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Fisher's geometrical model of evolutionary adaptation—Beyond spherical geometry

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Abstract

Fisher's geometrical model of evolutionary adaptation has recently been used in a variety of contexts of interest to evolutionary biologists. The renewed interest in this model strongly motivates generalizations that make it a more realistic description of evolutionary adaptation. Previously, the distribution of mutant effects has, for analytical tractability, rather than biological realism, been taken as spherically symmetric. Here we substantially extend Fisher's model, by allowing a wider class of mutational distributions that incorporate mutational bias and more general deviations from spherical symmetry such as correlations between mutant effects. We also incorporate work on generalized fitness landscapes, thereby reducing the number of artificial assumptions underlying the model. The generalized model exhibits a substantially increased flexibility and a far richer underlying geometry. We find that the distribution characterizing selection coefficients of new mutations is expressed in terms of a number of geometrical invariants associated with mutation, selection and the parental phenotype.

Keywords: Fisher's geometrical model; Evolutionary adaptation; Quantitative traits; Mutation; Stabilizing selection

1. Introduction

In his famous book *The Genetical Theory of Natural Selection*, Fisher outlined a view of evolutionary adaptation in terms of intuitive, geometrical considerations (Fisher, 1930). An organism was described as having n quantitative traits (i.e. n characters with effectively continuous variation). Examples of nine such characters that have been investigated in *Drosophila melanogaster* are viability, fecundity, hatchability, development time, longevity, mating speed, phototaxis, body length and abdominal bristle number (Keightley and Ohnishi, 1998).

Fisher viewed the quantitative characters of an organism as the Cartesian coordinates in an n-dimensional "space of characters," and a particular organism, with its particular set of n characters, was then geometrically represented as a point in this space. In the original formulation of Fisher, the level of adaptation of an organism was determined from its distance from a fixed point in the n-dimensional character space: the closer an organism is to this fixed point, the higher is its fitness. This fixed point was thus implicitly taken as a fitness optimum and since only the distance from this point is of significance, surfaces of constant fitness are hyperspheres surrounding the optimum, i.e. circles, if there are only $n = 2$ characters (see Fig. 1), spheres when there are $n = 3$ characters, ... The intention of Fisher was not obviously to provide a realistic model of adaptation, but rather to illustrate how adaptation is determined by a number of different features of an organism acting in concert.

In Fisher's geometric description, the change in characters associated with a mutation corresponds to a mutant offspring lying at a different position (in the character space), compared with that of its parent (we are assuming an asexual population). Such a change is beneficial—or adaptive—if it results in an increase in some measure of the organism's viability/reproductive success, i.e. its fitness. A mutation is adaptive if an individual carrying a newly arisen mutation is closer to the location of the fitness

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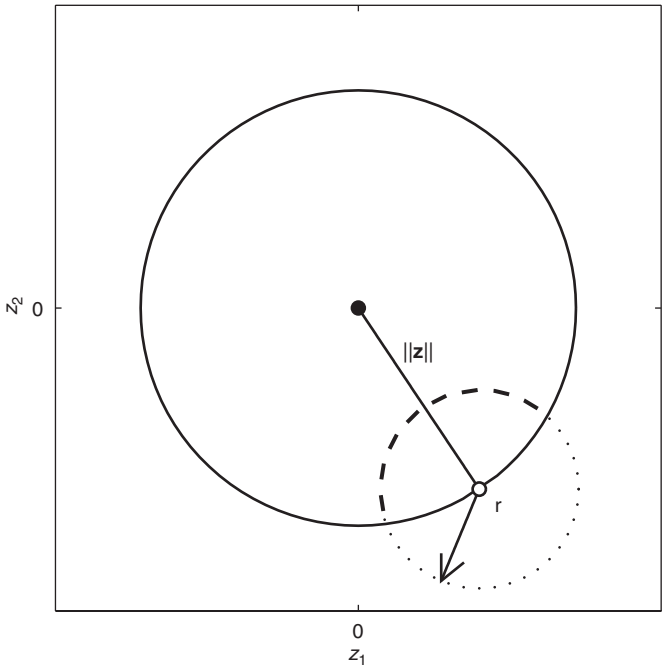

