somatic hypermutation. Perhaps the simplest way for the Ig mutator system to avoid that scenario would be to overwhelm the DNA repair system with so many mutations that they could not all be repaired before becoming fixed. But if that were the case, then $Pms2^{ko}/Pms2^{ko}$ mice should have a higher frequency of mutations at the Ig loci, as they have at other loci (6, *14*); in fact, the frequency is lower at the Ig loci. Another simple strategy for the Ig mutator system would be to throw a monkey wrench into the works to turn off or otherwise ensure that DNA repair was ineffective in hypermutable B cells. But if that were the case, then $Pms2^{ko}/Pms2^{ko}$ mice should have the same frequency of mutations at the Ig loci; in fact, the frequency is lower. Yet another strategy would be for the Ig mutator system to co-opt the DNA repair system to subvert it to create rather than prevent mutations. The third strategy would seem to be the only one that would explain the results of the experiments described here. Of course, the above argument applies only to a mismatch repair system requiring *Pms2*. How the Ig mutator system deals with other DNA repair pathways can only be discovered by experimentation.

The prototypic mismatch repair system in *E. coli* corrects the newly synthesized DNA strand, which is transiently unmethylated (*15*), using the old methylated DNA strand as a template. In eukaryotic cells, the basis for strand repair bias is not well understood, although it may involve single-strand breaks (*16*). We propose the following mechanism for the action of *Pms2* at the Ig loci: After mismatches have been introduced at an Ig locus in hypermutable cells by an unknown mechanism, the mismatch repair system identifies the "wrong," mutated strand as a template and thus fixes the mutations. In mice without mismatch repair, this model, in its simplest version, predicts that at the next replication the old strand will give rise to a nonmutant allele, whereas the new strand will give rise to an allele with one or more mutations. Thus, the frequency of mutations would be reduced by one-half. Because we found rather lower mutation frequencies in the absence of repair than would be predicted by this basic model, it might require some elaboration. For example, other repair mechanisms might correct mismatches in the absence of the repair system involving *Pms2*, and this would reduce the mutation frequency to less than one-half.

It has been reported that many human tumors exhibit high mutation rates (*17*). We envisage that the co-option of mismatch repair that we have described here for Ig hypermutation may also play a role in some of these tumor phenotypes. That would require, however, that the co-option not be limited to Ig genes but have a broad scope of action.

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Pleiotropy and the Preservation of Perfection

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A mathematical model is presented in which a single mutation can affect multiple phenotypic characters, each of which is subject to stabilizing selection. A wide range of mutations is allowed, including ones that produce extremely small phenotypic changes. The analysis shows that, when three or more characters are affected by each mutation, a single optimal genetic sequence may become common. This result provides a hypothesis to explain the low levels of variation and low rates of substitution that are observed at some loci.

Many continuously varying phenotypic characters are subject to stabilizing selection, so that the optimal phenotypic value lies between the minimum and maximum possible values (*1–7*). These phenotypic characters can be anything from the circumference of the stem of a plant to the distance between two subunits within a protein. Models of stabilizing selection often allow for a continuous range of mutations, so that some mutations have very small effects, whereas others have substantial effects (*2, 3, 8–14*). We follow this approach in the present study. Analyses of stabilizing selection have concentrated on models for which any given mutation affects only one phenotypic character. Nevertheless, mutations that affect multiple characters are well known and are commonly regarded as ubiquitous (*5, 14–25*). Here, we show that, when three or more characters are affected by each mutation, a single optimal genetic sequence may become predominant. This finding contrasts sharply with the usual finding that, in equilibrium, the optimal sequence is rare and many slightly suboptimal sequences are present.

Consider a simple nonpleiotropic model of viability selection in a very large population of haploid and asexual organisms (the results are expected to generalize to sex and diploidy). Parents produce offspring and then die, so that generations are discrete. After birth, offspring undergo viability selection, and the probability that an individual will survive depends on phenotype, which is described by measurements on k different characters. An individual's measurement on the ith character is denoted by z_i (where $-\infty < z_i < \infty$). These characters are chosen so that they affect fitness independently, and $z_i = 0$ is the optimal value for each character.

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We use a Gaussian fitness scheme, so that the probability of surviving viability selection for a particular individual is proportional to $\Pi_{i=1}^{k} \exp[-z_i^2/(2V)]$, where $V > 0$.

