Available online at www.sciencedirect.com
SCIENCE DIRECT
Theoretical Population Biology 69 (2006) 409–418
Theoretical Population Biology
www.elsevier.com/locate/tpb

The frequency of the perfect genotype in a population subject to pleiotropic mutation

D. Waxman*, J.R. Peck

Centre for the Study of Evolution, School of Life Sciences, University of Sussex, Brighton BN1 9QG, Sussex, UK

Received 17 November 2004
Available online 10 March 2006

Abstract

We consider a large population of asexual organisms characterised by a number of quantitative traits that are subject to stabilising selection. Mutation is taken to act pleiotropically, with every mutation generally changing all of the traits under selection. We focus on the equilibrium distribution of the population, where mutation and selection are in balance. It has been previously established that the equilibrium distribution of genotypic effects may be anomalous, as it may contain a singular spike—a Dirac delta function—corresponding to a non-zero proportion of the population having exactly optimal genotypic values. In the present work, we present exact results for the case where three traits are under selection. These results give the equilibrium genetic variance of the population, and the proportion of the population that have the optimal genotype. This is achieved for two different spherically symmetric distributions of mutant effects. Additionally, a simple and robust numerical approach is also presented that allows the treatment of some other mutation distributions, where there are an arbitrary number of selected traits.

Keywords: Mutation selection balance; Pleiotropy; Stabilising selection; Theory; Quantitative trait

1. Introduction

The way that quantitative genetic variation can be maintained by the balance between recurrent mutation and stabilising selection has received a great deal of attention in the population genetics literature. (For a review, see e.g. Bulmer, 1989; Bürger, 1998, and for the most recent work on sexual populations involving pleiotropy, see Zhang et al., 2004.) An implicit assumption underlying the majority of work on this subject is that the equilibrium distribution of genotypic effects is smooth and continuous. However, recent theoretical studies of models with mutations that affect multiple traits (i.e. mutations with pleiotropic effects) have come to different conclusions. In particular, Waxman and Peck (1998, 2000) performed calculations using the continuum-of-alleles model of mutation introduced by Crow and Kimura (1964). They considered an asexual population where no form of recombination can occur. In a large (effectively infinite) population, where genetic drift can be neglected, the distribution of genotypic effects is not always smooth or non-singular. As long as a mutation can simultaneously affect three or more traits, a range of parameter values may exist where the equilibrium distribution of genotypic effects is singular. To be specific, the distribution may contain a sharp "spike", a Dirac delta function (Dirac, 1958), that is located at the genotypic trait values that maximise fitness—the "optimal" or "perfect" genotype. Fig. 1 illustrates how the distribution of genotypic effects of a single trait, say trait 1, can differ in the form it takes, depending on the nature of mutation.

This singular behaviour corresponds to a finite proportion of the population having just one particular genotype—the optimal genotype—out of the infinite number of genotypes that are possible under a continuum-of-alleles model. The singular behaviour can also be viewed as there being a non-negligible probability that a randomly chosen individual will have the optimal genotype. When a spike is present in the equilibrium genotype distribution, the optimal genotype is unique, in that it occurs in the population at an appreciable frequency, while the frequency of any other particular genotype is negligible.

*Corresponding author. Fax: +44 01273 678433.
E-mail address: D.Waxman@sussex.ac.uk (D. Waxman).

0040-5809/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.tpb.2006.01.004

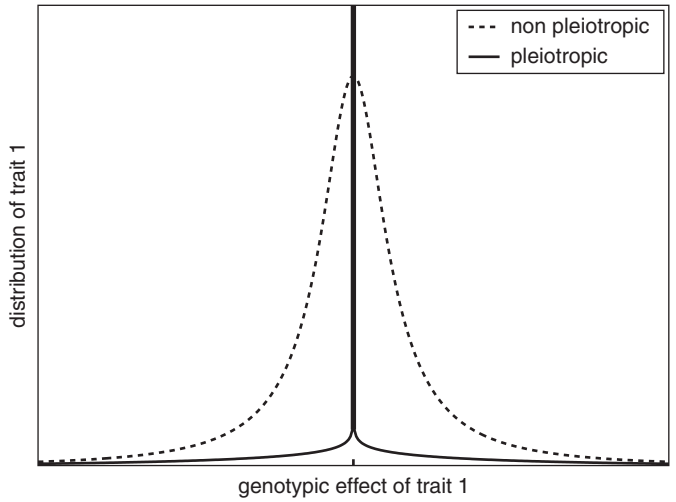

Fig. 1. The equilibrium distribution of genotypic effects for a single trait (trait 1) is plotted as a function of the genotypic effect of the trait. The population is large (effectively infinite). The broken curve is the distribution that results when mutation acts non-pleiotropically (i.e. where only a single trait is changed, when a mutation occurs). The solid curve is an example of the distribution that can result when mutation acts pleiotropically, with three traits simultaneously changed by each mutation. This latter distribution is singular in that it contains a Dirac delta function that may contain an appreciable proportion of the area of the distribution. The delta function is represented by the vertical line. This line is infinite in height, and its width should be infinitesimal; however, we have broadened it to allow visualisation. Despite the very different appearance of the two distributions, their variances may be very similar in value. For the distribution arising from pleiotropic mutations, the variance is u/s (see Section 4). For the non-pleiotropic case, the variance approximately coincides with this value (under the House of Cards approximation—see the end of Section 3).

Such singular behaviour is surprising, since it can arise from seemingly innocuous distributions of mutant effects, that is, distributions that have a completely continuous range of possible mutations, and that allow infinitesimally small changes as well as finite changes (singular equilibrium behaviour can, of course, arise from singular distributions of mutant effects, Kingman, 1978; Bürger and Bomze, 1996). The origin of the spike has been discussed elsewhere (Waxman and Peck, 1998, 2000) and arises from a suppression of mutations of non-optimal genotypes to genotypes that are near optimal. It has a robust, geometrical origin. In the Discussion, we give the rationale for a spike-like behaviour being likely in the case of more elaborate models, where genotypic effects are discrete.

In the present work we investigate, in some detail, the singular behaviour that can arise in pleiotropic models. When there are Ω traits, and when $\Omega \geqslant 3$, singular behaviour in the distribution of genotypic effects is, in principle, possible (Waxman and Peck, 1998, 2000). We write the genotypic effects on the Ω traits (also termed genotypic values) in the form $\mathbf{g} = (g_1, g_2, \ldots, g_\Omega)$. The equilibrium distribution of genotypic values is written as $\Phi(\mathbf{g})$ and has the interpretation that the probability of a randomly chosen individual having trait values in the infinitesimal region of "volume" $d^\Omega g \equiv dg_1\, dg_2 \ldots dg_\Omega$ centred at $\mathbf{g}$ is $\Phi(\mathbf{g})\, d^\Omega g$.

