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The Outcome of Evolution when Mutations are Highly Pleiotropic

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A mathematical model of mutation and selection in a very large population is given. Each mutation affects Ω different phenotypic characters, each of which is subject to stabilising selection. In the limit $\Omega \to \infty$, when all other parameters are held fixed, each mutation is lethal. Thus at equilibrium, the majority of individuals have the optimal genotype. A small proportion of individuals, however, have other genotypes. These are newly arisen mutants who will not survive to the next generation. In a separate model, we again take the limit $\Omega \to \infty$, but in this case we decrease the standard deviation of mutant effects on each character, so that mutations are generally not lethal. In this case we find that, at equilibrium, the distribution of genotypes and the distribution of fitnesses have unusual features. In particular, the marginal distribution of genotypic values of any single character has the form of a single sharp "spike" (Dirac delta function) corresponding to all individuals having an optimal value of the character. Despite the applicability of this for all characters, there still is variation in fitness over the population and the distribution of fitnesses consists of a series of sharp "spikes" at particular levels of fitness. This type of distribution arises at equilibrium even if a wide variety of genotypes are initially present.

Keywords: Pleiotropy, mutation, stabilising selection on phenotypic characters

1. Introduction

Any organism can be described by a large number of phenotypic characters, some of which affect fitness. When a mutation occurs, it may result in the value of more than one phenotypic character being changed. In this case, we say that we have an instance of pleiotropy. Pleiotropy is, at heart, a property of all of the alleles connected by mutation: The set of all mutants defines a space of phenotypic effects and the degree of pleiotropy, Ω, may be thought of as the minimal dimensionality of this space (G. P. Wagner, personal communication). Mutations that result in multiple characters being changed are well known and are often regarded as ubiquitous (Caspari, 1952; Bulmer, 1972; Wright, 1977; Lande, 1980; Turelli, 1985; Wagner, 1989; Barton and Turelli, 1989; Barton, 1990; Keightley and Hill, 1990; Kondrashov and Turelli, 1992; Gavrilets and Dejong, 1993; Caballero and Keightley, 1994; Wagner, 1996). Pleiotropy is thus apparently common.

In general, only a very limited number of phenotypic measurements are made in any one experiment and it is not clear how many characters, Ω, are usually affected by a single mutation. Experimental work, however, suggests that a single mutation can often affect multiple characters, even when these characters are selected in a fairly arbitrary way (Santiago et al., 1992; Mackay, 1996). We therefore expect that mutations that affect many characters are common and in this paper we study the impact of high degrees of pleiotropy on the long-term outcome of evolution.

In (Waxman and Peck, 1998) it was shown that the number of characters, Ω, affected by each mutation, can have a dramatic effect on the equilibrium distribution of genotypes. In a model with a continuous range of genotypes, it was proved that a critical value of Ω, called Ω_c, exists. If $\Omega < \Omega_c$, the distribution of genotypic values is smooth and any particular genotype, including the optimal one, constitutes only an infinitesimal proportion of the population at equilibrium. If, however, $\Omega \geq \Omega_c$, the distribution of

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genotypic values possesses an infinitely high "spike" of zero width but finite area that is located at the optimal genotype. Such a distribution is singular, and corresponds to a non-negligible proportion of the population having the optimal genotype. The transition that occurs at $\Omega = \Omega_c$ has been described as a kind of "crystallisation" that occurs when the "complexity" (i.e. Ω) is sufficiently high (Wagner, 1998).

At equilibrium, when $\Omega \geq \Omega_c$, the non-negligible proportion of individuals of optimal genotype might be thought to arise purely from high selection coefficients against mutants of these individuals. While selection coefficients increase with Ω (when all other parameters are held fixed) this is not the origin of the transition found. The transition originates from suppression of mutations to the optimal or near-optimal genotypes (Waxman and Peck, 1998). Increasing Ω decreases the volume in "genotypic space" available for such mutations and the transition typically occurs at $\Omega = 3$ since an extremely large decrease in this volume occurs in going from $\Omega = 2$ to $\Omega = 3$. When $\Omega \geq \Omega_c$, a consequence of the suppressed mutations is that non-optimal genotypes cannot, with any appreciable probability, mutate back to optimality or its close vicinity. The lineages descending from these will, over long times, be eliminated from the population. Thus at equilibrium, the entire population consists of individuals of the optimal genotype (which make up the spike in the distribution) and a cloud of recently mutated individuals originating from the optimal genotype. The essentially geometric origin of the transition in Ω (a volume change) makes it relatively insensitive to the precise strength of selection. Adjusting the strength of selection or the variance of mutant effects with Ω, so a mutation of an optimal genotype individual has, independently of Ω, the same mean selection coefficient against it, still typically results in a transition at $\Omega = 3$.

In the present work we explore further implications of pleiotropy on evolution. In particular we investigate what happens when the degree of pleiotropy, Ω, is extremely high. This is of intrinsic interest because, as pointed out above, it seems likely that many real mutations have highly pleiotropic effects.

1.1. The model

Consider a hypothetical population in which the number of individuals is sufficiently large that stochastic effects can be ignored. Reproduction is taken to be asexual and all parents produce offspring during the same relatively narrow interval of time and then die, so generations are discrete.

Our focus in this study is entirely upon the effects of a high degree of pleiotropy so we consider the simplest mathematical model incorporating pleiotropy. This corresponds to a single haploid locus that is under selection and has a mutation rate of μ. The results obtained have more general applications than just to this simple model. They apply to n-ploid asexuals with L mutable loci (n and L arbitrary) provided the distribution of mutant effects at each locus is of a "translation invariant" type that depends on differences of parental and offspring effects on the characters. Furthermore it is necessary to replace the mutation rate, μ, by the genomic mutation rate U of the n-ploids and neglect offspring that differ from their parent by more than a single mutation. This requires $U << 1$ so terms of order U^2 and higher order can be neglected.