After viability selection, the remaining individuals reproduce, and fertility is unaffected by phenotype. The phenotype of a particular offspring on the ith character is assumed to depend on its "genotypic value" on that character (x_i) plus a normally distributed environmental noise component, e_i (so $z_i = x_i + e_i$). The distribution of e_i has mean zero and variance V_e. For $i \neq j$, e_i and e_j are uncorrelated.

For the ith character, an individual's genotypic value (x_i) is identical to that of its mother, unless a new mutation has occurred in the part of the genetic sequence that controls the character. The rate of such mutations is denoted by Θ (where $0 \leq \Theta \leq 1$). For now, we assume that mutations that affect one character do not affect other characters and that mutations to different characters occur independently. Thus, the probability that an individual will have one or more new mutations (U) is given by $U = 1 - (1 - \Theta)^k$.

Most fitness-affecting characters are probably controlled by many codons. Therefore, we treat the genotypic value (x_i) as a continuous variable, and each possible value is associated with a different sequence of codons. Throughout this report, we will discuss gene sequences in terms of the sequence of codons, and we will treat two codons as identical if they code for the same amino acid (that is, we ignore "silent" variation).

Mutant values of x_i are distributed around the parental value. When a mutation occurs that alters x_i, the probability that the mutant offspring will have a value of x_i in the interval $y + dy > x_i > y$ is $f(y - x^*)dy$, where dy is infinitesimal and x^* is the value of x_i for the mutant's mother. We use the traditional Gaussian function

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

Thus, m gives the standard deviation of mutant effects for a single character.

Let us define $\alpha = \Theta V_s/m^2$, where $V_s = V + V_e$. For now, we assume that $\alpha \ll 1$.

Models similar to the one just described have been studied previously (*13*, *26*–*28*). Our analysis agrees with previous work in that we find that, at equilibrium, each character has a distribution of x_i values that is smooth and bell-shaped and has a peak at $x_i = 0$ (the optimum). The smoothness of this distribution implies that, regardless of the strength of selection and the mutation rate, the sequence of codons for which $x_i = 0$ (the optimal sequence) is virtually absent at equilibrium. Instead, many suboptimal sequences are present (Fig. 1A). (With a smooth distribution, any single value of x_i has infinitesimal frequency.) These results (and others reported below) are proved in (*29*).

Let us define w as the probability of surviving viability selection for an individual with a particular set of genotypic values ($x_1, x_2, \ldots, x_k$), relative to that of an individual of the optimal genotype. As demonstrated elsewhere (*13*), the value of w is given by

$$w = \prod_{i=1}^{k} \exp\left(\frac{-x_i^2}{2V_s}\right) \quad (2)$$

Let $\bar{w}$ represent the mean value of w at equilibrium (thus, $\bar{w}$ is proportional to the percentage of offspring that survive viability selection). We can show that, for this model, $\bar{w} > 1 - U$ [in agreement with Bürger (*27*, *28*)]. Thus, at equilibrium, the decrease in fitness caused by having a suboptimal sequence of codons for any character is typically less than Θ. Very rough estimates of Θ suggest that values as high as 10^{-2} apply for many phenotypic characters (*13*, *30*).

Pleiotropic mutations affect multiple characters. To introduce pleiotropy, we collect the characters into sets of size Ω (where Ω is a positive integer and k is a multiple of Ω). There are $Q = k/\Omega$ such sets. The Ω characters in any set have a common genetic basis, and a mutation affecting one character will affect each of the other $\Omega - 1$ characters in the same set. The rate at which the genetic sequences coding for the characters in any given set undergo codon-altering mutations is given by Θ, and sets mutate independently. Thus, the probability that any given individual will have one or more new mutations (U) is now given by $U = 1 - (1 - \Theta)^Q$. Mutant effects follow a multidimensional Gaussian distribution (*17*). In particular, pick any set and assign the characters that make it up the numbers $1, 2, \ldots, \Omega$. Consider an individual that undergoes a mutation to this set and who is born to a mother whose genotypic values on these characters are $x_1^*, x_2^*, \ldots, x_\Omega^*$, respectively. The probability that this individual will have x_1 in the interval $y_1 + dy_1 > x_1 > y_1$ and x_2 in the interval $y_2 + dy_2 > x_2 > y_2, \ldots$ is given by $\Pi_{i=1}^{\Omega}[f(y_i - x_i^*)dy_i]$, where the dy_i values are infinitesimal and $f(y_i - x_i^*)$ is given by Eq. 1. When $\Omega = 1$, this pleiotropic model is identical to the