When we use the phrase "singular" we do not mean distributions that simply diverge for some $\mathbf{g}$, for example $\Phi(\mathbf{g}) \propto \|\mathbf{g}\|^{-2}$ where $\|\mathbf{g}\| = \sqrt{g_1^2 + g_2^2 + \cdots + g_\Omega^2}$. Rather, by singular, we mean distributions that contain a Dirac delta function, $\delta(\mathbf{g})$, which may be thought of as an infinitely high, infinitely narrow spike, whose integral, over a range of $\mathbf{g}$ that contains the point $\mathbf{g} = \mathbf{0} \equiv (0, 0, \ldots, 0)$, is unity. If a term such as $A\delta(\mathbf{g})$ (where A is a constant) is present in $\Phi(\mathbf{g})$ then a proportion A of the population will have traits with values given by $\mathbf{g} = \mathbf{0}$ and, for the individuals constituting this proportion of the population, there will be no variation in their genotypic values around $\mathbf{g} = \mathbf{0}$. The remainder of the population do not lie "under the spike" and make up a proportion $1 - A$ of the population, with any single genotype, in this part of the population, being present at negligible frequency. There is variation in genotypic values of the traits associated with this non-optimal proportion of the population and even if A is close to unity, an appreciable variance in trait values may arise from non-optimal individuals. For example (and as we shall see), the variance of the marginal distribution of trait g_1 of a singular distribution containing a spike may, for small mutation rates, have a variance very close to the variance of a corresponding problem where mutations do not act pleiotropically (the corresponding distributions are plotted in Fig. 1). This occurs, even though in the non-pleiotropic problem, the equilibrium distribution of g_1 is everywhere finite, continuous and non-singular.

The proportion of the population lying under the spike, A, has not, so far, been analysed analytically over an appreciable range of mutation rates (or other parameters). It has been approximated only when close to $A = 1$, even though A can range from 0 to 1. Similarly, the analysis of the genetic variance on any trait, written as $V_{G,1}$, has also only received a limited analysis. There are a number of questions that remain unanswered or aspects of the problem that are uncertain because of the limited analysis. The present work aims to remedy this and illustrate key aspects of the problem by restricting discussion to the smallest number traits where a spike is possible ($\Omega = 3$) and using particular distributions of mutant effects that lead to exact results.

Thus we can ask:

(i) How accurate is the approximation that has been previously used in the small mutation rate regime—the House of Cards approximation—for the proportion of the population lying under the spike, A, and the genetic variance on any trait, $V_{G,1}$? (See later for more details of this approximation).

(ii) Increasing the mutation rate from a starting point of zero, there generally exists a critical mutation rate, beyond which A vanishes and no spike is present in the distribution. Do different distributions of mutant effects lead to the same critical mutation rate, or different ones?

(iii) In what way does A vanish, when the mutation rate approaches its critical value?
(iv) How does $V_{G,1}$ behave as a function of the mutation rate, when there is a spike in $\Phi(\mathbf{g})$?
(v) Are there any choices of the distribution of mutant effects that are not biologically implausible, where exact expressions can be derived for the proportion, A, of the population under the spike and the genetic variance, $V_{G,1}$?
(vi) In situations where the equilibrium distribution of genotypic effects, $\Phi(\mathbf{g})$, is singular, are there robust numerical approaches available for estimating the value of A?

It is clear that if we can answer questions (v) and (vi) then the answers to the previous questions automatically follow. Before, however, we can address these questions we need to specify the model in more detail.

2. Model

Consider an effectively infinite population of asexual organisms, which do not undergo any form of recombination, and where individuals are subject to selection on Ω different phenotypic traits. We assume that the phenotypic value of an individual on trait i is additively determined by the genotypic value of that trait, say g_i, and an environmental noise component, ε_i. The distribution of environmental effects is taken as independent of the distribution of genotypic effects, has mean zero, variance V_e for all ε_i, and has ε_i and ε_i statistically independent for $i \neq j$.

We write possible genotypic effects as $\mathbf{g} = (g_1, g_2, \ldots, g_\Omega)$ and each g_i is assumed to take continuous values ranging from $-\infty$ to ∞. Following Kimura (1965), we assume generations are overlapping and hence time is continuous. We restrict our analysis to a description of equilibrium (see below). However, the conclusions we arrive at apply, as an approximation, to populations with discrete generations, when subject to weak selection.

Births are, by an appropriate scaling of time, taken to occur at a rate of one per unit time and mutation is taken to occur at a rate (i.e. probability) of u per replication. We restrict all considerations of this work to spherically symmetric distributions of mutant effects. To see what this entails, consider a mutant offspring arising from an individual with genotypic effects $\mathbf{h} = (h_1, h_2, \ldots, h_\Omega)$. Spherical symmetry means the probability the offspring has genotypic effects lying in a region of infinitesimal "volume" $d^\Omega g = dg_1\, dg_2 \ldots dg_\Omega$, centred on $\mathbf{g}$, depends only on the magnitude of the mutational change, $\|\mathbf{g}-\mathbf{h}\|$. This probability is taken to be $f(\|\mathbf{g}-\mathbf{h}\|)\, d^\Omega g$, with $f(\|\mathbf{g}\|)$ termed the distribution of mutant effects. The variance of mutant effects on any single trait is taken to have a value of m^2 which is independent of Ω.

The Malthusian fitness of individuals with genotypic values $\mathbf{g} = (g_1, g_2, \ldots, g_\Omega)$ arises from an average over environmental effects of Malthusian fitness as a function of phenotypic values, and is taken to have the form $1 - s\|\mathbf{g}\|^2/\Omega$. Here s is a positive parameter whose value is a measure of the intensity of selection on genotypic values. This form of fitness is of a stabilising type, with an optimal genotypic value of $\mathbf{g} = \mathbf{0} \equiv (0, 0, \ldots, 0)$, since any deviation of $\mathbf{g}$ from $\mathbf{0}$ leads to a decreased value of fitness. The factor $1/\Omega$, which is present in the Malthusian fitness, results in a mean selection coefficient of sm^2 against the mutant offspring of parents with maximal fitness. Thus taking s to be independent of Ω ensures that s has an equivalent interpretation for different Ω. We note that the form of Malthusian fitness adopted may, in discrete time models, be considered closely equivalent to noroptimal selection (Haldane, 1954).

Following Kimura (1965), Bulmer (1989) or via the weak selection/small mutation approximation of a discrete time model, we can derive the equation describing the dynamics of the distribution of genotypic effects. At equilibrium this equation reduces to

$$\frac{s}{\Omega}\|\mathbf{g}\|^2\Phi(\mathbf{g}) - u\int f(\|\mathbf{g}-\mathbf{h}\|)\Phi(\mathbf{h})\, d^\Omega h = -\lambda\Phi(\mathbf{g}), \tag{1}$$

where λ is a constant that must be chosen so that $\Phi(\mathbf{g})$ is non-negative and normalised to unity: $\int \Phi(\mathbf{g})\, d^\Omega g = 1$. Both here and elsewhere, integrals with unspecified limits are taken to cover the full, $-\infty$ to ∞, range of all integration variables.

3. Approximate results for $\Omega = 3$

In order to set the context for the exact results we obtain, it is necessary to discuss approximate results. We note that the equilibrium variance of a sexual model with pleiotropy was analysed by Turelli (1985) using the House of Cards approximation. This approximation applies when mutant effects are, to a first approximation, unrelated to the corresponding parental effects (Turelli, 1984). This is very similar to the exact behaviour of the House of Cards *model* of mutation (Kingman, 1978). Our focus in this work is on the singular equilibrium genotypic distributions that can arise as a result of pleiotropy, when analysis is restricted to asexual populations. Like previous studies of this phenomenon, we shall use the House of Cards approximation to derive expressions for the proportion A of the population under the spike and the genetic variance, $V_{G,1}$. As we shall see (by comparison with the exact results developed in the next section), these expressions are adequate for small values of the mutation rate, u, and they are qualitatively informative, even for larger values of u.

Henceforth, we will treat only the case of $\Omega = 3$ (except in the Appendix, where some numerical results are generalised to larger values of Ω).

