, $1 - \overline{w} \simeq \overline{s}$, on the mutation rate u may be illustrated by plotting the list of $\overline{s}$ values established for different values of a, against the list of u values, also established for different values of a. Alternatively, if quantities are required for just a single mutation rate, then plotting a as a function of u, with interpolation as necessary, allows the value of a corresponding to any mutation rate of interest to be found (a Newton scheme could also be employed). The particular a obtained can be used to calculate whatever is of interest i.e. $\overline{s}$, moments of $\Phi(x)$ or $\phi_\infty(q)$.

Note that advantages of the above procedure include the following. (i) u does not appear in Eq. (11) so essentially arbitrary values of u can be chosen without numerical problems; in particular there is no limit on the smallness of u. (ii) Equation (3) may be observed to have the property that all observable quantities depend on V_s and u only in the combination $V_s \times u$ and numerical results highly accurately illustrate this property. (iii) The numerical procedure is robust; there is no great sensitivity on the discretisation of k, the size of the mutation rate, u, and furthermore every starting function for the iteration, i.e. every $\phi_0(q)$, has been found to lead to the same $\phi_\infty(q)$.

It is appropriate to follow up this last point and enquire why the above iteration scheme converges. We cannot give a rigorous answer to this question, whose proof would involve a detour into considerations of functional analysis and Banach spaces that lie outside the author's expertise. Furthermore, we shall not address any issues associated with discretisation of k and q and shall concentrate on the fundamental reasons for convergence of the iteration scheme. Firstly we note that little can be directly inferred from the Fourier transformed equation, Eq. (10), since in general, $F(k)$ need not be positive or even real. However Eq. (10) is the Fourier

transform of Eq. (7) and thus formally equivalent to it. Thus the relevant observation is that iteration of Eq. (10) is equivalent to iteration of Eq. (7) and this latter equation can be written as $\Phi(x) = \int M(x, y)\Phi(y)dy / \int M(x_1, y)\Phi(y)dx_1dy$ where $M(x, y) = [s(x) + a]^{-1} f(x - y)$ is a positive linear operator analogous to a positive matrix. Furthermore, the n'th iterate $\Phi_n(x)$ can be written in terms of the initial function, $\Phi_0(y)$, as

$$\Phi_n(x) = \int M^n(x, y)\Phi_0(y)dy / \int M^n(x_1, y)\Phi_0(y)dx_1dy \tag{13}$$

where $M^n(x, y) = \int M(x, x_1)M(x_1, x_2), ..., M(x_{n-1}, y)dx_1dx_2, ..., dx_{n-1}$ is analogous to the n'th power of a matrix. Pursuing this matrix analogy further, we non-rigorously infer that a discretisation of Eq. (13) would convert it to a Matrix equation where the Perron Frobenius theorem (see e.g. Hoppensteadt 1982) and the power method can be applied (see e.g. Burden et al., 1981). Thus under repeated iteration of Eq. (7), the solution converges to the right eigenfunction of $M(x, y)$ and the eigenfunction obtained is unique and positive. The denominator in Eq. (7), serves to rescale the eigenfunction, so that it is normalised to unity.

There is an inner consistency to the above, since non-negativity and normalisation are precisely the requirements that an equilibrium distribution must satisfy, along with Eq. (7) – which is equivalent to the original condition for equilibrium, Eq. (3).

4. Exact solution

To provide a useful testing ground of the numerical method of the previous section, as well as producing a result of general interest in its own right, let us make a particular choice of the distribution of mutant effects, $f(x)$, that allows an exact solution of Eq. (3). The particular choice is

$$f(x) = \frac{x}{m^2 \sinh\left(\dfrac{\pi x}{\sqrt{2}m}\right)}. \tag{14}$$

This is a symmetric, unimodal function of x with zero mean, variance m^2 and is, as far as appearance is concerned, very similar to a Gaussian distribution. In Fig. 1 the above form for $f(x)$ is illustrated along with a Gaussian distribution of the same variance.