Within the one locus haploid model, every mutation affects Ω different phenotypic characters, which are numbered 1, 2, …, Ω. Each character can be measured on a continuous scale, and an individual's measurement on the ith character is denoted by z_i where $\infty > z_i > -\infty$. For simplicity, assume that these characters are independent of each other in two different senses:

(i) each character affects fitness multiplicatively,

(ii) there is no correlation in the magnitudes or directions of the effects of mutations on the Ω different characters.

To be specific about the effects of mutations on phenotypes and fitness, we assume that the phenotype of a particular offspring on the ith character depends on its genotypic value on that character, x_i, plus a normally distributed environmental noise component, ε_i. Thus $z_i = x_i + \varepsilon_i$. The distribution of ε_i is independent of x_i has mean zero, variance V_e and, for $i \neq j$, ε_i and ε_j are uncorrelated.

Most fitness-affecting characters are probably controlled by many codons. It is possible that for some traits, only a very limited number of genotypic values are possible, even if many codons control the

trait, however, we know of no apriori reason for this to be the case. We thus use the traditional approach (Crow and Kimura, 1964) of treating genotypic values, x_i, as continuous variables ranging from $-\infty$ to ∞.

The genotypic values of an individual are identical to that of its parent, unless a new mutation has occurred during production of the individual. The rate of such mutations is μ ($1 \geq \mu \geq 0$) with every mutation simultaneously affecting all Ω characters. Mutant effects follow a multidimensional Gaussian distribution (Lande, 1980). In particular, consider an individual that undergoes a mutation, and who is produced by a parent whose genotypic values on the Ω different characters are $x_1^*, x_2^*, \ldots, x_\Omega^*$, respectively. With $dx_1, dx_2, \ldots$, infinitesimal, the probability that this individual will have x_1 in the interval $x_1^* + dx_1 > x_1 > x_1^*$, and x_2 in the interval $x_2^* + dx_2 > x_2 > x_2^*, \ldots$ is given by $\prod_{i=1}^{\Omega} [f(x_i - x_i^*)dx_i]$, where

$$f(x_i - x_i^*) = \sqrt{\frac{1}{2\pi m^2}} \exp\left(-\frac{(x_i - x_i^*)^2}{2m^2} \right) \qquad (1)$$

The parameter m gives, for a single character, the standard deviation of mutant effects about the parental value. These assumptions about mutation imply that the magnitude of changes due to mutation are uncorrelated among the Ω characters. Furthermore, mutations are unbiased in the sense that mutations that tend to increase the value of a particular phenotypic character have the same frequency and average magnitude as mutations that tend to decrease the value of the trait.

The probability that an individual survives to reproductive age depends on the individual's phenotype and we assume that each of the Ω characters is subject to stabilising selection. We adopt a Gaussian fitness scheme, where the optimal phenotypic value for each trait, z_i, is defined, without loss of generality, to lie at $z_i = 0$. Then the probability of surviving viability selection for a particular individual with phenotypic values, $z_1, z_2, \ldots, z_\Omega$ is

$$\prod_{i=1}^{\Omega} \exp[-z_i^2 / (2V)],$$

where $V > 0$. Let w be proportional to the probability of surviving to reproductive age for an individual with a particular set of genotypic values $x_1, x_2, \ldots, x_\Omega$. We obtain w by averaging the probability of surviving viability selection, for that individual, over all possible environmental effects ε_i. We scale w, so its value is unity for an individual with the optimal genotype, $x_1 = x_2 = \ldots x_\Omega = 0$. With this definition

$$w = \prod_{i=1}^{\Omega} \exp[-x_i^2 / (2V_s)],$$

where $V_s = V + V_e$ (Turelli, 1984). The mean value of w over the population is proportional to the fraction of offspring that survive viability selection.

The life cycle begins again with the production of new offspring, with fertility taken to be independent of genotype. Census is taken immediately after production of offspring.

2. Results

A derivation of all results is provided in the Appendix.

2.1. Results for small values of Ω

The model just described has been extensively studied for the case where $\Omega = 1$ (Turelli, 1984; Burger, 1986, 1988; Burger and Hofbauer, 1994; Waxman and Peck, 1998). When $\Omega = 1$ only a single trait is subject to selection and at equilibrium, x_1 has a smooth, symmetric, and unimodal distribution. Any single genotype (including the optimal one) constitutes only an infinitesimal fraction of the population. The peak of the genotypic distribution lies at $x_1 = 0$. The mean value of w over the population at equilibrium, is denoted by $\overline{w}$ and, when $\Omega = 1$, we always have $\overline{w} > 1 - \mu$ (see Burger and Hofbauer, 1994; Wax- man and Peck, 1998). The equilibrium distribution of fitnesses is smooth and finite except at $w = 1$. Near this point, the fitness distribution behaves as $k/\sqrt{(1 - w)}$ with k a positive constant.

Waxman and Peck (1998) have shown that when $\Omega = 2$ the equilibrium marginal distribution of x_1 and separately that of x_2, is smooth, symmetric and unimodal, just as in the case $\Omega = 1$. Thus for $\Omega = 2$ the optimal genotype ($x_1 = x_2 = 0$) constitutes an infinitesimal proportion of the population. Furthermore $\overline{w} > 1 - \mu$, as in the case $\Omega = 1$.