The House of Cards approximation in Eq. (1) is applicable if the range of $\mathbf{g}$ where $\Phi(\mathbf{g})$ is appreciable is much smaller than the range of $\mathbf{g}$ where $f(\|\mathbf{g}\|)$ varies appreciably. It simply entails replacing $\int f(\|\mathbf{g}-\mathbf{h}\|)\Phi(\mathbf{h})\, d^3h$

by $\int f(\|\mathbf{g}\|)\Phi(\mathbf{h})\,d^3h \equiv f(\|\mathbf{g}\|)$. This leads to

$$\frac{s}{3}\|\mathbf{g}\|^2\Phi_{\rm HC}(\mathbf{g}) - uf(\|\mathbf{g}\|) = -\lambda\Phi_{\rm HC}(\mathbf{g}) \tag{2}$$

and the subtlety of the problem depends on the size of u. If u is sufficiently large that $\lambda>0$ then Eq. (2) has the non-singular solution $\Phi_{\rm HC}(\mathbf{g}) = (3u/s)f(\|\mathbf{g}\|)/(\|\mathbf{g}\|^2 + 3\lambda/s)$ and λ is determined from normalisation: $\int \Phi_{\rm HC}(\mathbf{g})\,d^3g = 1$. We note that the value of u required for $\lambda>0$ may be too large for good accuracy of the approximation.

The ability to normalise $\Phi_{\rm HC}(\mathbf{g})$ should not be taken for granted, so let us consider the largest value that $\int \Phi_{\rm HC}(\mathbf{g})\,d^3g$ can have, prior to fixing λ from the requirement of normalisation. We note that when λ takes its smallest possible value, which is $\lambda = 0$ (see the Appendix for the reason for this), the integral $\int \Phi_{\rm HC}(\mathbf{g})\,d^3g$ takes its largest value, hence $\int \Phi_{\rm HC}(\mathbf{g})\,d^3g \leqslant (3u/s)\int f(\|\mathbf{g}\|)/\|\mathbf{g}\|^2\,d^3g$. When the quantity on the right side of this inequality is <1 the House of Cards solution, $\Phi_{\rm HC}(\mathbf{g})$, given above, cannot be normalised to unity and it no longer is a valid probability density. The resolution of this impasse is that when $\lambda = 0$, it is no longer legitimate to simply solve Eq. (2) by (i) collecting all terms in $\Phi_{\rm HC}$ together onto the left hand side, and then (ii) solving for $\Phi_{\rm HC}$ by dividing by $(s/3)\|\mathbf{g}\|^2 + \lambda$. When $\lambda = 0$ the quantity $(s/3)\|\mathbf{g}\|^2 + \lambda$ vanishes at $\mathbf{g} = \mathbf{0}$ and this allows the presence of a Dirac delta function in the solution (Dirac, 1958) and leads to a *singular* House of Cards solution:

$$\Phi_{\rm HC}(\mathbf{g}) = A_{\rm HC}\delta(\mathbf{g}) + \frac{3u}{s}\frac{f(\|\mathbf{g}\|)}{\|\mathbf{g}\|^2}. \tag{3}$$

Here $A_{\rm HC}$ is a constant equal to the House of Cards approximation for the proportion of the population under the spike, A; it is determined from the requirement of normalisation, $\int \Phi_{\rm HC}(\mathbf{g})\,d^3g = 1$, and given by

$$A_{\rm HC} = 1 - \frac{3u}{s}\int \frac{f(\|\mathbf{g}\|)}{\|\mathbf{g}\|^2}\,d^3g \equiv 1 - \frac{u}{u_{c,\rm HC}}, \tag{4}$$

where

$$u_{c,\rm HC} = \frac{s}{3\int f(\|\mathbf{g}\|)/\|\mathbf{g}\|^2\,d^3g}. \tag{5}$$

The result of Eq. (4) predicts that if $\int f(\|\mathbf{g}\|)/\|\mathbf{g}\|^2\,d^3g < \infty$ then $A = 1$ when $u = 0$ and that for sufficiently small u, A decreases approximately linearly with u. Given a form of $f(\|\mathbf{g}\|)$ it is possible to estimate the region where the approximation is accurate by determining where the variance of $\Phi_{\rm HC}(\mathbf{g})$ is very small compared with the variance of $f(\|\mathbf{g}\|)$.

A necessary condition for $\lambda = 0$, under the House of Cards approximation, is $u \leqslant u_{c,\rm HC}$. Since the validity of the House of Cards approximation requires that the variance of $\Phi_{\rm HC}(\mathbf{g})$ is small, which occurs when u is small, it is not obviously reasonable to give great significance to the relatively large value of u where $A_{\rm HC}$ actually vanishes, namely at $u = u_{c,\rm HC}$.

Lastly, the House of Cards approximation of the genetic variance, in the parameter region where $\lambda = 0$ and a spike is possible, is $V_{G,1,\rm HC} = \int g_1^2\Phi_{\rm HC}(\mathbf{g})\,d^3g \equiv \int \|\mathbf{g}\|^2\Phi_{\rm HC}(\mathbf{g})\,d^3g/3$ (the last result for $V_{G,1,\rm HC}$ following from spherical symmetry of $\Phi_{\rm HC}(\mathbf{g})$). It follows, from multiplying Eq. (3) by $\|\mathbf{g}\|^2$ and using $\|\mathbf{g}\|^2\delta(\mathbf{g}) \equiv 0$, that

$$V_{G,1,\rm HC} = u/s. \tag{6}$$

This is also the result we would obtain for the genetic variance under the House of Cards approximation of a non-pleiotropic problem, where the mutation distribution $f(\|\mathbf{g}-\mathbf{h}\|)$ is replaced by $\frac{1}{3}\sum_{j=1}^{3} f_1(g_j - h_j) \times \prod_{k=1(k\neq j)}^{3} \delta(g_k - h_k)$.

Let us now compare the above approximate results with some exact results.

4. Exact results for $\Omega = 3$

We present exact solutions of Eq. (1) when $\Omega = 3$, for two particular choices of the distribution of mutant effects, $f(\|\mathbf{g}\|)$. Calculational details are relegated to the Appendix. From the exact solutions we obtain exact expressions for (i) the proportion of the population lying under the spike, A (i.e. the proportion of the population having *exactly* the optimal genotypic value) and (ii) the genetic variance, $V_{G,1}$.

As a suitable reference distribution, we use an isotropic Gaussian distribution, which we denote as $f_0(\|\mathbf{g}\|)$

$$f_0(\|\mathbf{g}\|) = \left(\frac{1}{2\pi m^2}\right)^{3/2}\exp\left(-\frac{\|\mathbf{g}\|^2}{2m^2}\right). \tag{7}$$

The two forms of the distribution $f(\|\mathbf{g}\|)$, for which we can solve Eq. (1), are written as $f_1(\|\mathbf{g}\|)$ and $f_2(\|\mathbf{g}\|)$ and given by

$$f_1(\|\mathbf{g}\|) = -\frac{1}{2\pi m^2}\frac{1}{\|\mathbf{g}\|}\frac{\partial}{\partial\|\mathbf{g}\|}\frac{\|\mathbf{g}\|}{\sinh(\pi\|\mathbf{g}\|/(\sqrt{2}m))}, \tag{8}$$

$$f_2(\|\mathbf{g}\|) = \frac{1}{\pi m^3}\exp\left(-\frac{2\|\mathbf{g}\|}{m}\right). \tag{9}$$

Parameters in the two distributions have been chosen so that the variance of any single trait is m^2, i.e. identical to the variance of any single trait of the Gaussian distribution, Eq. (7).