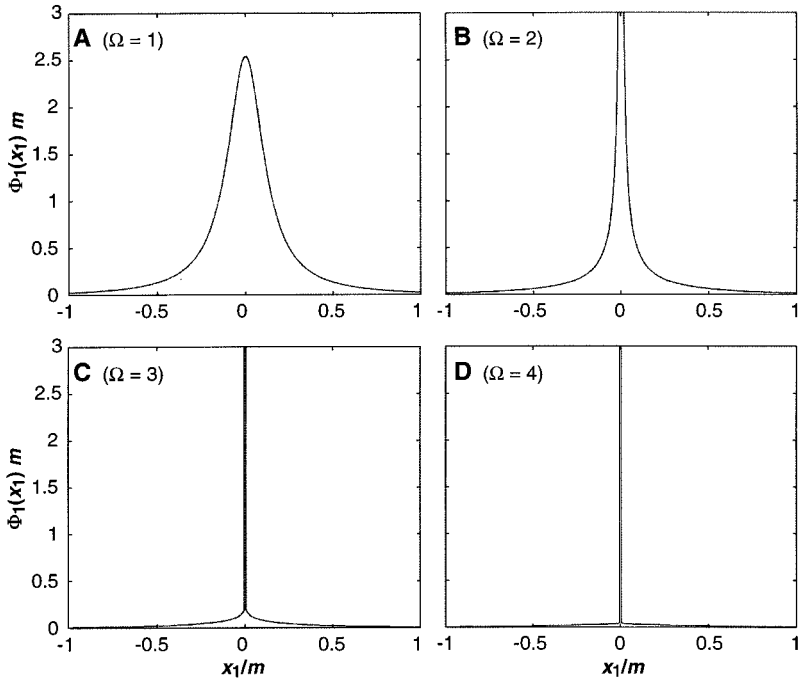

Fig. 1. The equilibrium distributions of genotypic effects for a single character, $\Phi_1(x_1)$, plotted as a function of genotypic effect, x_1. The scaling for both axes depends on m (the standard deviation of mutant effects), as indicated by the axis labels. In these examples, we set $\alpha = \Theta V_s/m^2 = 0.05$. (**A**) The nonpleiotropic model ($\Omega = 1$). (**B**) $\Omega = 2$, so that mutations simultaneously affect two phenotypic characters. In (A) and (B), the distribution is nonsingular at $x_1 = 0$, and so the proportion of individuals with an optimal genotypic value is infinitesimal. However, for $\Omega = 2$, the value of $\Phi_1(0)$ is large [$\Phi_1(0) = 1039/m$]. (**C**) A singularity does appear for $\Omega = 3$, and 90% of the population has $x_1 = 0$. (**D**) When $\Omega = 4$, $x_1 = 0$ for 95% of the population. The width of the line that rises above $x_1 = 0$ in (C) and (D) should be infinitesimal, because it represents a Dirac delta function. We broadened it to allow visualization. To produce these figures, we used Eqs. 9, 10 and 11.

nonpleiotropic model considered above.

The equilibrium distribution for a single character, x_1, when mutations affect two characters ($\Omega = 2$) is shown in Fig. 1B. The distribution is more peaked than that in Fig. 1A (the nonpleiotropic result) but is still continuous. This finding is in agreement with recent theoretical studies (*19–23*).

When mutations affect three or more characters ($\Omega \geq 3$), a qualitatively new phenomenon occurs. The distribution of any given character (i) contains a singularity at $x_i = 0$ (Fig. 1, C and D). Thus, a nonnegligible fraction of the population has perfect genomes. When $\Omega \geq 3$, the proportion of the population for which $x_1 \neq 0$ is of order $\alpha = \Theta V_s/m^2$. Individuals with the perfect genome for character 1 also are genetically perfect for characters 2, 3, . . . , Ω. Furthermore, if the proportion of the population for which $x_1 = 0$ is denoted by P, then the proportion of individuals who have the perfect genome with respect to all k traits is equal to $P^{k/\Omega}$. Previous analyses of similar models have suggested the possibility of singular behavior of the type noted here (*28, 31*). However, in these previous studies, only highly implausible fitness functions were shown to lead to singularities.