For $\Omega = 3$ the equilibrium genotypic distribution depends on $\mu V_s/m^2$. If $\mu V_s/m^2 << 1$ the optimal geno-

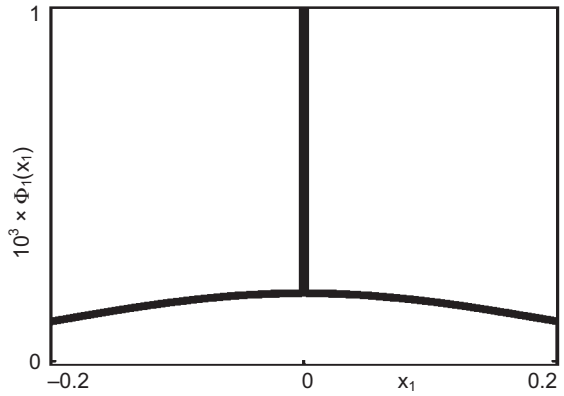

FIG. 1. The equilibrium distribution of genotypic effects for a single character, $\Phi_1(x_1)$, is plotted as a function of genotypic effect, x_1. In this case, we have taken $\Omega \to \infty$, so each mutation affects an infinite number of phenotypic characters. For the case shown, $V_s = 20$, $m = 0.2$, and $\mu = 10^{-4}$. Note that a singularity is present at $x_1 = 0$, indicating that a non-negligible proportion of the population have the optimal genotype (the proportion of optimal genotypes in this case is given by $1 - \mu = 0.9999$). The width of the line that rises above $x_1 = 0$ should be infinitesimal, since it represents a Dirac delta function, but we have broadened it to facilitate visualisation.

type ($x_1 = x_2 = x_3 = 0$) comprises a non-infinitesimal proportion of the population (Waxman and Peck, 1998). In fact, for many possible choices of parameters, the majority of the population has the optimal genotype. By contrast, any particular non-optimal genotype is present only as an infinitesimal proportion. Near $w = 1$, the fitness distribution consists of an infinite spike (a Dirac delta function) concentrated at $w = 1$ plus a term of the form $k/\sqrt{(1 - w)}$ where k is a positive constant. The spike describes individuals of optimal genotype.

If $\mu V_s/m^2 << 1$ does not hold, a non-negligible proportion of optimal genotypes may nevertheless appear when $\Omega = 3$. Even if this does not happen, Waxman and Peck (1998) show that, for any choice of μ, V_s and m, there always exists an Ω_c, such that the optimal genotype will constitute a non-negligible fraction of the population for $\Omega \geq \Omega_c$.

2.2. Results for the limit $\Omega \to \infty$

What happen in the limit $\Omega \to \infty$, when a very large number of independently selected characters are affected by each mutation? The answer is simple. In this limit, the equilibrium distribution of genotypic values is effectively a combination of an infinite spike and an Ω dimensional normal distribution in a relative proportions of $1 - \mu$ and μ, respectively. The spike is non-zero only at $x_1 = x_2 = \ldots x_\Omega = 0$. The normal distribution has a mean of $x_1 = x_2 = \ldots x_\Omega = 0$, a standard deviation of m each character and vanishing covariances between characters. The equilibrium marginal distribution for any given character, say x_1, is given by $\Phi_1(x_1) = (1 - \mu)\,\delta(x_1) + \mu f(x_1)$ where $\delta(x)$ denotes a Dirac delta function and $f(x)$ is given in Eq. (1). An example of this equilibrium genotype distribution is shown in Figure 1.

The equilibrium distribution of fitnesses has only two values of w present in the population at equilibrium, namely $w = 1$ and $w = 0$. Individuals for which $w = 1$ have an optimal genotype ($x_1 = x_2 = \ldots x_\Omega = 0$) whereas individuals for of $w = 0$ have one mutation. The distribution is given by $\Psi(w) = (1 - \mu)\,\delta(w - 1) + \mu\delta(w)$. In Figure 2 we illustrate $\Psi(w)$ by plotting spikes at the locations of the Dirac delta functions, where the height of the spikes plotted is given by the logarithm of the weighting factors multiplying the delta functions, i.e. by $\log_{10}(1 - \mu)$ and $\log_{10}(\mu)$, respectively.

The reason all mutants have a fitness of $w = 0$ is clear. In the limit $\Omega \to \infty$, each mutation has a negative effect on many traits that control fitness. Cumulatively, these effects are always fatal (because there are so many of them). However, this does not neces-

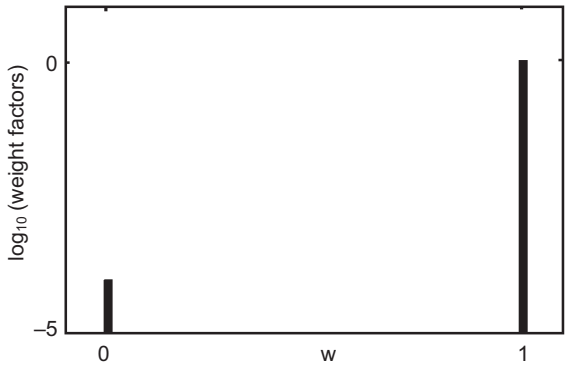

FIG. 2. The equilibrium distribution of relative fitnesses, $\Psi(w)$, is plotted as a function of w. The parameters used were the same as in Figure 1. The distribution consists of two Dirac delta functions, located at $w = 1$ and $w = 0$. The vertical lines represent Dirac delta functions. The height of the lines plotted is given by the logarithm (to base 10) of the proportion of individuals having various values of w, i.e. the logarithm of the weighting factors of the delta functions: $\log_{10}(1 - \mu)$ and $\log_{10}(\mu)$, respectively. Individuals with values of w other than $w = 1$ and $w = 0$ are entirely absent from the population once equilibrium has been achieved. In this case the proportion of individuals, at equilibrium, for which $w = 1$ is equal to $1 - \mu = 0.9999$ while for all other individuals, $w = 0$

sarily imply that in real population, highly pleiotropic mutations will always be devastating. If the effect of a mutation on each selected trait is sufficiently small, then mutations need not be fatal. With this in mind, we now study a different case where mutant offspring generally survive.