For $|x| \ll m$, $f(x)$ behaves like a Gaussian: $f(x) \approx f(0) \times (1 - x^2/(2c))$, $c = 6m^2/\pi^2$, while for $|x| \gg m$, it decays essentially exponentially: $f(x) \approx \left(2|x|/m^2\right) \exp(-\pi\,|x|\,/(\sqrt{2}m))$. Thus the function selected has perfectly reasonable behaviour for all x and, amongst other things, provides an arena for testing the numerical method.

The solution of Eq. (3), with $f(x)$ given by Eq. (14), may, by direct substitution, be verified to be

$$\Phi(x) = \int e^{-ikx}\,\mathrm{sech}^{\beta}\left(\frac{mk}{\sqrt{2}}\right)\frac{dk}{2\pi} \tag{15}$$

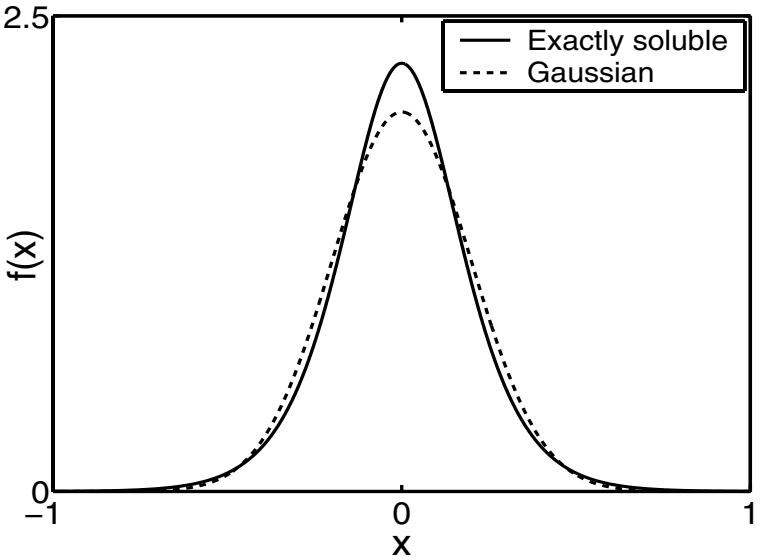

Fig. 1. The distribution of mutant effects $f(x) = x\left[m^2 \sinh\left(\pi x/(\sqrt{2}m)\right)\right]^{-1}$, that was adopted in this work, is plotted as a function of x (solid curve). This choice of $f(x)$ allows the weak selection equation, Eq. (3), to be solved exactly. In the plot, the parameter m, which is the standard deviation of mutant effects, has the value $m = 0.2$. In the same figure, a Gaussian distribution, with the same standard deviation, is plotted for comparison (dashed curve).

where

$$\beta = \frac{1}{2}\left(\sqrt{1 + \frac{16uV_s}{m^2}} - 1\right) \tag{16}$$

and

$$\bar{s} = \frac{m^2\beta}{4V_s}. \tag{17}$$

It is possible to evaluate the expression for $\Phi(x)$ in closed form (see Eq. 3.985 1 of Gradsteyn and Ryzhik 1980):

$$\Phi(x) = \frac{2^{\beta-3/2}}{\pi m}\frac{\left|\Gamma\left(\frac{\beta}{2} + i\frac{x}{\sqrt{2}m}\right)\right|^2}{\Gamma(\beta)} \tag{18}$$

where $\Gamma(\bullet)$ denotes Euler's Gamma function. The distribution $\Phi(x)$ in Eq. (18) is non-negative and normalised to unity. In Fig. 2, a plot based on Eq. (18), illustrates the different behaviour $\Phi(x)$ has for a wide range of mutation rates.