We note that both $f_1(\|\mathbf{g}\|)$ and $f_2(\|\mathbf{g}\|)$ are decreasing functions of $\|\mathbf{g}\|$, with a finite maximum value that is proportional to m^{-3}. At large $\|\mathbf{g}\|$ both distributions fall off essentially exponentially with $\|\mathbf{g}\|$. This is a slower decrease than that of the Gaussian distribution, Eq. (7), but it does not appear to have any significant implications.

In order to compare the distributions f_0, f_1 and f_2 we have produced two different plots of them. In Fig. 2a, we plot the distributions as functions of $\|\mathbf{g}\|$ while in Fig. 2b we plot $4\pi\|\mathbf{g}\|^2 f(\|\mathbf{g}\|)$ as a function of $\|\mathbf{g}\|$. The quantity $4\pi\|\mathbf{g}\|^2 f(\|\mathbf{g}\|)\,d\|\mathbf{g}\|$ is the probability that the *magnitude* of a mutational change, $\mathbf{g}$, lies in the infinitesimal range $\|\mathbf{g}\|$ to $\|\mathbf{g}\| + d\|\mathbf{g}\|$.

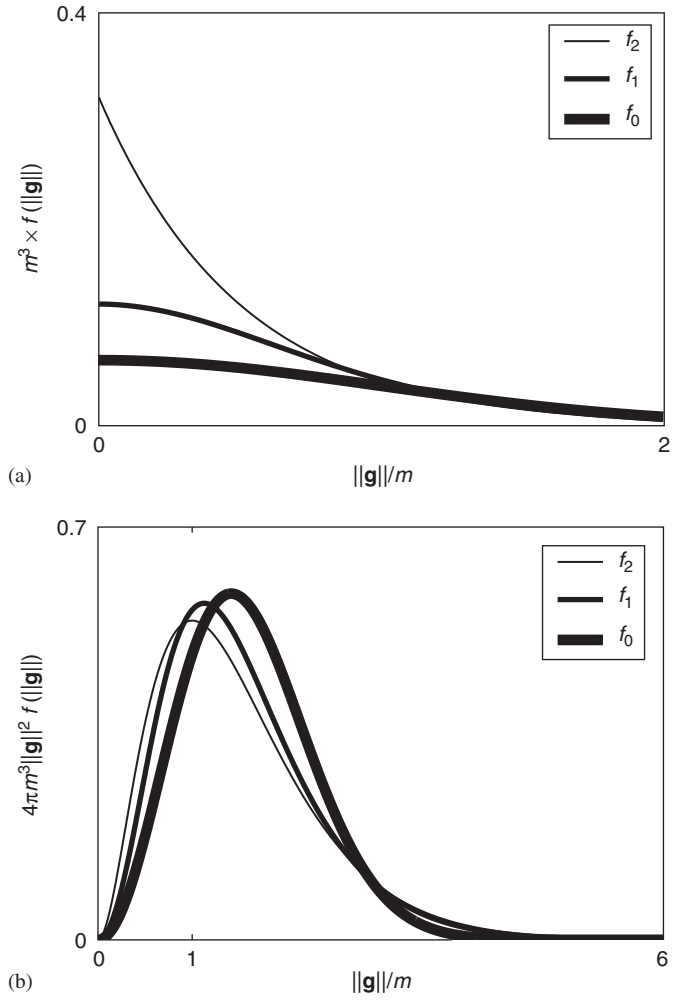

Fig. 2. (a) The distributions of mutant effects, $f_0(\|\mathbf{g}\|)$, $f_1(\|\mathbf{g}\|)$ and $f_2(\|\mathbf{g}\|)$ of Eqs. (7)–(9), are plotted as a function of $\|\mathbf{g}\|$. All distributions are normalised to unity: $\int f(\|\mathbf{g}\|)\, d^3g = 1$, and parameters in the distributions are chosen so that the variance of any single trait is m^2: $\int g_i^2 f(\|\mathbf{g}\|)\, d^3g = m^2$. (b) The distribution of mutant effects $f(\|\mathbf{g}\|)$ has a distribution of magnitudes of mutational changes of $4\pi\|\mathbf{g}\|^2 f(\|\mathbf{g}\|)$ and this is plotted as a function of $\|\mathbf{g}\|$. This distribution appears in any spherically symmetric integrals involving $f(\|\mathbf{g}\|)$ and all three distributions have a maximum close to $\|\mathbf{g}\| = m$, where m^2 is the variance on any single trait.

We write the equilibrium proportion of the population lying under the spike for distribution f_i as $A(f_i)$ and the corresponding genetic variance as $V_{G,1}(f_i)$. With $\Gamma(\bullet)$ denoting Euler's Gamma function (Abramowitz and Stegun, 1970) we find that for the distribution f_1

$$A(f_1) = \begin{cases} \dfrac{\sqrt{\pi}}{\Gamma\left(\dfrac{3+\sqrt{1+8u/u_{c,1}}}{4}\right)\Gamma\left(\dfrac{3-\sqrt{1+8u/u_{c,1}}}{4}\right)}, & u < u_{c,1}, \\ 0, & u \geqslant u_{c,1}, \end{cases} \tag{10}$$

where

$$u_{c,1} = sm^2/3 \tag{11}$$

and for $u \leqslant u_{c,1}$, $V_{G,1}(f_1) = u/s$.

For the distribution f_2 we find

$$A(f_2) = \begin{cases} \dfrac{\sin((\pi/2)\sqrt{1+3u/u_{c,2}})}{\sqrt{1+3u/u_{c,2}}}, & u < u_{c,2}, \\ 0, & u \geqslant u_{c,2}, \end{cases} \tag{12}$$

where

$$u_{c,2} = sm^2/4 \tag{13}$$

and for $u \leqslant u_{c,2}$, $V_{G,1}(f_2) = u/s$.

The quantities $u_{c,1}$ and $u_{c,2}$ are the critical mutation rates, beyond which there is no spike in the equilibrium distribution. They do not coincide with the House of Cards approximation given in Eq. (5), but are significantly larger: $u_{c,1}/u_{c,1,\mathrm{HC}} = 2\ln 2 \simeq 1.4$ and $u_{c,2}/u_{c,2,\mathrm{HC}} = 1.5$.

In Fig. 3 we plot $A(f_1)$ and $A(f_2)$ as a function of mutation rate u and, for comparison, plot the numerically determined result for a Gaussian distribution, $A(f_0)$.

In the regime where a spike exists, the genetic variances $V_{G,1}(f_i)$ for $i = 0$, 1 and 2 are all exactly equal to the leading result of the House of Cards approximation, u/s. This result applies, in fact, for any spherically distribution of mutant effects, for any value of Ω, when a spike exists.

It may be directly verified from Eqs. (10) and (12) that by assuming $u/(sm^2) \ll 1$ and keeping terms only up to linear order in u, the coefficients A_1 and A_2 agree with the House of Cards approximation, Eq. (4).