2.3. Results for the limit $\Omega \to \infty$ *and* $m \to 0$

We again take $\Omega \to \infty$, however, this time, as the value of Ω increases, we simultaneously decrease m. In particular, we assume that $m = m^*/\sqrt{\Omega}$ with m^* constant. Thus as $\Omega \to \infty$ the value of m becomes vanishingly small. As a result, as $\Omega \to \infty$, mutations are not necessarily fatal. At equilibrium, the marginal distribution of genotypic values of a single character, say x_1, is $\Phi_1(x_1) = \delta(x_1)$ corresponding to all individuals having the optimal value of the character, $x_1 = 0$. The marginal distribution, $\Phi_1(x_1)$ is plotted in Figure 3. (An alternative, but equivalent limiting procedure would be to hold m fixed, but

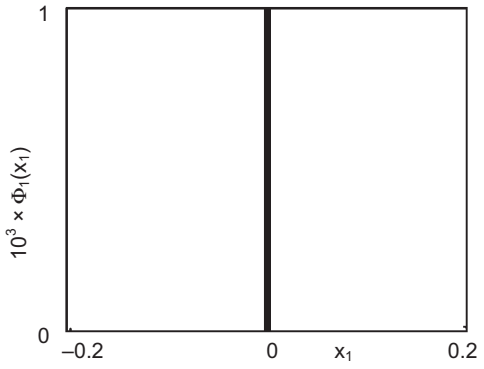

FIG. 3. The equilibrium distribution of genotypic effects for a single character, $\Phi_1(x_1)$, plotted as a function of genotypic effect, x_1. In this case, we have taken the limit $\Omega \to \infty$ and $m \to 0$ such that Ωm^2 is finite (as described in the main text). For the case shown, $V_s = 20$, $m^* = 0.2$, and $\mu = 10^{-4}$. The distribution consists of a Dirac delta function which is located at x_1, indicating that for character number 1 (and similarly for all other characters), no individual has more than an infinitesimal deviation from the optimal genotypic value. We have broadened the line rising above $x_1 = 0$ to facilitate visualisation.

weaken the strength of selection, with Ω, by setting $V_s = V_s^* \times \Omega$ with V_s^* constant.)

Despite the simplicity of the result for $\Phi_1(x_1)$, the distribution of fitnesses, $\Psi(w)$, under the present assumptions, is not simple. In terms of

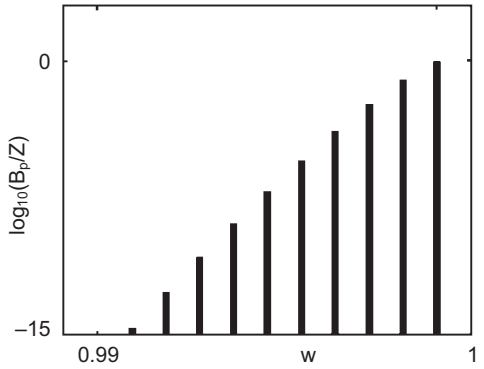

FIG. 4. The equilibrium distribution of relative fitnesses, $\Psi(w)$, is plotted as a function of w. The parameters used are the same as in Figure 3. The vertical lines represent the locations of Dirac delta functions. The height of the lines plotted is given by the logarithm (to base 10) of the proportion of individuals having various values of w, i.e. the logarithm of the weighting factors of the delta functions, see Eq. (3). Individuals with values of w other than those corresponding to spikes are entirely absent from the population once equilibrium has been achieved.

$$\Delta = \exp\left(-\frac{m^{*2}}{2V_s}\right), \quad B_0 = 1,$$

$$B_p = \left(\frac{\mu}{1-\mu}\right)^p \prod_{q=1}^{p} \frac{\Delta^{q-1}}{1-\Delta^q}, \quad p = 1, 2, 3 \ldots \qquad (2)$$

the distribution of fitnesses consists of a sum of spikes at locations $1, \Delta, \Delta^2, \ldots$ with different weighting factors.

$$\Psi(w) = Z^{-1} \sum_{p=0}^{\infty} B_p \delta(w - \Delta^p), \quad Z = \sum_{p=0}^{\infty} B_p . \qquad (3)$$

The singular distribution is achieved at long times even if, initially, the distribution of w is non-singular. In Figure 4 we illustrate this distribution by plotting spikes at the locations of the Dirac delta functions in $\Psi(w)$. The height of the spikes plotted is given by the logarithm of the weighting factors, i.e. by $\log_{10}(B_p/Z)$. The weighting factors give the relative equilibrium proportions (or frequencies) of individuals of different fitness. Thus the frequency of individuals with $w = \Delta^p$ ($p = 0, 1, 2, \ldots$) is given by B_p/Z. Equation (3) is quite complex, however, a much simpler result follows when $1 - \Delta >> \mu$. In this case the frequency of individuals with $w = 1$ is $B_0/Z = 1 - \mu/(1 - \Delta) + O(\mu^2)$ while that of individuals with $w = \Delta$, is $B_1/Z = \mu/(1 - \Delta) + O(\mu^2)$. The frequency of individuals with $w = \Delta^2, \Delta^3, \ldots$, are $O(\mu^2)$ or smaller.

3. Discussion

In this study we have focused on the consequences of pleiotropy when a very large number of independently selected traits are affected by each mutation. We considered the consequences of increasing the number of mutations affected by each character, Ω, to a very high value. When this is done without altering any other parameter of the model, all mutations become fatal, and the equilibrium distribution of fitnesses takes on a simple form of the sort shown in Figure 2. This is not difficult to understand, as a large value of Ω means that each mutation causes a large number of deleterious phenotypic changes, and collectively, these changes are fatal when Ω is sufficiently large.

A different result arises, however, when we increase Ω and simultaneously decrease the standard deviation of mutant effects, m, in such a way that most mutations are not fatal. If most mutations are highly pleiotropic, then this model is more plausible than the one in which m and Ω are not varied together, because many mutations are not fatal (Crow, 1979; Peck and Eyre-Walker, 1997; Fry et al., 1999).