In Figs. 3 and 4, $\Phi(x)$ is plotted against x, for two different choices of the mutation rate, u, along, in each case, with a relevant approximation to $\Phi(x)$. In Fig. 3 the "House of Cards" approximation is relevant since for the parameters

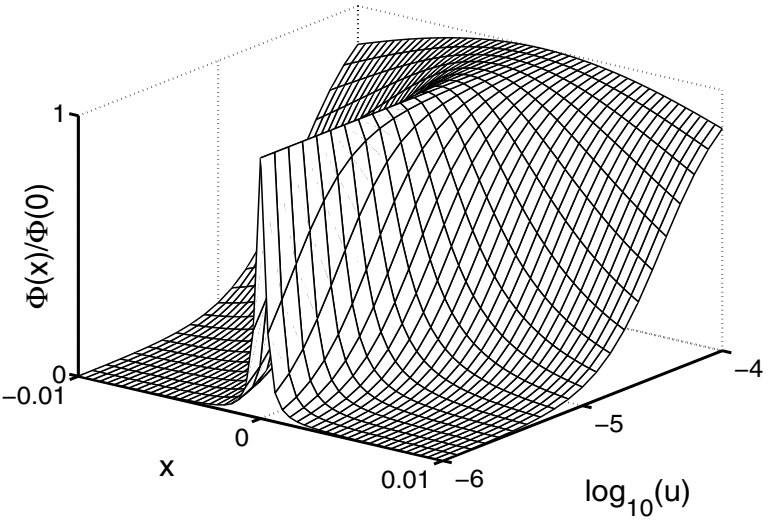

Fig. 2. With $\Phi(x)$ the exact distribution of allelic effects of Eq. (18), the ratio $\Phi(x)/\Phi(0)$ is plotted for $m = 0.2$ and $V_s = 20$ when mutation rates range over two orders of magnitude. The height of $\Phi(x)$ varies very strongly with mutation rate and the ratio $\Phi(x)/\Phi(0)$ allows comparison of the very different shapes of $\Phi(x)$ for different mutation rates.

used, $uV_s/m^2 \ll 1$ (Turelli 1984; Bürger 2000, p121–123), while in Fig. 4, the relevant approximation corresponds to a Gaussian distribution and is applicable when $uV_s/m^2 \gg 1$ (Kimura 1965; Turelli 1984; Bürger 2000, p120–121).

The numerical method presented in the previous section involved parameterising the problem in terms of the quantity $a = u - \overline{s}$. We can express $\beta, \overline{s}$ and u in terms of a: substituting $\overline{s}$ from Eq. (17) into Eq. (4) and performing some algebra yields

$$\beta = 2\sqrt{\frac{aV_s}{m^2}}, \qquad \overline{s} = \frac{1}{2}\sqrt{\frac{am^2}{V_s}}, \qquad u = a + \frac{1}{2}\sqrt{\frac{am^2}{V_s}}. \tag{19}$$

Thus a specification of a determines the distribution $\Phi(x)$, the approximate load $\overline{s}$, and the mutation rate u.

Moments of $\Phi(x)$ can be straightforwardly determined from Eq. (15) in terms of derivatives of $\text{sech}^{\beta}\left(mk/\sqrt{2}\right)$ at $k = 0$. Odd moments vanish and the first few even moments are, with $\overline{x^2} \stackrel{\text{def}}{\equiv} \int x^2\Phi(x)dx$ etc.,

$$\begin{aligned} \overline{x^2} &= m^2\beta/2 \\ \overline{x^4} &= m^4(3\beta^2 + 2\beta)/4 \\ \overline{x^6} &= m^6(15\beta^3 + 30\beta^2 + 16\beta)/8. \end{aligned} \tag{20}$$