Fig. 1. An illustration of Fisher's geometrical model is shown for the case of two traits z_1 and z_2, when fitness and mutation are spherically symmetric. The fitness optimum lies at $(z_1, z_2) = (0, 0)$ and is represented by a filled dot. The unfilled dot represents the state of a parent and the arrow stemming from this point represents a mutational change, $\mathbf{r}$. The quantity $\|\mathbf{z}\|$ is the distance of the parental phenotype from the optimum. All points on the solid circle, with radius $\|\mathbf{z}\|$, correspond to the same value of fitness. All points on the small circle with radius r are equally likely to be reached by a single mutation. The dashed arc shows the proportion of those mutations that are closer to the optimum than the parental henotype and are thus beneficial.

optimum than that of its parent—see Fig. 1. The mutational changes considered by Fisher were taken to have the simplest distribution, namely that of being equally likely to occur in all directions in the character space (spherically symmetric).

Fisher's considerations amount to an explicit model of evolutionary adaptation, with analytical or quantitative results derivable for results such as the proportion of beneficial mutations.

Quite recently, there has been renewed interest in this model because, despite being highly simplistic, there is the implicit belief that certain features it exhibits may be robust to modifications of the underlying assumptions and hence allow its conclusions to have wider applicability. The recent work, which uses Fisher's model in its original form, includes investigation of the size of mutations contributing to adaptation (Orr, 1998, 1999; Hartl and Taubes, 1998; Burch and Chao, 1999), topics such as drift load (Hartl and Taubes, 1996; Peck et al., 1997; Poon and Otto, 2000), hybridization (Barton, 2001) and evolutionary rates (Orr, 2000; Welch and Waxman, 2003). Generalizations of Fisher's model have also been considered (Rice, 1990; Whitlock et al., 2003; Waxman and Welch, 2005).

The renewed interest in this model strongly motivates generalizations that make it a more realistic description of evolutionary adaptation. Here we make some progress in this direction, by not only incorporating recent work on generalized fitness functions of a stabilizing form (Waxman and Welch, 2005) but, more importantly, by incorporating a wider class of distributions of mutational effects, beyond the spherically symmetric ones that have been considered to date. Thus, with the ultimate aim of setting out a somewhat more general framework for Fisher's geometrical model, we consider distributions of mutant effect that incorporate mutational bias and allow correlations between the mutational changes on different traits. In the framework presented, the distribution of mutant effects has surfaces of constant probability density that are ellipses or their higher dimensional analogues (ellipsoids) and the distribution has a functional form that includes a normal distribution as a special case. The present work therefore reduces some of the artificial assumptions about mutation that have been present in Fisher's geometrical model to date, and provides a useful tool for subsequent work employing the model.

The generalized model, outlined above, exhibits a substantially increased flexibility and a far richer underlying geometry. The present work concentrates on a fundamental quantity; a distribution characterizing new mutations and exposes the way the richer geometry manifests itself in quantities of interest associated with such mutations.

2. Model

Consider a population of asexual organisms that are subject to selection and mutation on the values of n quantitative characters, $z_1, z_2, \ldots, z_n$, which make up the relevant phenotype of an individual. Each of the different characters continuously ranges from $-\infty$ to ∞ and we neglect any environmental component of the characters. It is convenient to collect all n characters into the column vector $\mathbf{z} = (z_1, z_2, \ldots, z_n)^{\mathrm{T}}$ where the superscript T denotes the transpose of a matrix.

2.1. Mutation

The change in characters, due to mutation, is given by n random numbers $\mathbf{r} = (r_1, r_2, \ldots, r_n)^{\mathrm{T}}$. The mutant offspring of an organism with phenotype $\mathbf{z}$ has phenotype $\mathbf{z} + \mathbf{r}$. Generally, all n characters are changed by a mutation, indicating that in this model mutation exhibits a high level of pleiotropy.