For mutation rates in the vicinity of the exact critical mutation rates (i.e. $u \simeq u_{c,1}$ or $u_{c,2}$) we find $A_1 \simeq (\frac{2}{3})(1 - u/u_{c,1})$ and $A_2 \simeq (3\pi/16)(1 - u/u_{c,2})$. Hence although A_1 and A_2 vanish at $u_{c,1}$ or $u_{c,2}$, they do so with different values of the slope, $dA/du|_{u=u_c}$, and with a different slope to the

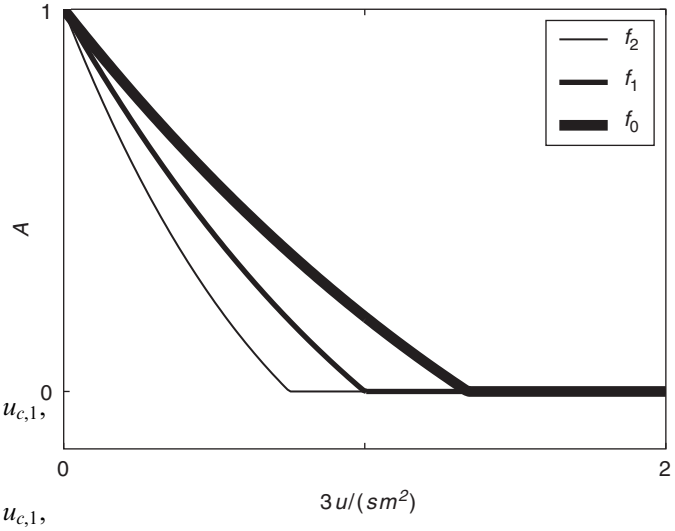

Fig. 3. The proportion of the population "under the spike," A, is plotted as a function of mutation rate u. The three cases plotted correspond to the distributions of mutant effects of Eqs. (7)–(9). The curve arising from the Gaussian distribution $f_0(\|\mathbf{g}\|)$ of Eq. (7) was calculated numerically, using the method of Section 5. The curves arising from the other two distributions were calculated from Eqs. (10) and (12) and are indistinguishable from numerically calculated curves.

House of Cards approximation for A, when extrapolated to large u.

5. Numerical method

To complement the exact analytical results of the previous section, we present here a very simple and robust numerical approach to calculate the proportion of individuals under the spike, A, when the distribution of mutant effects is, as previously assumed, spherically symmetric and there are three traits. Details of the rationale behind this approach are given in the Appendix, as well as a generalisation to an arbitrary number of traits.

The numerical approach requires knowledge of the Fourier transform of the distribution of mutant effects. The Fourier transform is denoted by $F(\|\mathbf{q}\|)$ and defined by $F(\|\mathbf{q}\|) = \int e^{-i\mathbf{q}\cdot\mathbf{g}} f(\|\mathbf{g}\|)\, d^3g$, where $\mathbf{q}\cdot\mathbf{g}$ denotes the scalar product of $\mathbf{q}$ and $\mathbf{g}$.

Given $F(\|\mathbf{q}\|)$, we numerically solve the differential equation $(s/3)\, d^2\chi(r)/dr^2 + uF(r)\chi(r) = 0$ for $\chi(r)$, subject to the initial conditions $\chi(0) = 0$, $d\chi(r)/dr\big|_{r=0} = 1$. The value of $d\chi(r)/dr$, when r is large and positive, is a significant quantity. When $\lim_{r\to\infty} d\chi(r)/dr$ is positive it coincides with the proportion of the population under the spike, A, and when $\lim_{r\to\infty} d\chi(r)/dr$ is not positive, A is zero. Given the high accuracy of numerical differential equation solvers and the property of $\chi(r)$ that it asymptotically changes linearly with r, it follows that $d\chi(r)/dr$, for large but finite r, robustly coincides with A, when the result is positive.

In Fig. 4, we plot a numerically determined form of $\chi(r)$ following from the distribution of mutant effects, f_1, of Eq. (8).

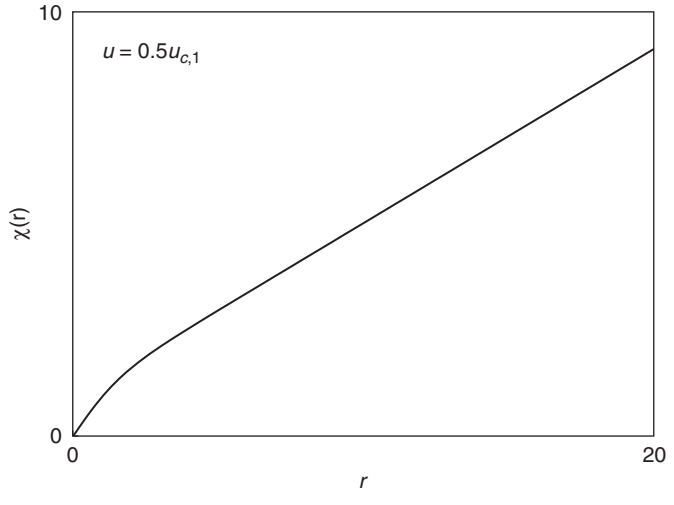

Fig. 4. The function $\chi(r)$ of Section 5 is plotted as a function of r. The coefficient of r in the linearly changing, large r, region coincides with the proportion of the population "under the spike," A. The case plotted is for the distribution $f_1(\|\mathbf{g}\|)$ of Eq. (8), for $u = 0.5sm^2/3 \equiv 0.5u_{c,1}$. Comparing the analytical result of Eq. (10) with the numerically determined coefficient of r (using Matlab's differential equation solver with default settings) leads to a numerical error of order $10^{-3}\%$.

6. Discussion

The present work has considered two distributions of mutant effects that appear qualitatively similar to an isotropic Gaussian distribution; they are both spherically symmetric (depend only on the magnitude of mutational changes), are unimodal and have a finite maximum value. As we have shown in an exact analysis, they can both lead to a spike in the equilibrium distribution of genotypic effects. They constitute explicit examples of mutational distributions where the distribution of genotypic effects can have a very different shape from that of a smooth distribution. Despite this difference in shape, we have also shown that when the distribution of genotypic effects is most different from a smooth distribution, by having a spike present, the genetic variance is little changed from that of the House of Cards approximation, and has the exact value u/s.

Given that in reality there are only countably many sequence variants that affect the expression of any locus, the spike in the distribution of genotypic effects may be objected to, as being biologically trivial. In a sufficiently large population with discrete genotypic effects, the optimal sequence will *always* make up a finite fraction of the population at equilibrium, and hence has a finite probability of occurring in a randomly chosen individual, irrespective of details such as the number of traits. So how is this different, in principle, from the presence of the spike described throughout this work, which also represents the optimal sequence being present with finite probability in the population? The answer to this question requires us to recognise that there are two possible alternatives for the equilibrium distribution of discrete genotypes (Waxman, 2003). Namely there are equilibrium distributions where either

(i) sequences with fitness close to that of the fittest sequence are at a comparable frequency to that of the most fit sequence
or
(ii) sequences with fitness close to that of the fittest sequence are at a very significantly reduced frequency, compared with that of the most fit sequence.

If alternative (i) holds then a conventional sort of distribution arises, which could reasonably be approximated as a continuous function of genotypic values of the type that is standard in quantitative genetics. If, however, alternative (ii) holds then a single genotype (the one conferring highest fitness) has a significantly higher representation in the population than would be naively expected, and a non-conventional sort of distribution describes the population. If this distribution is approximated as a function of continuous genotypic values then it will be of the singular type introduced in the earlier work of Waxman and Peck (1998, 2000). It is alternative (ii) that this paper has aimed to describe and, when applicable, the

spike in the distribution of genotypic effects may be viewed as the way the continuum-of-alleles model of mutation correctly reproduces the anomalously high frequency of the optimal genotype.

From the work of Waxman (2003) it follows that alternative (ii) is likely to apply when the difference in values of adjacent discrete genotypic effects on any trait is very small compared with the standard deviation of mutant effects on that trait. As far as pleiotropic mutations are concerned, this is an important hidden assumption that needs to be satisfied if continuum-of-alleles models can be used in place of discrete effect models.