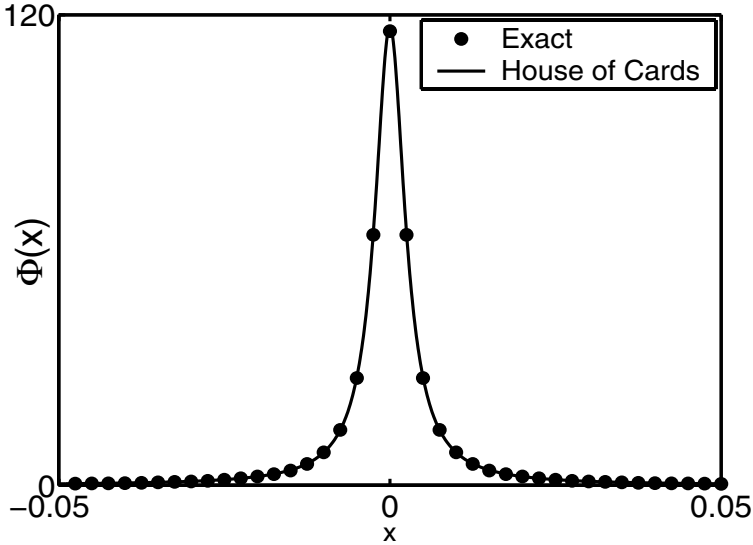

Fig. 3. The exact distribution of allelic effects of Eq. (18) is plotted along with the "House of Cards" approximation, $\Phi_{HC}(x) = 2uV_s f(0)/(x^2 + \beta^2 m^2/2)$ where $\beta = 4uV_s/m^2$ and parameter values are $m = 0.2$, $V_s = 20$ and $u = 10^{-5}$.

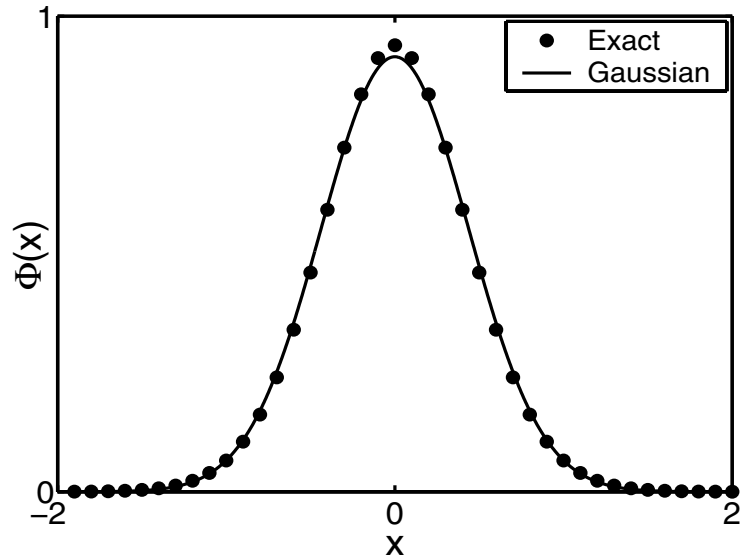

Fig. 4. The exact distribution of allelic effects of Eq. (18) is plotted along with the Gaussian approximation, $\Phi_G(x) = (\pi\beta m^2)^{-1/2} \exp\left[-x^2/(\beta m^2)\right]$ where $\beta = 2\sqrt{uV_s/m^2}$ and parameter values are $m = 0.2$, $V_s = 20$ and $u = 5 \times 10^{-2}$.

In Appendix B it is shown how the exact results interpolate between the result of the "House of Cards" approximation when uV_s/m^2 is small (Turelli 1984) and the Gaussian approximation when uV_s/m^2 is large (Turelli 1984; Kimura 1965).

5. Comparison of numerical and exact solutions

The numerical approximation to $\phi(k)$ follows from Eq. (11) and this requires $F(k)$, the Fourier transform of $f(x)$, along with the parameters V_s and m that appear in Eqs. (2) and (14). We have

$$F(k) = \int f(x)e^{ikx}dx = \operatorname{sech}^2\left(mk/\sqrt{2}\right) \tag{21}$$

and following the analysis of empirical data (Turelli 1984), V_s was taken to equal 20. Furthermore, the expected value of the mutational variance, m^2, was taken to equal 0.04 and arose from Lande's (1976) extrapolation of the data of Russell et al. (1963).

As a test of the numerical method, Eq. (11) has been iterated to convergence for 10 values of a in the range 10^{-11} to 10^{-2}, corresponding to mutation rates in the range 10^{-7} to 10^{-2}. The quantity k was taken to run from $-7/m$ to $7/m$ in steps of 0.175 and for each value of a it required less (sometimes far less) than 100 iterations for $\phi_n(k)$ to converge. The criterion adopted for convergence was that $\phi_n(k)$ differ, from one iteration to the next, by less than 1 part in 10^{14}. Fitting a polynomial in k to $\phi_\infty(k)$ in the vicinity of $k = 0$ allows estimation of the various moments of $\Phi(x)$. Table 1 contains the numerically calculated mutation rates and the mutation rates calculated from the exact solution.