When Ω and m are varied together as described above, the equilibrium distribution of fitnesses is a series of sharp spikes, with most genotypes absent, and only those with certain specific fitnesses present. This originates in the law of large numbers (Brunk, 1975). A realisation of this is contained in Eq. (14), which states that when $\Omega \to \infty$, all single-mutant offspring of a parent of fitness w will have a fitness *exactly* equal to $\Delta \times w$ (where $\Delta < 1$). This arises as follows. A single mutation causes changes in each phenotypic character and the size of these changes varies from one trait to another. When Ω is very large the consequences of the trait changes can be predicted with very little error because large changes compensate by for small ones, and vice versa. The net effect of these changes is to cause the fitness of offspring to be smaller by a fixed factor than the parents. Variations in the offspring fitness vanish as $\Omega \to \infty$. Thus all offspring of an individual containing a single (highly pleiotropic) mutation, will not have a range of fitnesses, but all have the same fitness. This phenomenon ultimately leads to a distribution of fitness values consisting of a series of spikes, as shown in Figure 4.

It is interesting to note that the distribution shown in Figure 4 arises at equilibrium even when the initial distribution of fitnesses is smooth, and no particular genotype has a non-negligible frequency. The reason is that, when Ω is very large, all individuals are ultimately descended from an individual of optimal genotype, just as in standard models of "Muller's Ratchet" (Haigh, 1978). Only individuals of optimal genotype have possibility of producing a long-lasting lineage. All members of such a lineage will be separated from the optimal genotype by a number of mutational steps, and each step produces a particular change in fitness, which is completely determined because of the law of large numbers. Thus, as long as the optimal genotype is initially present, the presence of any other genotype has no effect on the long-term outcome of evolution.

Another feature of the limit $\Omega \to \infty$, when $m \to 0$, as described above, is the contrast between the distribution of fitnesses shown in Figure 4 and the marginal distribution of a single genotypic value, $\Phi_1(x_1)$, shown in Figure 3. Variation in fitness amongst members of the population is not apparently accompanied by variation in any single genotypic character. To understand this, we first note that each spike in the distribution of fitnesses corresponds to a spherical shell of zero thickness in "genotypic space" (where position is specified by the coordinates $x_1, x_2, \ldots, x_\Omega$). The shell corresponding to a spike in $\Psi(w)$ at $w = \Delta^p$, lies distance $\|\mathbf{x}\| = \sqrt{pm^*}$ from the origin where $\|\mathbf{x}\| = \sqrt{x_1^2 + x_2^2 + \ldots x_\Omega^2}$. In Figure 5 we provide an illustration of the multiple shell structure when only 3 genotypic dimensions are shown. How does a singly spiked marginal distribution arise from the multiple shells in genotypic space? The existence of shells and the singly spiked marginal distribution of a single character can be viewed as separate aspects of the $\Omega \to \infty$ limit. To distinguish these properties, imagine a situation where Ω is finite, but for some reason, the population is distributed, in genotypic space, over a zero-thickness shell of radius R. The marginal distribution of x_1 from the shell is proportional to $(1 - x_1^2/R^2)^{(\Omega-3)/2}$ for $x_1^2 < R^2$ and zero otherwise [as follows from Eq. (15)]. Only for $\Omega > 3$ is the marginal distribution peaked around $x_1 = 0$ and it approaches a Dirac delta function only in the limit of very large Ω, when it becomes more an more sharply

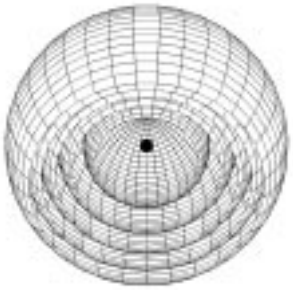

FIG. 5. When $\Omega \to \infty$ and $m \to 0$ such that Ωm^2 is finite (as described in the main text), each spike in the equilibrium distribution of fitnesses corresponds to a spherically symmetric shell of zero thickness in genotypic space. We have plotted the first few shells, when only 3 dimensions of genotypic space are shown. At the centre of the shells, lies a black sphere, representing the zero-radius shell that corresponds to optimum fitness. We have made it of finite radius to facilitate visualization.
Each shell makes a contribution to the marginal distribution of a single character, e.g. x_1, of the form constant $\times$ $\delta(x_1)$ where $\delta(x_1)$ denotes a Dirac delta function, so the marginal distribution itself is simply $\delta(x_1)$, as illustrated in Figure 3.

peaked around $x_1 = 0$. In this way we can understand that, in equilibrium, the high dimensionality of genotypic space results in every shell making a contribution to $\Phi_1(x_1)$ that is proportional to a spike, $\delta(x_1)$. Since $\Phi_1(x_1)$ is the sum of all these contributions, it is, itself, a spike. Thus variation in the fitness of the population and lack of variation in the marginal genotypic distributions of single characters are compatible, if surprising, aspects of highly pleiotropic problems.

When the number of characters is large but finite, each of the shells present at equilibrium acquires a width of order Ω^{-1}. The exception is the zero radius shell, corresponding to optimal fitness, which remains at zero radius. At finite but large Ω, the marginal distribution of a single genotypic character becomes a single delta function (from the zero radius shell) superimposed on a smooth symmetric distribution with a peak at the origin of width or order Ω^{-1} (from shells of non-zero radius).

We conclude by noting that the analysis presented in the present work deals only with infinite populations. What happens in populations of finite size is the subject of ongoing research. Preliminary numerical evidence indicates that for finite populations (e.g. with 10^4 or 10^5 individuals) there is a qualitatively different behaviour in cases of $\Omega = 1$ and 2, compared with $\Omega = 3$, in line with the predictions made in (Waxman and Peck, 1998). We plan to present these results along with other results elsewhere.

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APPENDIX

A derivation of results used in the main part of the paper are given here. We use the convention that integrals with unspecified limits cover the full range of all integration variables.