When $\Omega = 2$, mean fitness ($\bar{w}$) is greater than $1 - U$ (just as when $\Omega = 1$). However, for $\Omega \geq 3$, we have $\bar{w} = 1 - U$.

To gain an intuitive understanding of these results, consider two modified versions of our model, each of which makes the unrealistic assumption that all mutations are deleterious. For the first of these models, assume that only two genotypes are possible, one optimal and one suboptimal. Let $(1 - s)$ represent the relative viability of suboptimal individuals. Optimal individuals mutate to suboptimal ones at a rate U, but not vice versa. In this well-known model, if $s > U$, then, at equilibrium, the frequency of optimal individuals is given by $1 - (U/s)$ and $\bar{w} = (1 - U)$. However, if $s < U$, then, at equilibrium, optimal individuals are entirely absent from the population and $\bar{w} = (1 - s)$. Thus, $\bar{w} > (1 - U)$.

When $s < U$, this model resembles the nonpleiotropic model ($\Omega = 1$). In both models, the optimal genotype vanishes, and $\bar{w} > (1 - U)$. However, in the nonpleiotropic model, deleterious mutations affect slightly suboptimal genotypes, as well as optimal ones. Nevertheless, some of these deleterious mutations are, effectively, canceled out, because when $\Omega = 1$, nearly optimal genotypes are created at a nonnegligible rate by beneficial mutations. When $\Omega = 1$ and $x_1 \neq 0$, 50% of mutations will move x_1 toward the direction of the optimum (although some will push x_1 beyond the optimum). The creation of nearly optimal genotypes by mutation is also likely when $\Omega = 2$ (*29*). In contrast, when $\Omega \geq 3$, mutations that improve fitness and produce a nearly optimal genotype on all Ω affected characters are extremely unlikely (*29*). Roughly speaking, this is because, when $\Omega \geq 3$, only a very small region of "genotypic space" corresponds to near optimality.

A second modified model illuminates the impact of this shift in favor of deleterious mutations. Say that when offspring are produced, they may undergo a certain number of mutational steps, each of which decreases fitness by a factor of $(1 - s)$, where $0 < s < 1$. The number of mutational steps follows a Poisson distribution with mean and variance equal to λ. Thus U, the genome-wide probability of at least one new mutation, is given by $U = 1 - e^{-\lambda}$. This is a well-known model (*32*), and, at equilibrium, $\bar{w} = 1 - U$ and the optimal genotype takes a nonnegligible frequency. This model is analogous to the pleiotropic model above when $\Omega \geq 3$. In both models, $\bar{w} = 1 - U$ and the optimal genotype is preserved at equilibrium because there is a strong tendency for mutations to degrade fitness in nearly optimal genotypes. When $\Omega \geq 3$, the loss of nearly optimal genotypes because of selection is not compensated for by a substantial gain of such genotypes because of beneficial mutations, and thus the superiority of the optimal genotype allows it to rise to a nonnegligible frequency.

What happens when our assumption that $\alpha = \Theta V_s/m^2 \ll 1$ does not hold? For any value of α, the frequency of the optimal genotype is negligible when $\Omega = 1$ and $\Omega = 2$. However, there is always a critical value of Ω, say Ω^*, such that when $\Omega \geq \Omega^*$, a nonnegligible frequency of the optimal genotype appears. When $\alpha \ll 1$, $\Omega^* = 3$. However, if $\alpha \ll 1$ is not satisfied, then we may have $\Omega^* > 3$ (*29*).

For many proteins, there is very little within-population variation (*33–35*). Low amounts of variation can lead to low substitution rates (*3, 9, 11*), and proteins exist that have apparently not changed at all for at least 100 million years (*34, 36*). Lack of variation can be a consequence of small population size and genetic drift, but drift will not stop substitutions. In some cases, natural selection is clearly the cause of low amounts of variation (*36–38*) or infrequent substitutions (*34, 36*). In large populations, stabilizing selection on one or two characters can produce low amounts of variation and substitution only if mutations that have very small selective effects are exceedingly rare. However, our results show that, when each mutation affects three or more phenotypic characters, variation (and thus, substitution) can be suppressed in favor of an optimal sequence even when mutations of very small effect are common.