In Table 2 the numerically calculated and exact moments of $\Phi(x)$ are given when a sixth order polynomial in k was fitted to $\phi(k)$ for 21 values of k in the range $1.75 \geq k \geq -1.75$.

All of the results, with the exception of the highest moment, $\overline{x^6}$, show that the numerical results are an excellent approximation of the exact results. The results for $\overline{x^6}$ are in error by up to 10% however accuracy of sixth moments is a very stringent test of a numerically determined distribution. These results can, however,

Table 1. Comparison of numerical and exact mutation rates and mutational loads.

a	$u_{\text{numerical}}$	u_{exact}	$\bar{s}_{\text{numerical}}$	$\bar{s}_{\text{exact}}$
10^{-11}	7.0728×10^{-8}	7.0721×10^{-8}	7.0718×10^{-8}	7.0711×10^{-8}
10^{-10}	2.2373×10^{-7}	2.2371×10^{-7}	2.2363×10^{-7}	2.2361×10^{-7}
10^{-9}	7.0818×10^{-7}	7.0811×10^{-7}	7.0718×10^{-7}	7.0711×10^{-7}
10^{-8}	2.2463×10^{-6}	2.2461×10^{-6}	2.2363×10^{-6}	2.2361×10^{-6}
10^{-7}	7.1717×10^{-6}	7.1711×10^{-6}	7.0717×10^{-6}	7.0711×10^{-6}
10^{-6}	2.3362×10^{-5}	2.3361×10^{-5}	2.2360×10^{-5}	2.2361×10^{-5}
10^{-5}	8.0712×10^{-5}	8.0711×10^{-5}	7.0712×10^{-5}	7.0711×10^{-5}
10^{-4}	3.2360×10^{-4}	3.23611×10^{-4}	2.2360×10^{-4}	2.2361×10^{-4}
10^{-3}	1.7069×10^{-3}	1.7071×10^{-3}	7.0686×10^{-4}	7.0711×10^{-4}
10^{-2}	1.2222×10^{-2}	1.2236×10^{-2}	2.2221×10^{-3}	2.2361×10^{-3}

Table 2. Comparison of numerical and exact results for higher moments.

a	$\overline{x^4}_{\text{numerical}}$	$\overline{x^4}_{\text{exact}}$	$\overline{x^6}_{\text{numerical}}$	$\overline{x^6}_{\text{exact}}$
10^{-11}	1.1318×10^{-7}	1.1316×10^{-7}	1.7478×10^{-8}	1.8107×10^{-8}
10^{-10}	3.5807×10^{-7}	3.5801×10^{-7}	5.5302×10^{-8}	5.7291×10^{-8}
10^{-9}	1.1339×10^{-6}	1.1338×10^{-6}	1.7520×10^{-7}	1.8150×10^{-7}
10^{-8}	3.6023×10^{-6}	3.6017×10^{-6}	5.5718×10^{-7}	5.7724×10^{-7}
10^{-7}	1.1555×10^{-5}	1.1554×10^{-5}	1.7937×10^{-6}	1.8585×10^{-6}
10^{-6}	3.8182×10^{-5}	3.8177×10^{-5}	5.9964×10^{-6}	6.2151×10^{-6}
10^{-5}	1.3715×10^{-4}	1.3714×10^{-4}	2.2400×10^{-5}	2.3241×10^{-5}
10^{-4}	5.9779×10^{-4}	5.9777×10^{-4}	1.1139×10^{-4}	1.1598×10^{-4}
10^{-3}	3.5311×10^{-3}	3.5314×10^{-3}	9.4927×10^{-4}	1.0004×10^{-4}
10^{-2}	2.7557×10^{-2}	2.7578×10^{-2}	1.4666×10^{-2}	1.6106×10^{-2}

be easily improved by taking a finer mesh for k, e.g. halving the splitting of k to 0.0875 reduces the error on $\overline{x^6}$ to less than 3%. This takes longer to compute, but the computation time is not a significant factor. For example, the total time for the combined production of Tables 1 and 2 was less than 3 seconds using MATLAB® on a standard PC.