We begin with the lifecycle. Newly produced individuals undergo viability selection, after which the mature individuals produce offspring and die shortly afterward. The offspring produced may contain mutations and with $\mathbf{x}$ a vector of genotypic values: $\mathbf{x} = (x_1, x_2, \ldots, x_\Omega)$, the distribution of offspring in generation t (= 0, 1, 2, …), namely $\Phi(\mathbf{x}, t)$, obeys

$$\Phi(\mathbf{x}, t+1) = \frac{(1-\mu)w(\mathbf{x})\Phi(\mathbf{x},t) + \mu \int M(\mathbf{x}-\mathbf{y})w(\mathbf{y})\Phi(\mathbf{y},t)d^{\Omega}y}{\int w(\mathbf{y})\Phi(\mathbf{y},t)d^{\Omega}y} \qquad (4)$$

where

$$w(\mathbf{x}) = \prod_{i=1}^{\Omega} \exp[-x_i^2/(2V_s)],$$

$$M(\mathbf{x}) = \prod_{i=1}^{\Omega} (2\pi m^2)^{-1/2} \exp[-x_i^2/(2m^2)],$$

and $d^{\Omega}x = dx_1 dx_2 \ldots dx_\Omega$. $\Phi(\mathbf{x}, t)$ is a probability density describing generation t, and the proportion of the population with genotypic values in the infinitesimal volume $d^{\Omega}x$ centered at $\mathbf{x}$ is $\Phi(\mathbf{x}, t)\, d^{\Omega}x$.

The intrinsic complexity of the model is associated with the dimensionality, Ω, of the space of genotypic values. Any appreciable value of Ω poses problems in determining $\Phi(\mathbf{x}, t+1)$ since Eq. (4) involves Ω dimensional integrals.

Consider the distribution of relative fitnesses of individuals in the population (henceforth we shall omit the adjective "relative"). It is clear that great simplifications occur when we focus on this distribution since fitness is a one-dimensional trait (a single number lying in the interval 0 to 1). Thus changing Ω has no effect on the dimensionality of the space of fitnesses. By contrast, changing Ω changes the dimension of the space of genotypic values.

The distribution of fitnesses in generation t is denoted by $\Psi(w, t)$ and $\Psi(w, t)\, dw$ is the proportion of the population with fitness in the infinitesimal interval w to $w + dw$. It is defined by $\Psi(w, t) = \delta(w - w(\mathbf{x}))\, \Phi(\mathbf{x}, t)\, d^{\Omega}x$ where $\delta(w)$ denotes a Dirac delta function and $1 \geq w \geq 0$. To find the equation that determines $\Psi(w, t)$, multiply Eq. (4) by $\delta(w - w(\mathbf{x}))$ and integrate over all $\mathbf{x}$. This yields

$$\Psi(w, t+1) = \frac{(1-\mu) w \Psi(w,t) + \mu \int_0^1 F(w, w_1) w_1 \Psi(w_1, t) dw_1}{\overline{w}_t},$$

$$\overline{w}_t = \int_0^1 w \Psi(w, t) dw. \qquad (5)$$

The function $F(w, w_1)$ can be determined using polar coordinates in Ω dimensions, but its explicit form is quite lengthy and not required in the present work. What we do require, however, are the moments of $F(w, w_1)$ and these are found most simply from the equation that in essence defines $F(w, w_1)$, namely $F(w, w(\mathbf{y})) = \int \delta(w - w(\mathbf{x}))\, M(\mathbf{x} - \mathbf{y})\, d^{\Omega}y$. Multiplying this by w^r and integrating over w yields

$$\int_0^1 w^r F(w, w_1) dw = (1 + r/\zeta)^{-\Omega/2} w_1^{\frac{r}{1+r/\zeta}}, \quad \zeta = V_s / m^2. \qquad (6)$$

In what follows, we take $\zeta >> 1$ (Turelli, 1984).

Given a mutation occurs, $F(w, w_1)\, dw$ is the probability that a parent with fitness w_1 will produce an offspring whose fitness lies in the infinitesimal range w to $w + dw$. The behaviour of $F(w, w_1)$ depends sensitively on Ω, in particular,

$$F(w, 1) = \int \delta(w - w(\mathbf{x})) M(\mathbf{x}) d^{\Omega}x = \frac{\zeta^{\Omega/2} [\ln(w^{-1})]^{(\Omega-2)/2} w^{\zeta-1}}{\Gamma(\Omega/2)} \qquad (7)$$

where $\Gamma(x)$ denotes Euler's Gamma function.

At equilibrium, we can write Eq. (5) as

$$[\overline{w} - (1-\mu) w]\, \Psi(w) = \mu \int_0^1 F(w, w_1) w_1 \Psi(w_1) dw_1 \qquad (8)$$

and $\overline{w}$ is determined by the condition that $\Psi(w)$ is non-negative and normalized to unity:

$$\int_0^1 \Psi(w) dw = 1.$$

Equilibrium distribution of fitnesses for $\Omega = 1, 2$

For $\Omega = 1$ and $\Omega = 2$, $F(w, w_1)$ does not vanish anywhere except at $w = 0$. Thus for $w \neq 0$ Eq. (8) yields $[\overline{w} - (1-\mu) w]\, \Psi(w) > 0$ and because $\Psi(w)$ is non-negative, it follows that $[\overline{w} - (1-\mu) w] > 0$. The non-vanishing of $\overline{w} - (1-\mu) w$ for all w allows us to write Eq. (8) as

$$\Psi(w) = \mu \int_0^1 F(w, w_1) w_1 \Psi(w_1) dw_1 \; / \; [\overline{w} - (1-\mu) w]$$

and an approximation for $\Psi(w)$ then follows by applying the "House of Cards" Approximation (Kingman, 1978; Turelli, 1984). It corresponds to