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29. The proofs we present here are in accordance with the rather general mathematical results of Bürger and collaborators (*26–28, 39*). The population is described in equilibrium by the distribution $\Psi(x_1, x_2, \ldots, x_k)$. Thus, the proportion of the population with genotypic values in the infinitesimal volume $d^k x \equiv dx_1 dx_2 \ldots dx_k$ centered at $(x_1, x_2, \ldots, x_k)$ is $\Psi(x_1, x_2, \ldots, x_k) d^k x$. Every mutation affects Ω characters, and we deal with the sets of characters $(x_1, x_2, \ldots, x_\Omega)$, $(x_{\Omega+1}, x_{\Omega+2}, \ldots, x_{2\Omega})$, ...

It is possible to show that, in equilibrium, the probability density factorizes into the form $\Psi(x_1, x_2, \ldots, x_k) = \Phi(x_1, x_2, \ldots, x_\Omega)\Phi(x_{\Omega+1}, x_{\Omega+2}, \ldots, x_{2\Omega}) \ldots$. From the life cycle that we have specified, it follows that with $\mathbf{x} \stackrel{\text{def}}{\equiv} (x_1, x_2, \ldots, x_\Omega)$, $\Phi(\mathbf{x})$ obeys

$$\Phi(\mathbf{x}) = \frac{(1 - \Theta) w_1(\mathbf{x})\Phi(\mathbf{x}) + \Theta \int f_1(\mathbf{x} - \mathbf{y}) w_1(\mathbf{y})\Phi(\mathbf{y}) d^\Omega y}{\int w_1(\mathbf{y})\Phi(\mathbf{y}) d^\Omega y} \quad (3)$$

where

$$w_1(\mathbf{x}) = \prod_{i=1}^{\Omega} \exp\left(\frac{-x_i^2}{2V_s}\right) \quad (4a)$$

$$f_1(\mathbf{x}) = \prod_{i=1}^{\Omega} \left(\frac{1}{\sqrt{2\pi m^2}}\right) \exp\left(\frac{-x_i^2}{2m^2}\right) \quad (4b)$$

and all integrals cover the full range of the integration

variables. Equation 3 can be written as

$$[\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})]\Phi(\mathbf{x})$$

$$= \Theta \int f_1(\mathbf{x} - \mathbf{y})w_1(\mathbf{y})\Phi(\mathbf{y})d^{\Omega}y \quad (5)$$

where $\overline{w}_1 \stackrel{\text{def}}{\equiv} \int w_1(\mathbf{y})\Phi(\mathbf{y})d^{\Omega}y$ and this quantity is determined by the condition that $\Phi(\mathbf{x})$ is normalized to unity, namely

$$\int \Phi(\mathbf{x})d^{\Omega}x = 1 \quad (6)$$

General features of $\Phi(\mathbf{x})$ follow from $f_1(\mathbf{x} - \mathbf{y})$, $w_1(\mathbf{x})$ and $\Phi(\mathbf{x})$ being ≥ 0. In particular, from Eq. 5, it follows that $[\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})] \geq 0$. The smallest value of $[\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})]$ occurs at $\mathbf{x} = (0, 0, \ldots, 0) \equiv \mathbf{0}$, where $w_1(\mathbf{0}) = 1$; hence, generally, $\overline{w}_1 \geq 1 - \Theta$ [closely related results have been derived by Bürger and his collaborators (*26, 28, 39*)]. The inequality $\overline{w}_1 > 1 - \Theta$ and the equality $\overline{w}_1 = 1 - \Theta$ lead to qualitatively different forms for $\Phi(\mathbf{x})$, and we discuss these separately.

Case i: $\overline{w}_1 > 1 - \Theta$: This case yields, from Eq. 5,

$$\Phi(\mathbf{x}) = \frac{\Theta \int f_1(\mathbf{x} - \mathbf{y})w_1(\mathbf{y})\Phi(\mathbf{y})d^{\Omega}y}{\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})} \quad (7)$$