The distribution (or probability density) of mutant effects is written as $f(\mathbf{r})$, and the probability of mutational changes on the n traits lying in the infinitesimal range $\mathbf{r}$ to $\mathbf{r} + \mathrm{d}\mathbf{r}$ is $f(\mathbf{r})\,\mathrm{d}r_1\,\mathrm{d}r_2 \ldots \mathrm{d}r_n \equiv f(\mathbf{r})\,\mathrm{d}^n r$.

In contrast to previous work on this subject, we shall *not* make the analytically simplest choice for the distribution of mutant effects. That is, we shall not assume that mutations are equally likely to occur in all directions in the n-dimensional phenotypic space, by assuming $f(\mathbf{r})$

is a spherically symmetric function (depends only on $\|\mathbf{r}\| \equiv \sqrt{r_1^2 + r_2^2 + \cdots + r_n^2}$). Rather, we shall consider a class of mutation distributions that include spherically symmetric distributions as a special case, but are more general than these, and hence incorporate important statistical aspects of mutation. Specifically, we consider distributions of mutant effects that only depend on mutational changes, $\mathbf{r}$, in the quadratic combination $(\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b})$. That is,

$$f(\mathbf{r}) = \text{function of } A, \quad A = (\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b}), \tag{1}$$

where $\mathbf{b}$ is a fixed column vector and $\mathbf{C}$ is a real $n \times n$ symmetric positive definite matrix. For mutational distributions of the form just described, the variance–covariance matrix of mutational changes can be shown to be proportional to the matrix $\mathbf{C}$ and we shall make an appropriate choice of scaling of the distribution, so that variance–covariance matrix *exactly* coincides with $\mathbf{C}$. This choice of scaling puts a single condition on the dependence of $f(\mathbf{r})$ on A, but beyond this and the requirement of normalization, the possible dependence on A is general (see Appendix A for details).

Note that positive definiteness of $\mathbf{C}$ results in this matrix having positive diagonal elements—corresponding to the variances of mutational changes on different characters. Positive definiteness of $\mathbf{C}$ does not, however, require its off-diagonal elements to be positive, so covariances of either sign (or zero) can be accommodated in the above framework.

The above class of mutation distributions has the following properties:

(i) Surfaces of constant probability density are ellipses when $n = 2$ and higher dimensional analogues of an ellipse when $n > 2$ (i.e., n-dimensional ellipsoids). This follows directly from the set of $\mathbf{r}$ values that correspond to $A =$ constant, and which, in appropriately translated and rotated coordinates ($\mathbf{r}^*$), can be written as the simplest representation of an n-dimensional ellipsoid: $\sum_{i=1}^{n} m_i^{-2} r_i^{*2} =$ constant, where m_i^2 are the eigenvalues of $\mathbf{C}$. Thus, the class of mutation distributions considered here go beyond the spherically symmetric ones previously considered and only coincide with the previously studied distributions in the special case where $\mathbf{b}$ vanishes and $\mathbf{C}$ is proportional to the $n \times n$ identity matrix.

(ii) The mean mutational change of the n traits is $\mathbf{b}$, i.e.

$$\int \mathbf{r} f(\mathbf{r})\, \mathrm{d}^n r = \mathbf{b} \tag{2}$$

(see Appendix B) where here and elsewhere, all integrals with unspecified limits cover the full, $-\infty$ to ∞, range of all integration variables. The ith trait experiences mutations that are not symmetrically distributed around the parental trait value, z_i, but are symmetrically distributed around the trait value $z_i + b_i$. Such a mutation scheme can be said to exhibit *mutational bias* and this has been observed in quantitative traits (Santiago et al., 1992; Mackay, 1996; Keightley and Ohnishi, 1998) and investigated theoretically (Waxman and Peck, 2003, 2004).

(iii) The variance–covariance matrix of mutational changes, $\mathbf{C}$, is, in general, non-diagonal, in which case the mutational changes on different traits are correlated.