We note that there has been theoretical work questioning the existence of the spike in the equilibrium distribution of mutant effects (Wingreen et al., 2003). The authors of this work considered a form for the distribution of mutant effects that differed from the Gaussian distribution originally adopted by Waxman and Peck (1998, 2000). For $\Omega = 3$ the distribution of Wingreen et al. (2003) is (in the notation of the present work) proportional to $\|\mathbf{g}\|^{-2}\exp(-\|\mathbf{g}\|^2/(2m_0^2))$, where m_0 is a constant. One of the properties of this distribution is that it possesses a form of correlations not present in a Gaussian distribution. These are not the standard sort of correlations between mutational effects on different traits—which are included in earlier work (Turelli, 1985) and which do not prevent a spike in the distribution of genotypic effects. Rather, they are correlations between the *magnitudes* of mutational changes on different traits and which could be characterised by the covariance $\mathrm{Cov}(g_i^2, g_j^2) = E[(g_i^2 - E[g_i^2])(g_j^2 - E[g_j^2])]$, where $E[\ldots]$ denotes an expectation taken with respect to the distribution of mutant effects. Wingreen et al. (2003) chose, however, to characterise the correlations between the magnitudes of mutational changes in a different way. They used a conditional expectation: the expected value of the squared mutational change of trait i ($i \neq 1$), g_i^2, when the squared mutational change of trait 1 (i.e. g_1^2) has a given value. We write this as $E[g_i^2|g_1^2]$. Then with $\kappa = g_1^2/(2m_0^2)$ and for $\Omega = 3$, Wingreen et al. found a result equivalent to $E[g_i^2|g_1^2] = m_0^2((\exp(-\kappa)/\int_\kappa^\infty \exp(-u)/u\,du) - \kappa)$ and these authors plotted $E[g_i^2|g_1^2]/m_0^2$ against $\ln(g_1^2/m_0^2)$ in their Figure 2. We have reproduced this curve as a dashed curve in Fig. 5.

The dashed curve is monotonically increasing, indicating a positive correlation in the magnitude of mutations for different selected traits. The corresponding result for the Gaussian distribution, Eq. (7), if plotted on this same graph, would produce a horizontal line, because it does not have any correlations between magnitudes of mutational changes. Wingreen et al. (2003) stated that:

"... in the standard model for pleiotropic mutations (Turelli, 1985), the magnitudes of the effects of a single mutation on distinct traits are uncorrelated. The absence of correlation leads directly to (a) the suppression of mutations of small overall effect and (b) the preservation of the perfect phenotype (Waxman and Peck, 1998)".

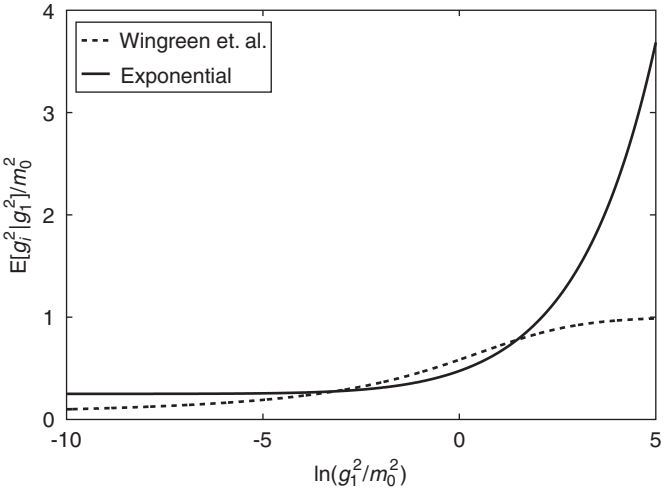

Fig. 5. For the case $\Omega = 3$, the conditional expectation of squared mutational effects, $E[g_i^2|g_1^2]/m_0^2$, is plotted as a function of $\ln(g_1^2/m_0^2)$. The dashed line represents the conditional expectation for the mutational distribution of Wingreen et al. (2003), which is proportional to $\|\mathbf{g}\|^{-2}\exp(-\|\mathbf{g}\|^2/(2m_0^2))$. The solid line represents the conditional expectation for the exponential distribution of mutant effects, $f_2(\|\mathbf{g}\|)$, of Eq. (9). The parameter m appearing in $f_2(\|\mathbf{g}\|)$ has been chosen to equal $m_0/\sqrt{3}$ so that both distributions used for the plot have the same value of the standard deviation of mutant effects on any single trait.

The exponential mutation distribution given in Eq. (9) provides an explicit counterexample to the above claim. We have already established that the distribution of Eq. (9) can yield a spike in the distribution of genotypic effects. Defining $\Lambda = 2|g_1|/m$, the distribution of Eq. (9) has the conditional expectation $E[g_i^2|g_1^2] = (m/2)^2(\Lambda^2 + 3\Lambda + 3)/(\Lambda + 1)$. To aid comparison with the result of Wingreen et al. we set $m = m_0/\sqrt{3}$ so that the standard deviation of mutant effects on each trait in both models is identical (and equal to $m_0/\sqrt{3}$). The solid line in Fig. 5 gives the value of $E[g_i^2|g_1^2]/m_0^2$ as a function of $\ln(g_1^2/m_0^2)$ for the exponential mutation distribution of Eq. (9). The curve is a monotonically increasing function of $\ln(g_1^2/m_0^2)$, indicating positive correlations between magnitudes of mutational changes. The shape of the curve is different from the curve of Wingreen et al. (dashed line); however, both curves are broadly comparable in value, over the range of g_1^2 plotted, thereby indicating comparable positive correlations of squared mutational changes on different traits.

The work of Wingreen et al. (2003) has been cited in the work of Johnson and Barton (2005). The absence of any correlations in the mutational distribution adopted by Waxman and Peck (1998) (Eq. (7)) was taken as the sole reason that a spike was present in our earlier results and hence that there is "... a possible inadequacy of the model ..." (Johnson and Barton, 2005). In view of the exactly soluble counterexample given above, where the exponential mutation distribution allows both a spike *and* correlations in the *magnitude* of mutational changes, it is evidently the case that the existence of a spike is robust to some deviations from the model of Waxman and Peck and the objection of Johnson and Barton appears unjustified.

The reason the mutational distribution of Wingreen et al. does not predict any spike in the distribution of genotypic effects is, we believe, solely associated with the divergence of their distribution at $\mathbf{g}=\mathbf{0}$ and the presence or absence correlations of magnitudes of mutation effects appears to be an irrelevant side issue.

Pursuing this last point, the analysis of Section 3 indicates that in a regime of very low mutation rates, a House of Cards approximation would predict a spike in the equilibrium distribution of genotypic effects. Necessarily, the mutation rate, u, should be small compared with the critical mutation rate, $u_{c,\mathrm{HC}}$ (see Eq. (4)). However, using the mutation distribution of Wingreen et al. (2003) it follows that $\int f(\|\mathbf{g}\|)/\|\mathbf{g}\|^2\, d^3g=\infty$ and hence, from Eq. (5), that $u_{c,\mathrm{HC}}=0$. The vanishing of $u_{c,\mathrm{HC}}$ means that for any non-zero mutation rate, no matter how small, there will be no spike present. The vanishing of $u_{c,\mathrm{HC}}$ holds, in fact, for general Ω, for the mutation distribution of Wingreen et al. (2003). It is an empirical question whether the behaviour of the mutation distribution at $\mathbf{g}=\mathbf{0}$ is such that it drives the critical mutation rate to vanish or allows it to remain finite. We do not address this empirical issue here.