$\Phi(\mathbf{x})$ is a peaked but nonsingular function of $\mathbf{x}$, because for $\mathbf{x} = \mathbf{0}$, the right-hand side is finite. The constant $\overline{w}_1$ is determined by the condition of normalization (Eq. 6). The application of the normalization condition, Eq. 6, to Eq. 7 leads to the $\mathbf{x}$ integral: $\int f_1(\mathbf{x} - \mathbf{y})/[\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})]d^{\Omega}x$, and this, as a function of $\overline{w}_1$, is unbounded from above when $\Omega = 1$ and $\Omega = 2$. As a consequence, irrespective of how small Θ is, $\overline{w}_1$ can be chosen so that $\Phi(\mathbf{x})$ in Eq. 7 is normalized to unity. Therefore, the case $\overline{w}_1 > 1 - \Theta$ applies for $\Omega = 1$ and $\Omega = 2$. If $\alpha \ll 1$, this case cannot apply for $\Omega \geq 3$. If we do not assume $\alpha \ll 1$, then $\overline{w}_1 > 1 - \Theta$ may apply for larger values of Ω and hence yield nonsingular distributions for these values of Ω. As an example, if $V_s/m^2 = 100$, then we numerically find that when $\alpha < 0.67$, $\overline{w}_1 > 1 - \Theta$ will only apply for $\Omega = 1$ and $\Omega = 2$, but if $1.67 > \alpha > 0.67$, $\overline{w}_1 > 1 - \Theta$ will apply for $\Omega = 1$, $\Omega = 2$, and, additionally, $\Omega = 3$.

Case ii: $\overline{w}_1 = 1 - \Theta$: For this case, we cannot simply solve Eq. 5 to obtain the result of Eq. 7 because $[\overline{w}_1 - (1 - \Theta)w_1(\mathbf{x})]$ vanishes as $\mathbf{x} = \mathbf{0}$ and the solution to Eq. 5 must include the singular function $\delta(\mathbf{x}) \equiv \Pi_{i=1}^{\Omega}\delta(x_i)$, where $\delta(x)$ is a Dirac delta function of argument x. Derivatives of Dirac delta functions cannot be present in the solution because they correspond to distribution functions that are negative for some $\mathbf{x}$. Thus, when $\overline{w}_1 = 1 - \Theta$, Eq. 5 is equivalent to

$$\Phi(\mathbf{x}) = A\delta(\mathbf{x}) + \left(\frac{\Theta}{1 - \Theta}\right)\frac{\int f_1(\mathbf{x} - \mathbf{y})w_1(\mathbf{y})\Phi(\mathbf{y})d^{\Omega}y}{1 - w_1(\mathbf{x})} \quad (8)$$

where A (≥ 0) is determined by normalization (Eq. 6). When $\Omega = 1$ and $\Omega = 2$, the $\mathbf{x}$ integral that results from the normalization condition, $\int f_1(\mathbf{x} - \mathbf{y})/[1 - w_1(\mathbf{x})]d^{\Omega}x$, diverges and hence definitely rules out these Ω values. For $\Omega \geq 3$, the same integral is finite, and when $\alpha \ll 1$, the delta function term must be present (that is, $A \neq 0$) in order that $\Phi(\mathbf{x})$ is normalized to unity. Thus, $\Phi(\mathbf{x})$ contains a singular delta function part for $\Omega \geq 3$ when $\alpha \ll 1$.

If, for a given value of Ω, the mutation rate Θ (and hence α) is large enough that the condition of normalization yields $A < 0$, then we can infer that the case $\overline{w}_1 = 1 - \Theta$ does not apply to this value of Ω. For example, if $V_s/m^2 = 100$, then, when $1.67 > \alpha > 0.67$, case ii does not apply to $\Omega = 3$, although it does apply for $\Omega \geq 4$.

Distributions: We determine approximate forms for the distribution of a single character, say x_1, and we denote the single character distribution by $\Phi_1(x_1)$. We use the house-of-cards approximation (*13, 31*), which entails replacing $\int f_1(\mathbf{x} - \mathbf{y})w_1(\mathbf{y})\Phi(\mathbf{y})d^{\Omega}y$ in Eqs. 7 and 8 by $f_1(\mathbf{x})w_1(\mathbf{0})\int \Phi(\mathbf{y})d^{\Omega}y = f_1(\mathbf{x})$. This approximation can be shown to be highly accurate when $\alpha \ll 1$. Assuming $m^2/V_s \ll 1$, which is apparently reasonable (*13*), and, furthermore, that $\Omega \ll V_s/m^2$, we can replace the Gaussian $w_1(\mathbf{x})$ by $1 - \Sigma_{i=1}^{\Omega}x_i^2/(2V_s)$ without any substantial loss of accuracy. When $\Omega = 1$, $\Phi_1(x_1) \equiv \Phi(x_1)$ and we obtain

$$\Phi_1(x_1) \approx \left(\frac{\alpha}{\sqrt{2\pi m^2}}\right)\frac{\exp\left(\frac{-x_1^2}{2m^2}\right)}{\frac{x_1^2}{2m^2} + \pi\alpha^2} \quad (9)$$