6. Numerical determination of $\Phi(x)$

To numerically determine the distribution of allelic effects, $\Phi(x)$ there are two ways we can proceed. The direct way, mentioned in Section 3, is to iterate Eq. (7) and a situation where this method is useful is for a distribution of allelic effects that has a broad peak. Apart the obvious case of relatively large mutation rates, a non-trivial example where this occurs is when the fitness optimum increases uniformly with time (due to environmental change). After the distribution has settled down to a form that tracks the changing optimum, the distribution is very significantly broader than that with a static fitness optimum, and a variant of the above method may be applied in this case (Waxman and Peck 1999).

A second way of proceeding is to use the information we already possess about $\phi(k)$ from numerically iterating Eq. (11). This is knowledge of $\phi(k)$ in the region where $F(k)$, of Eq. (9), is appreciably different from zero. Let us write this region as $\Lambda > k > -\Lambda$; in Section 5 we took $\Lambda = 7/m$. The limited knowledge we possess of $\phi(k)$ is completely sufficient for our purposes. To see this note that $\Phi(x) = \int e^{-ikx}\phi(k)dk/(2\pi)$ and it is possible to split up the integral into three ranges: $\int_{-\infty}^{\infty} = \int_{-\Lambda}^{\Lambda} + \int_{\Lambda}^{\infty} + \int_{-\infty}^{-\Lambda}$. While we do not know $\phi(k)$ in the ranges of the second and third integrals we can use Eq. (10) to extend our knowledge of $\phi(k)$ outside of the region $\Lambda > k > -\Lambda$. In Appendix B the details of this analysis are given. The result is, with $\varepsilon \stackrel{\text{def}}{\equiv} \sqrt{2V_s a}$,

$$\Phi(x) = \int_{-\Lambda}^{\Lambda} e^{-ikx}\phi(k)\frac{dk}{2\pi} + \frac{uV_s}{2\pi\varepsilon}e^{-\varepsilon\Lambda} \times \left(\frac{e^{-i\Lambda x}}{\varepsilon + ix}\int_{-\Lambda}^{\Lambda} e^{\varepsilon k}F(k)\phi(k)dk + \frac{e^{i\Lambda x}}{\varepsilon - ix}\int_{-\Lambda}^{\Lambda} e^{-\varepsilon k}F(k)\phi(k)dk\right).$$

This result requires $\phi(k)$ only for k in the interval $\Lambda > k > -\Lambda$ and yields a numerically robust result for $\Phi(x)$. A comparison of exact and numerical results when $u = 10^{-5}$, $V_s = 20$ and $m = 0.2$ for $0.05 > x > -0.05$ yielded an error on $\Phi(x)$ that was smaller than 2%.

7. Summary

In this work numerical and exact solutions have been presented for the distribution of allelic effects in a one locus haploid model under weak selection. The agreement between the numerical and exact solutions is extremely good, and the computing resources needed for the numerical method are very modest. In languages such as MATLAB®, where linear algebra operations such as matrix multiplication are an integral part of the language, the numerical algorithm of this work can be written in roughly a dozen lines.

The numerical method introduced in this work can be applied to other problems, incorporating features not treated here, such as pleiotropy. It can also be used in problems not necessarily having a continuum of allelic effects. For example, it can be shown to apply (with some changes) to a discrete allele, stepwise model of mutation (Slatkin 1987; Bulmer 1989). Thus while derived and applied here in the context of continuum of alleles models, the numerical method also has applications in some discrete allele problems and it is likely to be an efficient way of proceeding.

The exact result for the distribution of allelic effects in equilibrium, $\Phi(x)$, was derived in Section 4 for a particular distribution of mutant effects that has completely reasonable (or unremarkable) properties. The exact result has a variety of uses. It provides the only explicit solution (to the author's knowledge) that continuously spans the House of Cards and Gaussian regimes – without requiring separate approximate treatments for these two extreme cases as well as covering all intermediate regimes. Additionally it constitutes a testing ground where we can now mathematically investigate features of biologically relevant quantities that include the equilibrium distribution of allelic effects, the genetic load, the genetic variance, the kurtosis and other equilibrium quantities. Indeed properties explicitly exhibited by the solution presented in this work may be properties that hold for a class of biologically interesting mutant distributions, and hence may motivate discovery - and ultimately proof – of these properties. This may be one very significant benefit of the result presented.