(iv) Apart from some restrictions of the dependence of the distribution of mutant effects, $f(\mathbf{r})$, upon A, which arise from normalization and the scaling requirement (mentioned above), the functional dependence on A is otherwise unspecified. It follows that, generally, mutational changes on different traits will not be statistically independent, and will not, by any linear transformation, be convertible to statistically independent changes (unlike mutational changes that are multivariate normal, which is a special case of the mutational distributions considered here).

2.2. Selection

Selection is taken to be stabilizing, with the characters defined in such a way that the optimum of the fitness function lies at the coordinate origin, $\mathbf{z} = \mathbf{0} \equiv (0, 0, \ldots, 0)^{\mathrm{T}}$. In Fisher's original formulation (Fisher, 1930), the fitness landscape was implicitly taken to be spherically symmetric, which means that fitness depends only on the Euclidean distance, $\|\mathbf{z}\| \equiv \sqrt{z_1^2 + z_2^2 + \cdots + z_n^2}$, of a phenotype from the origin. To combine the z_i in this way means that they must, of course, all be measured in the same units.

In the work of Waxman and Welch (2005) and the present work, we adopt a more general fitness function of the form motivated by Haldane (Waxman and Welch, 2005; Haldane, 1932), namely

$$w(\mathbf{z}) = \exp(-\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{z}), \tag{3}$$

where $\mathbf{S}$ is a real symmetric $n \times n$ matrix. Such a form for $w(\mathbf{z})$ can be derived from the Taylor series of $\ln(w(\mathbf{z}))$, by expanding to quadratic deviations in $\mathbf{z}$, from a fitness optimum (Waxman and Welch, 2005).

If selection is stabilizing, as we assume, then fitness decreases as $\mathbf{z}$ moves away from the fitness maximum ($\mathbf{z} = \mathbf{0}$) in all directions in the n-dimensional character space. This follows only if $\mathbf{S}$ is a positive definite matrix. It also follows that surfaces of constant fitness are generally n-dimensional ellipsoids (higher-dimensional analogues of an ellipse): such surfaces are the set of $\mathbf{z}$ values satisfying $\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{z} =$ constant, and this last equation can, in an appropriately rotated set of coordinates ($\mathbf{z}^*$), be written as the simplest representation of an n-dimensional ellipsoid: $\sum_{i=1}^{n} \sigma_i z_i^{*2} =$ constant, where the σ_i are the eigenvalues of $\mathbf{S}$.

In Fig. 2 we give an example, for $n = 3$, of a surface of constant fitness, where a particular parental phenotype lies (large ellipsoid). The same figure contains some of the possible mutational changes of the parental phenotype (partially visible small ellipsoid).

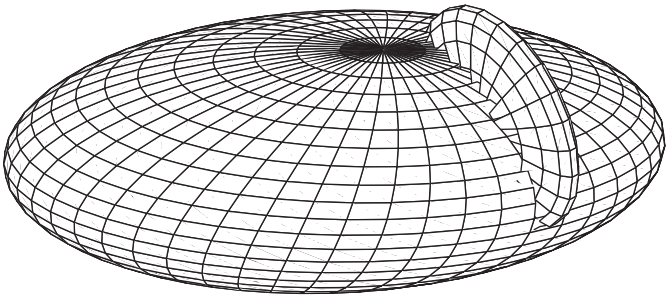

Fig. 2. This figure applies for the case of $n = 3$ characters. The large ellipsoid represents a surface of constant fitness that contains a parental phenotype, $\mathbf{z}$. Surfaces of yet higher fitness lie inside the large ellipsoid illustrated. The small, partially visible ellipsoid represents equiprobable mutational changes of the parental phenotype. The parts of the small ellipsoid visible represent non-adaptive mutations, since they correspond to mutant phenotypes that have lower fitness than the parental phenotype. The geometry of the problem is complex, since the fitness and mutational ellipsoids can be at arbitrary orientations and locations, relative to one another.