$$\Psi(w) \approx \mu F(w, 1) / [\overline{w} - (1-\mu) w]$$

and applies when the "width" (i.e. variance) of $\Psi(w)$, which is $O(\mu)$, is small compared with the width, with respect to w_1, of $F(w, w_1)$, which is of order ζ^{-1}. Thus the approximation applies for $\mu\zeta << 1$. We define

$$\alpha = \mu V_s / m^2 \qquad (9)$$

then the approximation applies for $\alpha << 1$. In all that follows, we assume $\alpha << 1$. Using Eq. (7) and determining $\overline{w}$ using normalization yields

$$\Psi(w) \approx \begin{cases} \dfrac{\alpha}{\sqrt{\pi\zeta}} \dfrac{w^{\zeta-1}}{\sqrt{\ln(w^{-1})(1 + c_1/\zeta - w)}}, & c_1 = \pi\alpha^2, \quad \Omega = 1 \\ \alpha \dfrac{w^{\zeta-1}}{1 + c_2/\zeta - w}, & c_2 = \exp(-\gamma - \alpha^{-1}), \quad \Omega = 2 \end{cases} \qquad (10)$$

where $\gamma = 0.5772 \ldots$ is Euler's constant.

Equilibrium distribution of fitnesses for $\Omega = 3$

For $\Omega = 3$, $F(w, w_1)$ is positive everywhere except at the isolated points $w = 0$ and $w = 1$. Equation (8) then allows the possibility that $\overline{w} - (1-\mu)w$ can vanish at one of these points. For small α, $\Psi(w)$ is only normalizable if $\overline{w} - (1-\mu)w$ does indeed vanish. Since $\overline{w} - (1-\mu)w$ cannot become negative without violating Eq. (8), it must vanish at $w = 1$, thus $\overline{w} = 1-\mu$. Additionally, the vanishing of $\overline{w} - (1-\mu)w$ prevents us from directly dividing Eq. (8) through by this factor, unless we correct for its vanishing by including, after division, the additional term $A\delta(1-w)$ where A is a constant. This yields

$$\Psi(w) = A\delta(1-w) + \frac{\mu}{1-\mu}\frac{\int_0^1 F(w,w_1)w_1\Psi(w_1)dw_1}{1-w} \quad (11)$$

and A is determined from normalization. Under the House of Cards approximation,

$$\Psi(w) \approx (1-2\alpha)\delta(1-w) + \frac{2\alpha\sqrt{(\zeta/\pi)\ln(w^{-1})}w^{\zeta-1}}{1-w}. \quad (12)$$

Equilibrium distribution of fitnesses for $\Omega \to \infty$ *with m fixed*

For large, but finite Ω, we can argue, as for the case $\Omega = 3$, that $[\overline{w} - (1-\mu)w]$ must vanish at $w = 1$ so $\overline{w} = 1-\mu$, and $\Psi(w)$ has the form given in Eq. (11). To determine the solution, we need the limiting behaviour of $F(w, w_1)$ as $\Omega \to \infty$ at fixed m. This is most simply achieved from the moments, Eq. (6). When $\Omega \to \infty$ at fixed m, $\int_0^1 w^r F(w,w_1)dw$ has the value of 1 if $r = 0$, and vanishes if $r > 0$. This indicates that

$$\lim_{\substack{\Omega\to\infty \\ m \text{ fixed}}} F(w,w_1) = \delta(w). \quad (13)$$

With this form for $F(w, w_1)$, and on determining A from normalization, we obtain

$$\Psi(w) = (1-\mu)\,\delta(1-w) + \mu\delta(w).$$

Equilibrium distribution of fitnesses for $\Omega \to \infty$ *with* $m = m^*/\sqrt{\Omega}$

In this case we have $\zeta = V_s\Omega/m^{*2}$ and, from Eq. (6)

$$\lim_{\substack{\Omega\to\infty \\ m=m^*/\sqrt{\Omega}}} \int_0^1 w^r F(w,w_1)dw = w_1^r\Delta^r$$

where $\Delta = \exp(-m^{*2}/(2V_s))$. This indicates that

$$\lim_{\substack{\Omega\to\infty \\ m=m^*/\sqrt{\Omega}}} F(w,w_1) = \delta(w-\Delta w_1). \quad (14)$$

Inserting this into Eq. (11) and solving the resulting equation yields Eq. (3).

Marginal distribution of a single character

The marginal distribution of a single genotypic character, say x_1, is denoted by $\Phi_1(x_1)$ and is defined by $\Phi_1(x_1) = \int \Phi(\mathbf{x})\, dx_1 dx_2 \ldots dx_\Omega$. Provided Eq. (4), at equilibrium, has a unique non-negative and normalizable solution, as we shall assume, it can be proved that the solution $\Phi(\mathbf{x})$ is radially symmetric. Thus $\Phi(\mathbf{x}) \equiv \Phi(\|\mathbf{x}\|)$ where $\|\mathbf{x}\| = \sqrt{x_1^2 + x_2^2 + \ldots x_\Omega^2}$ is the Euclidean length of the vector $\mathbf{x}$. This allows us to use polar coordinates to write

$$\Phi_1(x_1) = S_{\Omega-1}\int_0^\infty \rho^{\Omega-2}\Phi(\sqrt{x_1^2+\rho^2})\,d\rho$$

with $\Omega = 2, 3, \ldots$ and $S_\Omega = 2\pi^{\Omega/2}/\Gamma(\Omega/2)$ is the surface area of a unit radius sphere in Ω dimensional space. We can relate $\Phi(\|\mathbf{x}\|)$ to the distribution of fitnesses $\Psi(w)$, since w is a measure of radial distance and a short calculation yields

$$\Phi_1(x_1) = \frac{S_{\Omega-1}}{S_\Omega}\int_0^1 \frac{dw}{R(w)}\left(1-\frac{x_1^2}{R^2(w)}\right)^{(\Omega-3)/2}\Theta(R^2(w)-x_1^2)\Psi(w),$$

$$R(w) = \sqrt{2V_s\ln(w^{-1})}. \quad (15)$$

Here $\Theta(x)$ denotes a Heaviside step function ($\Theta(x) = 1$ for $x > 0$ and is zero otherwise) and $R(w)$ is the radial distance in genotypic space from $\mathbf{x} = 0$ to positions corresponding to fitness w, i.e.