To obtain the single character distribution, $\Phi_1(x_1)$, in a pleiotropic model, we integrate $\Phi(\mathbf{x})$ over x_2, $x_3, \ldots, x_{\Omega}$. When $\Omega = 2$, we have

$$\Phi_1(x_1) \approx \left(\frac{\alpha \exp(c_2)}{\sqrt{2\pi m^2}}\right)\frac{\Gamma\left(\frac{1}{2}, \frac{x_1^2}{2m^2} + c_2\right)}{\sqrt{\frac{x_1^2}{2m^2} + c_2}} \quad (10)$$

where $c_2 = \exp(-\gamma - \alpha^{-1})$. For $\Omega \geq 3$, we have

$$\Phi_1(x_1) \approx \left[1 - \frac{2\alpha}{\Omega - 2}\right]\delta(x_1) + \Gamma\left(\frac{-(\Omega - 3)}{2}, \frac{x_1^2}{2m^2}\right)\left(\frac{\alpha}{\sqrt{2\pi m^2}}\right)\left(\frac{x_1^2}{2m^2}\right)^{(\Omega-3)/2} \quad (11)$$

In the above, $\gamma = 0.5772\ldots$ is Euler's constant and $\Gamma(a,b) \stackrel{\text{def}}{\equiv} \int_b^{\infty} u^{a-1}\, e^{-u}\, du$ is the incomplete gamma function.

Origin and explanation of the results: The fundamental origin of the results we have produced arises from the suppression of beneficial mutations when pleiotropic mutations are present. To see this, consider a single mutation that affects the genotypic value $\mathbf{x}$ in one of the sets of Ω characters. The probability that the mutation will change this genotype to a genotype with associated fitness lying in the range w_1 to $w_1 + dw_1$ is, when $w_1 \approx 1$, approximately porportional to

$$f_1(\mathbf{x})(1 - w_1)^{(\Omega-2)/2}dw_1 \quad (12)$$

When $\Omega \geq 3$, this probability is much smaller than that for $\Omega = 1$ or $\Omega = 2$. When $\alpha = \Theta V_s/m^2 \ll 1$, it is the suppression of beneficial mutations to $w_1 \approx 1$ that results in singular distributions for $\Omega \geq 3$. Larger values of α may push the delta function singularity to occur at a larger value of Ω.

Inspection of cases i and ii considered above indicates the mathematical reason why delta functions in $\Phi(\mathbf{x})$ are not possible when $\Omega = 1$ or $\Omega = 2$ yet are possible when $\Omega \geq 3$. The reason is that the integral, with respect to $x_1, x_2, \ldots, x_{\Omega}$, of $1/(x_1^2 + x_2^2 + \ldots x_{\Omega}^2)$ over a region near (and including) the origin, $\mathbf{x} = \mathbf{0}$, is divergent when $\Omega = 1$ or $\Omega = 2$ but finite when $\Omega \geq 3$. The extension of the results given in this work to more general fitness functions is straightforward, and the convergence of analogous integrals is the key to the presence of delta functions in $\Phi(\mathbf{x})$.

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Sensorimotor Adaptation in Speech Production

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Human subjects are known to adapt their motor behavior to a shift of the visual field brought about by wearing prism glasses over their eyes. The analog of this phenomenon was studied in the speech domain. By use of a device that can feed back transformed speech signals in real time, subjects were exposed to phonetically sensible, online perturbations of their own speech patterns. It was found that speakers learn to adjust their production of a vowel to compensate for feedback alterations that change the vowel's perceived phonetic identity; moreover, the effect generalizes across phonetic contexts and to different vowels.

When human subjects are asked to reach to a visual target while wearing displacing prisms over their eyes, they are observed to miss the target initially, but to adapt rapidly such that within a few movements their reaching appears once again to be rapid and natural. Moreover, when the displacing prisms are subsequently removed subjects are observed to show an aftereffect; in particular, they miss the target in the direction opposite to the displacement. This basic result has provided an important tool for investigating the nature of the sensorimotor control system and its adaptive response to perturbations (*1*).

The experiment described in this report is based on an analogy between reaching movements in limb control and articulatory movements in speech production. Although reaching and speaking are qualitatively very different motor acts, they nonetheless share the similarity of having sensory goals—

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