3. Results/methods

In the present work we determine a distribution characterizing the selection coefficients of new mutations. This distribution is derived for mutations characterized by Eq. (1). Any notions about the size of mutations that contribute to the distribution characterizing selection coefficients (however size is defined) need not be addressed since all mutations can make a contribution, irrespective of any of their attributes.

To proceed, we note that a random mutational change $\mathbf{r}$ of parental phenotype $\mathbf{z}$ results in an offspring with a selection coefficient of

$$s = w(\mathbf{z}+\mathbf{r})/w(\mathbf{z}) - 1. \tag{4}$$

In the work of Waxman and Welch (2005), it was found advantageous to deal not with the selection coefficients directly, but rather with a variable Q that is closely related to selection coefficients and defined by

$$Q = \ln(1+s) \equiv \ln[w(\mathbf{z}+\mathbf{r})/w(\mathbf{z})]. \tag{5}$$

In Eq. (5), the parental phenotype, $\mathbf{z}$, is a fixed parameter but Q is a random variable because it depends on the random mutational change $\mathbf{r}$. Knowledge of the distribution of Q is, of course, equivalent to knowledge of the distribution of s, however, the advantage in dealing with Q is that its distribution has a simpler form than that of s. In particular, it was shown that when the distribution of mutant effects is spherically symmetric, and $n \gg 1$, the distribution of Q for mutations with a fixed size (i.e. having a fixed value of $\|\mathbf{r}\|$) is well approximated by a normal distribution (Waxman and Welch, 2005).

The normal approximation for the distribution of Q is a particularly convenient way of proceeding, since the entire distribution is determined from just two parameters: the mean and the variance of Q. Furthermore, it leads to qualitatively good predictions for properties of direct biological interest. Consider, for example, selection coefficients of new mutations in the simplest case of Fisher's geometrical model—the original formulation—where there is no variation of the size of mutations and surfaces of constant fitness are spherically symmetric (Fisher, 1930). Approximate normality of Q means that this variable has a distribution that is (approximately) symmetric about its mean value. The distribution of selection coefficients (commonly termed the distribution of fitness effects) is not symmetric in s, yet is well captured by the normal approximation for Q. Indeed, when Q has the distribution $\psi(q)$, the distribution of selection coefficients is $(1+s)^{-1}\psi(\ln(1+s))$ and this is not generally symmetric in s. We can calculate the exact distribution of selection coefficients (for the original formulation of Fisher's geometrical model) and compare it with the distribution following from the normal approximation for Q. Taking the "worst case" of mutations of size $r = 2\|\mathbf{z}\|$, where no mutations are beneficial, and the relatively small n value, say $n = 12$, we obtain Fig. 3, indicating a very reasonable qualitative agreement of the two distributions over a wide range of s. The agreement increases with increasing n, and the relatively small value of n was only adopted to provide a figure with discernible differences between the two distributions. We note that for the case plotted, where $r = 2\|\mathbf{z}\|$ (and no mutations are beneficial), the proportion of beneficial mutations predicted by the normal approximation adopted in the present work is $\mathrm{erfc}\left(\sqrt{n/2}\right)/2 \sim \exp(-n/2)/\sqrt{2\pi n}$ and this is $\ll 10^{-5}$ for $n \geqslant 20$, indicating that there are some, but really rather few beneficial mutations predicted. In the less extreme case $r = \|\mathbf{z}\|/2$, we obtain a proportion of beneficial mutations,