Appendix A

In this Appendix we consider two different ways of regulating the number of individuals in populations with overlapping generations under stabilising selection. A comparison is then made of the condition of equilbrium of these populations and the corresponding condition of equilibrium for a population with discrete generations and subject to weak selection.

To illustrate the above, it suffices to consider selection on a single phenotypic trait in an infinite population of haploid individuals.

The two ways of regulating population number are by adjusting either the birth rate or the death rate. The first approach is based on the method presented by the

author and J. R. Peck (Waxman and Peck 1999). In this case the death rate of individuals with genotypic value x, denoted by $D(x)$, was taken to be $D(x) = 1 + V_E/(2V) + x^2/(2V)$ where $V > 0$ and V_E is the environmental variance. Consider now a very small time interval where the non-overlapping events of births and deaths occur. If births occur at a rate of $B(t)$ and mutations occur at each birth with probability u then it follows that

$$\begin{aligned} -\partial\Phi(x,t)/\partial t = &\left[D(x) - (1-u)B(t)\right]\Phi(x,t) \\ &- u\,B(t)\int f(x-y)\Phi(y,t)dy \\ &- \Phi(x,t)\left[\int D(y)\Phi(y,t)dy - B(t)\right]. \end{aligned}$$

Many natural populations have numbers or densities that remain effectively constant in time; this feature is incorporated into the model by setting the birth rate equal to the mean death rate of the population: i.e. for all times we set $B(t) = \int_{-\infty}^{\infty} D(y)\Phi(y,t)dy \equiv \overline{D}(t)$. Thus at equilibrium, $0 = \left[D(x) - (1-u)\overline{D}\right]\Phi(x) - u\overline{D}\int f(x-y)\Phi(y)dy$. This equation does not coincide with the weak selection, discrete time equilibrium equation, Eq. (3), because of the term $u\overline{D}\int f(x-y)\Phi(y)dy$, which couples mean death rate and mutation.

In the second approach, we assume the birth rate has a constant value, B, while death rate is given by $D(x) + \Delta(t)$, where $D(x)$ is form used above and the additional death rate term, $\Delta(t)$, will be adjusted so that population number is regulated. These assumptions lead to

$$\begin{aligned} -\partial\Phi(x,t)/\partial t = &\left[D(x) + \Delta(t) - (1-u)B\right]\Phi(x,t) \\ &- u\,B\int f(x-y)\Phi(y,t)dy \\ &- \Phi(x,t)\left[\int \left[D(y) + \Delta(t)\right]\Phi(y,t)dy - B\right]. \end{aligned}$$

To regulate population size, we again require that the mean death rate equals the birth rate. This entails choosing $\Delta(t) = B - \overline{D}(t)$ and leads, at equilibrium, to $0 = \left[D(x) - \overline{D} + uB\right]\Phi(x,t) - uB\int f(x-y)\Phi(y,t)dy$. This equation has an identical *form* to the weak selection, discrete time equilibrium equation, Eq. (3).

It follows, from the above, that there may or may not be a complete equivalence of continuous time models and weak selection, discrete time models, depending on the precise way population number is regulated in the continuous time models.

Appendix B

In this Appendix, it is shown how results of the "House of Cards" approximation (Turelli 1984) and the Gaussian approximation (Kimura 1965) follow from the exact results of Section 4 in the regimes of small and large uV_s/m^2.