Let us return now to the questions posed at the beginning of this paper. The results we have presented allow us to provide the following answers to these:

(i) The proportion of the population under the spike, A, as calculated from the House of Cards approximation, is in agreement with the results derived from the exact expressions, when the latter are expanded to linear order in the assumed small quantity $u/(sm^2)$. Additionally, the leading House of Cards approximation for the genetic variance, $V_{G,1}$, coincides with the exact result for this quantity, when a spike is present in the equilibrium distribution of genotypic effects.

(ii) Different distributions of mutant effects generally lead to different critical mutation rates, u_c, beyond which A is zero.

(iii) The way the proportion A vanishes as the mutation rate approaches the critical mutation rate, u_c, depends on the distribution of mutant effects; in the cases we have looked at, A vanishes linearly at $u=u_c$, but with different slopes for different distributions.

(iv) For all spherically symmetric distributions of mutant effects that can lead to a spike in the equilibrium distribution of genotypic effects, $\Phi(\mathbf{g})$, the genetic variance, $V_{G,1}$, exactly equals u/s, when a spike is actually present in $\Phi(\mathbf{g})$.

(v) We have been able to find two cases of the distribution of mutant effects where exact expressions can be derived for the proportion A of the population under the spike and the genetic variance, $V_{G,1}$.
We approached the problem by first calculating the characteristic function of $\Phi(\mathbf{g})$ (i.e. its Fourier transform) and then derived the expression for A from this. More generally we can use the characteristic function to determine equilibrium expectations of combinations of powers of the various g_j.

(vi) We have been able to provide a robust numerical approach that can determine A and more generally the characteristic function of $\Phi(\mathbf{g})$.

A comparison of the numerical approach with the exact results suggests that the numerical methods presented here work to extremely high accuracy.

There is always a suspicion, when only approximate results are available, that one may not be in possession of the full story. The exact results presented in this paper firmly demonstrate that the singular equilibrium distribution of genotypic values predicted by Waxman and Peck (1998) exists in continuum of alleles models of mutant effects. The results also show that the singularity (the spike) possesses a level of robustness; it exists for more than one distribution of mutant effects, and can coexist with correlations between *magnitudes* of mutational changes on different traits, despite claims to the contrary that have appeared in the literature.

Additionally, the arguments presented above also make it clear that there is not just mathematical correctness to the existence of a spike in the equilibrium distribution of genotypic effects. There is also a genuine biological meaning to the spike, when the difference of adjacent discrete genotypic effects on any trait are very small compared with the standard deviation of mutant effects on the trait.

Acknowledgments

We thank Günter Wagner for stimulating discussions on related issues. We also thank three anonymous referees for constructive comments that have improved this work. One of us (D. W.) acknowledges support of the Leverhulme Trust.

Appendix A

In this appendix, we give the theoretical background to results stated in the main text.

A.1. Analytical results

We start with Eq. (1) and note that if $\lambda>0$ then there is no possibility of a spike = Dirac delta function, $\delta(\mathbf{g})$, being present in $\Phi(\mathbf{g})$. Writing $\sigma=s/\Omega$, this follows since if $\lambda>0$, then

$$\Phi(\mathbf{g})=u\int f(\|\mathbf{g}-\mathbf{h}\|)\Phi(\mathbf{h})\,d^{\Omega}h/[\sigma\|\mathbf{g}\|^2+\lambda] \tag{A.1}$$

and if $\Phi(\mathbf{g})=A\delta(\mathbf{g})+\cdots$ with A a constant, the left-hand side of Eq. (A.1) contains $A\delta(\mathbf{g})$, while the right-hand side does not contain any delta function singularity, hence A must be identically zero. When $\lambda=0$ this conclusion breaks down, since deriving Eq. (A.1) involves dividing by

$\sigma\|\mathbf{g}\|^2 + 0$ and this latter quantity vanishes at $\mathbf{g} = 0$. This leads to the behaviour of $\Phi(\mathbf{g})$ being undetermined at $\mathbf{g} = 0$.

Note that λ cannot be <0 since if it is, apart from singular behaviour arising at $\|\mathbf{g}\|^2 = |\lambda|/\sigma$, the quantity $\sigma\|\mathbf{g}\|^2 + \lambda \equiv \sigma\|\mathbf{g}\|^2 - |\lambda|$ that is present in Eq. (A.1) changes sign as $\|\mathbf{g}\|^2$ passes through $|\lambda|/\sigma$ and hence so does $\Phi(\mathbf{g})$. Thus, to avoid negative probability densities, λ must be $\geqslant 0$.

Given our focus, in this paper, on the properties of a spike in the equilibrium distribution of genotypic effects, $\Phi(\mathbf{g})$, when $\Omega = 3$, we shall restrict Ω to this value and restrict all further discussion to the case where a spike can occur, namely $\lambda = 0$. We then need to investigate the conditions under which $\Phi(\mathbf{g})$ is a meaningful probability density for $\lambda = 0$ and this involves studying properties of

$$\frac{s}{3}\|\mathbf{g}\|^2\Phi(\mathbf{g}) - u\int f(\|\mathbf{g}-\mathbf{h}\|)\Phi(\mathbf{h})\,d^3h = 0. \tag{A.2}$$

We proceed by Fourier transforming Eq. (A.2) (i.e. by multiplying by $\exp(-i\mathbf{q}\cdot\mathbf{g})$, where $\mathbf{q}\cdot\mathbf{g}$ denotes the scalar product of $\mathbf{q}$ and $\mathbf{g}$, and integrating over all $\mathbf{g}$). We use the notation $\varphi(\mathbf{q}) = \int \Phi(\mathbf{g})\exp(-i\mathbf{q}\cdot\mathbf{g})\,d^3g$ and $F(\|\mathbf{q}\|) = \int e^{-i\mathbf{q}\cdot\mathbf{g}} f(\|\mathbf{g}\|)\,d^3g$ and note $\varphi(\mathbf{0}) = 1$, since $\Phi(\mathbf{g})$ is normalised to unity. We then obtain

$$-\frac{s}{3}\nabla^2\varphi(\mathbf{q}) - uF(\|\mathbf{q}\|)\varphi(\mathbf{q}) = 0, \tag{A.3}$$

where $\nabla^2 = \partial^2/\partial q_1^2 + \partial^2/\partial q_2^2 + \partial^2/\partial q_3^2$ is the Laplacian operator in three dimensions.

It may be very plausibly argued that a spherically symmetric solution is the long term outcome of dynamics for $\Phi(\mathbf{g})$ and hence also $\varphi(\mathbf{q})$. The latter is thus taken to be a function of $q \overset{\text{def}}{\equiv} \|\mathbf{q}\|$ and ∇^2 may be replaced, in Eq. (A.3), by just its "radial" derivative part, $d^2/dq^2 + (2/q)\,d/dq$.

Eq. (A.3) takes its simplest form in terms of the function

$$\chi(q) \overset{\text{def}}{\equiv} q\varphi(\mathbf{q}), \tag{A.4}$$

which obeys

$$\left(\frac{s}{3}\frac{d^2}{dq^2} + uF(q)\right)\chi(q) = 0, \tag{A.5}$$

$$\chi(0) = 0, \quad d\chi(q)/dq|_{q=0} = 1, \tag{A.6}$$

with the conditions on $\chi(q)$ at $q = 0$ arising from $\varphi(\mathbf{0}) = 1$ and Eq. (A.4). Thus the problem at hand has reduced to an initial value problem, where knowledge of $\chi(0)$ and $d\chi(q)/d|q_{q=0}$ along with Eq. (A.5) are sufficient to determine $\chi(q)$ for all positive q.