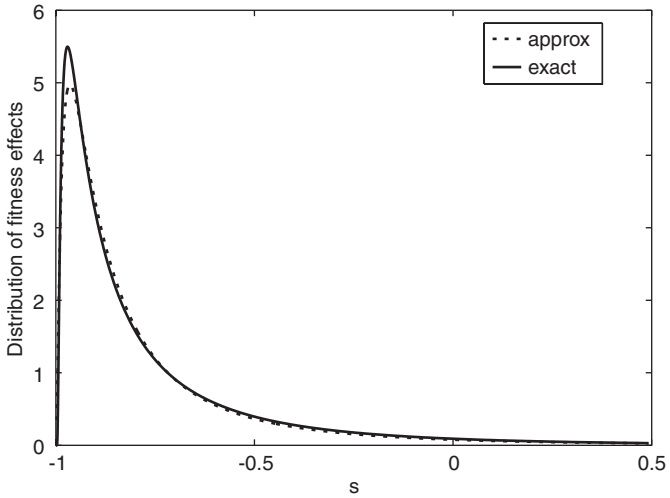

Fig. 3. The exact distribution of fitness effects is plotted, as a function of selection coefficient, s, for the original formulation of Fisher's geometrical model (solid curve). Also plotted is the corresponding distribution that follows from the normal approximation of the distribution of Q, that the current work is based upon (broken curve). For the case plotted, the number of characters is $n = 12$ and the size of mutations is $r = 2\|\mathbf{z}\|$, where no mutations are beneficial. A very reasonable qualitative agreement of the two distributions is obtained over a wide range of s and increased agreement follows for larger values of n.

following from the normal approximation for Q, that differs from the exact result (of approximately 0.1372) by less than 4%, when $n \geqslant 20$.

Going beyond the original formulation of Fisher's geometrical model, we find the distribution of Q that besides incorporating non-spherically symmetric fitness functions (Waxman and Welch, 2005) also incorporates the wide class of mutation distributions that are not spherically symmetric—as outlined in Eq. (1). This involves, however, an extra level of averaging compared with the results of Waxman and Welch (2005) because here all mutations, without restriction, contribute to the distribution of Q. As a consequence of this, the probability density of Q, which we write as $\psi(q)$, takes the approximate form of an average of a Gaussian distribution (see Appendix B for details)

$$\psi(q) = \int_0^\infty \sqrt{\frac{1}{2\pi v(R)}} \exp\left(-\frac{(q-\mu(R))^2}{2v(R)}\right) F(R)\,\mathrm{d}R. \tag{6}$$

Here $F(R)$ is a non-negative function associated with the distribution of mutations, i.e. associated with the function $f(\mathbf{r})$ of Eq. (1) and is arbitrary, apart from two conditions:

$$\int_0^\infty F(R)\,\mathrm{d}R = 1, \tag{7}$$

$$\frac{1}{n}\int_0^\infty R^2 F(R)\,\mathrm{d}R = 1. \tag{8}$$

The first of these two conditions, Eq. (7), ensures normalization of $f(\mathbf{r})$ while the second, Eq. (8), is a "scaling" requirement that ensures $\mathbf{C}$ coincides precisely with the variance–covariance matrix of mutational changes on different traits. If, for example, the distribution of mutant effects is the multivariate Gaussian $f(\mathbf{r}) \propto \exp(-(\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b})/2)$ then $F(R) \propto R^{n-1}\exp(-R^2/2)$. If we wish to specialize to spherically symmetric mutations with fixed magnitude r (cf. Fisher, 1930), then we need to take $F(R) = \delta(R-\sqrt{n})$ and $\mathbf{C} = r^2\mathbf{I}/n$, where $\delta(\bullet)$ denotes a Dirac delta function and $\mathbf{I}$ is the n by n identity matrix. Other forms of $F(R)$ are, of course, possible. Indeed, if $\widetilde{F}(r)$ is any non-negative function satisfying $\int_0^\infty \widetilde{F}(R)\,\mathrm{d}R = a$ and $\int_0^\infty R^2\widetilde{F}(R)\,\mathrm{d}R = b$, then $F(R) = \lambda\widetilde{F}(\lambda R)/a$ with $\lambda = \sqrt{b/(na)}$ satisfies Eqs. (7) and (8) and hence is an acceptable function with which to characterize mutations.