When $16uV_s/m^2 \ll 1$, we have $\beta = \frac{1}{2}\left(\sqrt{1 + \frac{16uV_s}{m^2}} - 1\right) \simeq 4uV_s/m^2$ and the genetic variance is $\int x^2\Phi(x)dx = m^2\beta/2 \simeq 2uV_s$. This is the prediction

of the "House of Cards" approximation. Furthermore, the smallness of β means $\text{sech}^{\beta}\left(mk/\sqrt{2}\right)$ in Eq. (15) stays roughly constant until large $|k|$ is achieved, by which time $\text{sech}\left(mk/\sqrt{2}\right)$ is well into its asymptotic form $2\exp(-m|k|/\sqrt{2})$. Thus $\Phi(x) \simeq \int e^{-ikx}\exp(-\beta m|k|/\sqrt{2})dk/(2\pi)$ and this can be written as $\Phi(x) \simeq 2uV_s f(0)/(x^2+\beta^2 m^2/2)$. This is the "House of Cards" approximation for $\Phi(x)$ when $|x| \ll m$.

When $16uV_s/m^2 \gg 1$, we have $\beta \simeq 2\sqrt{uV_s/m^2}$ and the genetic variance is $m^2\beta/2 \simeq \sqrt{uV_s m^2}$. This is the prediction of the Gaussian approximation. Furthermore, the largeness of β allows $\text{sech}^{\beta}\left(mk/\sqrt{2}\right)$ in Eq. (15) to be approximated by its small k behaviour $\text{sech}^{\beta}\left(mk/\sqrt{2}\right) \simeq \exp\left(-\beta m^2 k^2/4\right)$ so $\Phi(x) \simeq (\pi\beta m^2)^{-1/2}\exp\left[-x^2/(\beta m^2)\right]$ - a Gaussian.

The moments, as given in Eq. (20) can be similarly analysed. For $16uV_s/m^2 \ll 1$, $\beta \simeq 4uV_s/m^2$ and the expression for each moment is dominated by the lowest power of β; keeping just this contribution corresponds to the "House of Cards" approximation. For $16uV_s/m^2 \gg 1$, $\beta \simeq 2\sqrt{uV_s/m^2}$ and the expression for each moment is dominated by the highest power of β; keeping just this contribution corresponds to the Gaussian result.

Appendix C

In this Appendix an expression is derived for the distribution $\Phi(x)$, for all x, in terms of its Fourier transform $\phi(k)$ when k lies in the interval $\Lambda > k > -\Lambda$. Outside of this interval, the Fourier transform of $f(x)$, namely $F(k)$, is assumed to be negligibly small.

To proceed we begin with $\Phi(x) = \int e^{-ikx}\phi(k)dk/(2\pi)$ which can be written

$$\Phi(x) = \int_{-\Lambda}^{\Lambda} e^{-ikx}\phi(k)\frac{dk}{2\pi} + I \tag{22}$$

where

$$I = \int_{\Lambda}^{\infty}\left[e^{-ikx}\phi(k) + e^{ikx}\phi(-k)\right]\frac{dk}{2\pi}. \tag{23}$$

To simplify I, Eqs. (10) and (12) allow us to replace $\phi(k)$ by $u\int_{-\Lambda}^{\Lambda} G_a(k-q)F(q)\phi(q)dq$ (the limits on q are $\pm\Lambda$ since $F(q)$ is negligible for q beyond these points). Thus

$$I = u\int_{\Lambda}^{\infty}\frac{dk}{2\pi}\int_{-\Lambda}^{\Lambda} dq\left[e^{-ikx}G_a(k-q) + e^{ikx}G_a(k+q)\right]F(q)\phi(q). \tag{24}$$

Since $k > |q|$ we can replace $G_a(k \pm q)$ on the right-hand-side of Eq. (24) by $V_s/\varepsilon\exp(-\varepsilon(k \pm q))$ where we have defined $\varepsilon = \sqrt{2V_s a}$. Carrying out the k integration yields

$$I = \frac{uV_s}{2\pi\varepsilon}e^{-\varepsilon\Lambda}\left(\frac{e^{-i\Lambda x}}{\varepsilon + ix}\int_{-\Lambda}^{\Lambda} dq e^{\varepsilon q}F(q)\phi(q) + \frac{e^{i\Lambda x}}{\varepsilon - ix}\int_{-\Lambda}^{\Lambda} dq e^{-\varepsilon q}F(q)\phi(q)\right)$$

and this result, when used in Eq. (22), yields the desired expression for $\Phi(x)$.

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