$$w = \exp[-R^2(w)/(2V_s)].$$

Equation (15) is ambiguous if $\Psi(w)$ contains a term $c\delta(1-w)$ (c = constant), since $R(w)$ vanishes at $w = 1$. Such a term arises from the term $c\delta(\mathbf{x})$ in $\Phi(\mathbf{x})$ and the correct contribution to $\Phi_1(x_1)$ is $c\delta(x_1)$. This may be obtained by a limiting process, where we modify the term to read $c\delta(\lambda - w)$ and, after determining its contribution to $\Phi_1(x_1)$, take the limit $\lambda \to 1_-$.

Marginal distribution of x_1 for $\Omega = 1$, 2 and 3

For $\Omega = 1$ we determine $\Phi_1(x_1)$ directly from the House of Cards approximation and for $\Omega = 2$, 3 we apply Eq. (15) to Eqs (10) and (12). This yields the results in (Waxman and Peck, 1998): namely with $\rho = x_1^2/(2m^2)$ and $\Gamma(a,b) = \int_b^\infty u^{a-1}e^{-u}du$, these are,

for $\Omega = 1$:

$$\sqrt{2\pi m^2}\,\Phi_1(x_1) \approx \alpha \exp(-\rho)/(\rho + \pi\alpha^2)$$

for $\Omega = 2$:

$$\sqrt{2\pi m^2}\,\Phi_1(x_1) \approx \alpha \exp(c_2)\Gamma(1/2, \rho + c_2)/\sqrt{\rho + c_2}$$

where c_2 is given in Eq. (10), and for $\Omega = 3$:

$$\sqrt{2\pi m^2}\,\Phi_1(x_1) \approx (1-2\alpha)\delta(\sqrt{\rho}) + \alpha\Gamma(0,\rho).$$

Marginal distribution of x_1 for $\Omega \to \infty$ with m fixed

The simplest way to obtain $\Phi_1(x_1)$, when $\Omega \to \infty$ at fixed m is to work with the characteristic function $\chi_1(k)$ which is defined by $\chi_1(k) = \int \exp(ikx_1)\,\Phi_1(x_1)\,dx_1$. Using Eq. (15) and making the change of variables $x_1 = R(w)\,u$ yields

$$\chi_1(k) = (S_{\Omega-1}/S_\Omega)\int_0^1 dw \int_{-1}^1 du (1-u^2)^{(\Omega-3)/2} \exp(ikR(w)u)\Psi(w)$$

$$\approx \int_0^1 dw \exp[-k^2R^2(w)/(2\Omega)]\Psi(w) \qquad (16)$$

$$= \int_0^1 w^{V_s k^2/\Omega}\Psi(w)dw.$$

The second equation applies for large Ω, when $(1-u^2)^{(\Omega-3)/2}$ is accurately approximated by $\exp(-\Omega u^2/2)$, and the limits of the u integration are harmlessly extended to $\pm\infty$. The approximations become exact in the limit $\Omega \to \infty$. The third equation follows when $R(w)$ from Eq. (15) is used. We apply Eq. (16) to the equilibrium from Eq. (5) and obtain

$$\chi_1(k) = \Bigg[(1-\mu)\int_0^1 w^{V_s k^2/\Omega+1}\Psi(w)dw + \mu\int_0^1 dw \int_0^1 dw_1 w^{V_s k^2/\Omega} F(w,w_1) w_1 \Psi(w_1)/\overline{w}.$$

When $\Omega \to \infty$ at fixed m, the term $\int_0^1 w^{V_s k^2/\Omega+1}\Psi(w)dw \to \overline{w}$. Additionally, using Eq. (6), with $r = V_s k^2/\Omega$, we have

$$\int_0^1 dw \int_0^1 dw_1 w^{V_s k^2/\Omega} F(w,w_1) w_1 \Psi(w_1) = \left(1 + \frac{V_s k^2}{\Omega\zeta}\right)^{-\Omega/2} \int_0^1 w_1^a \Psi(w_1)dw_1 \qquad (17)$$

$$a = \frac{V_s k^2/\Omega}{1 + V_s k^2/(\Omega\zeta)} + 1$$

and as $\Omega \to \infty$ at fixed m this becomes $\exp(-m^2k^2/2)\overline{w}$ thus

$$\lim_{\substack{\Omega\to\infty \\ m\ fixed}} \chi_1(k) = (1-\mu) + \mu\exp(-m^2k^2/2)$$

and this yields $\Phi_1(x_1) = (1-\mu)\,\delta(x_1) + \mu f(x_1)$ with $f(x)$ given in Eq. (1).

Marginal distribution of x_1 for $\Omega \to \infty$ with $m \to m^*/\sqrt{\Omega}$

The steps are essentially identical to the previous case and differences only occur because m is now $m^*/\sqrt{\Omega}$. The limit of both $\int_0^1 w^{V_s k^2/\Omega+1}\Psi(w)dw$ and $\int_0^1 dw \int_0^1 dw_1 w^{V_s k^2/\Omega} F(w,w_1) w_1 \Psi(w_1)$ is $\overline{w}$ as follows from Eq. (17) when ζ is replaced by $V_s/(m^{*2}/\Omega)$. Thus

$$\lim_{\substack{\Omega\to\infty \\ m=m^*/\sqrt{\Omega}}} \chi_1(k) = 1$$

and this yields $\Phi_1(x_1) = \delta(x_1)$.

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