The large q behaviour of $\chi(q)$ determines the magnitude, A, of any spike present in $\Phi(\mathbf{g})$. To see this note that since $|\varphi(\mathbf{q})| \leqslant 1$, it follows that $|\chi(q)| \leqslant q$. Thus for $F(q)$ such that $\lim_{q\to\infty} qF(q) = 0$, it follows that at large q, Eq. (A.5) approaches $(s/3)\,d^2\chi(q)/dq^2 = 0$ and $\chi(q)$ approaches $Aq + B$ where A and B are constants. This large q behaviour of $\chi(q)$ corresponds to $\varphi(\mathbf{q})$ behaving (for large q) as $A + B/q$ and this means that A is the coefficient of $\delta(\mathbf{g})$ in $\Phi(\mathbf{g})$ (only singular functions have Fourier transforms that do not decay to zero at large q). Combinations of parameters leading to A exactly vanishing correspond to the critical-case where there is no delta function present in $\Phi(\mathbf{g})$, but $\lambda = 0$. Combinations of parameters leading to $A<0$ correspond to the region where $\lambda = 0$ no longer applies: the solution can then be negative for some $\mathbf{g}$ and it is then necessary to introduce a non-zero value of λ. The resulting equilibrium distribution, $\Phi(\mathbf{g})$, is non-singular.

The virtue of the distributions of mutant effects, $f(\|\mathbf{g}\|)$, of Eqs. (8) and (9) is that they have very simple Fourier transforms that lead to exact solution of Eq. (A.5). For the distribution of Eq. (8), the Fourier transform is $F_1(q) = \text{sech}^2(mq/\sqrt{2})$ and for $u \leqslant u_{c,1}$ (where $u_{c,1}$ is given in Eq. (11)). The corresponding solution of Eq. (A.5) is $\chi_1(q) = (\sqrt{2}/m)\tanh(mq/\sqrt{2})F(a_+, a_-; \frac{3}{2}, \tanh^2(mq/\sqrt{2}))$ where $F(a,b;c;z)$ denotes a hypergeometric function (Abramowitz and Stegun, 1970), $a_\pm = (3 \pm \sqrt{1 + 8u/u_{c,1}})/4$ and $u_{c,1}$ is the critical mutation rate given in Eq. (11). For the distribution of Eq. (9), the Fourier transform is $F_2(q) = (1 + (m^2q^2/4))^{-2}$ and for $u \leqslant u_{c,2}$ (where $u_{c,2}$ is the critical mutation rate given in Eq. (13)), the solution of Eq. (A.5) is $\chi_2(q) = (\sqrt{4/m^2 + q^2}/\beta)\sin(\beta\arctan(mq/2))$ where $\beta = \sqrt{1 + 3u/u_{c,2}}$.

From the large q behaviour of these solutions, the coefficient of q, when it is non-negative, coincides with the coefficient A multiplying the delta function in the equilibrium distribution, $\Phi(\mathbf{g})$. The resulting A's are given in Eqs. (10) and (12) of the main text.

By contrast, the small q behaviour of the solutions is given by $\chi(q) = q - V_{G,1}q^3/2 + O(q^5)$ and from this we can obtain the resulting $V_{G,1}$'s. However, given spherical symmetry of $\Phi(\mathbf{g})$, it is simplest to determine $V_{G,1}$ for $\lambda = 0$ by integrating Eq. (A.2) over all $\mathbf{g}$ with the exact result that $V_{G,1} = \int \|\mathbf{g}\|^2\Phi_{\text{HC}}(\mathbf{g})\,d^3g/3 = u/s$.

A.2. Numerical results

The numerical technique given in Section 5 also follows from the same approach, since we proceed by numerically solving Eq. (A.5), subject to Eq. (A.6), and determine A (when it is non-negative) from the coefficient of q in the solution at large q.

Lastly we note that there is an alternative numerical approach that applies when there are Ω traits (not just three, as above). In this case the radial part of ∇^2 is $d^2/dq^2 + ((\Omega-1)/q)\,d/dq$ and we solve $-(s/\Omega)[d^2\varphi(q)/dq^2 + ((\Omega-1)/q)\,d\varphi(q)/dq] - uF(q)\varphi(q) = 0$ for $\varphi(q)$, again as an initial value problem. To determine the initial data, we assume a power series solution for $\varphi(q)$: $\varphi(q) = 1 + aq + bq^2/2 + \cdots$. Ensuring the series solves the equation leads, generally, to $a = 0$, hence we have $\varphi(0) = 1$, $d\varphi(q)/dq|_{q=0} = 0$ and we have sufficient information to determine $\varphi(q)$. The large q value of $\varphi(q)$ coincides with the magnitude, A, of any spike present in $\Phi(\mathbf{g})$. There is a slight subtlety of this approach, since we impose conditions at $q = 0$ and the differential equation contains a factor q^{-1}

which diverges at this point. Taking the initial point as a small positive value of q rather than $q = 0$, say $q = 10^{-6}$, yields satisfactory results.

References

Abramowitz, M., Stegun, I., 1970. Handbook of Mathematical Functions. Dover Publications Inc., New York.

Bulmer, M.G., 1989. Maintenance of genetic variability by mutation-selection balance: a child's guide through the jungle. Genome 31, 761–767.

Bürger, R., 1998. Mathematical properties of mutation-selection balance models. Genetica 102/103, 279–298.

Bürger, R., Bomze, I.M., 1996. Stationary distributions under mutation selection balance: structure and properties. Adv. Appl. Probab. 28, 227–251.

Crow, J.F., Kimura, M., 1964. The theory of genetic loads. Proceedings of the XIth International Congress of Genetics, vol. 2, pp. 495–505.

Dirac, P.A.M., 1958. The Principles of Quantum Mechanics, fourth ed. Oxford University Press, Oxford.

Haldane, J.B.S., 1954. The measurement of natural selection. In: Montalenti, G., Chiarugi, A. (Eds.), Proceedings of the Ninth International Congress of Genetics, Bellagio, Italy, August 1953, Part 1, pp. 480–487.

Johnson, T., Barton, N., 2005. Theoretical models of selection and mutation on quantitative traits. Philos. Trans. R. Soc. B 360, 1411–1425.

Kimura, M., 1965. A stochastic model concerning the maintenance of genetic variability in quantitative characters. Proc. Nat. Acad. Sci. USA 54, 731–736.

Kingman, J.F.C., 1978. A simple model for the balance between selection and mutation. J. Appl. Probab. 15, 1–12.

Turelli, M., 1984. Heritable genetic variation via mutation selection balance: Lerche's zeta meets the abdominal bristle. Theor. Popul. Biol. 25, 138–193.

Turelli, M., 1985. Effects of pleiotropy on predictions concerning mutation-selection balance for polygenic traits. Genetics 111, 165–195.

Waxman, D., 2003. The balance between pleiotropic mutation and selection, when alleles have discrete effects. Theor. Popul. Biol. 63, 105–114.

Waxman, D., Peck, J.R., 1998. Pleiotropy and the preservation of perfection. Science 279, 1210–1213.

Waxman, D., Peck, J.R., 2000. The outcome of evolution when mutations are highly pleiotropic. Selection 1, 181–191.

Wingreen, N.S., Miller, J., Cox, E.C., 2003. Scaling of mutational effects in models for pleiotropy. Genetics 164, 1221–1228.

Zhang, X.S., Wang, J.L., Hill, W.G., 2004. Influence of dominance, leptokurtosis and pleiotropy of deleterious mutations on quantitative genetic variation at mutation-selection balance. Genetics 166, 597–610.