The quantities $\mu(R)$ and $v(R)$ appearing in Eq. (6) are given by

$$\mu(R) = -\left(2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \mathbf{b}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \frac{R^2}{n}\,\mathrm{Tr}(\mathbf{CS})\right), \tag{9}$$

$$v(R) = \frac{4R^2}{n}(\mathbf{z}+\mathbf{b})^{\mathrm{T}}\mathbf{S}\mathbf{C}\mathbf{S}(\mathbf{z}+\mathbf{b}) + \frac{2R^4}{n(n+2)}\left(\mathrm{Tr}(\mathbf{CSCS}) - \frac{[\mathrm{Tr}(\mathbf{CS})]^2}{n}\right). \tag{10}$$

For the class of mutation distributions considered here, there is no guarantee that the R^2 term in Eq. (10) is larger than the R^4 term (cf. Waxman and Welch, 2005).

With the results of Eqs. (6), (9) and (10), we can provide results for any quantity that involves an average over selection coefficients of new mutations. For example, the fraction of all mutations that are beneficial, P_{ben}, is simply the probability that $Q>0$, i.e. the area under $\psi(q)$ where $q>0$, and can be written as $P_{ben} = \int_0^\infty \psi(q)\,\mathrm{d}q$. Similarly, the fraction of all mutations that are both beneficial and fix in the population, P_{fix} (cf. Kimura, 1983) is $P_{fix} = \int_0^\infty \Pi(\mathrm{e}^q - 1)\psi(q)\,\mathrm{d}q$ where $\Pi(s)$ is the fixation probability of mutations with selection coefficient s. As a last example, the rate of change of log fitness in a single-mutant adaptive walk, which figures prominently in the "cost of complexity" (Orr, 1998), can be written as the expectation of $\ln(1+s)\Pi(s)$ (see Eq. (2) of Welch and Waxman, 2003). The expectation for the rate of change of log fitness can again be written in terms of $\psi(q)$ as $E[\Delta \ln w] = \int_{-\infty}^\infty q\Pi(\mathrm{e}^q - 1)\psi(q)\,\mathrm{d}q$. With the introduction of

$$\rho(R) = -\mu(R)/\sqrt{v(R)} \tag{11}$$

we obtain, using Eq. (6), and the substitution $t = (q-\mu(R))/\sqrt{v(R)}$,

$$P_{ben} \simeq \int_0^\infty \left(\int_{\rho(R)}^\infty \frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t\right) F(R)\,\mathrm{d}R,$$

$$P_{fix} \simeq \int_0^\infty \left(\int_{\rho(R)}^\infty \Pi(\mathrm{e}^{\sqrt{v(R)}(t-\rho(R))} - 1) \times \frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t\right) F(R)\,\mathrm{d}R,$$

$$E[\Delta \ln w] \simeq \int_0^\infty \sqrt{v(R)}\left(\int_{\rho(R)}^\infty (t-\rho(R))\Pi(\mathrm{e}^{\sqrt{v(R)}(t-\rho(R))} - 1) \times \frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t\right) F(R)\,\mathrm{d}R.$$

Simpler results emerge in the last two results if the important q contributing to the integral are $\ll 1$ in which case we can make the additional approximations $\Pi(\mathrm{e}^q - 1) \simeq \Pi(q) \simeq 2q$.

3.1. Additional approximation

The Gaussian approximation of Eq. (6), supplemented by Eqs. (9) and (10), indicates a somewhat complicated result for the distribution of Q. To obtain significantly simpler, and more readily interpretable results, we shall make some additional approximations, beyond large n, that are based on additional plausible assumptions.

We note that the functions $\mu(R)$ and $v(R)$ appearing in Eqs. (9) and (10) are not rapidly changing functions of R. Additionally, the scaling relation of Eq. (8) indicates that the mean value of R^2 equals n: $\int_0^\infty R^2 F(R)\,\mathrm{d}R = n$. This makes it plausible that the typical value of R is close to $\sqrt{n}$.

In particular, if for all positive k, the mean value R^k is close to $n^{k/2}$ in the sense

$$\int_0^\infty R^k F(R)\,\mathrm{d}R = n^{k/2} \times (1 + O(n^{-1})), \tag{12}$$

then this implies, amongst other things, that the variance of R is $O(n^0)$, which is much smaller than the mean value of R, which is $O(n^{1/2})$. It may be verified that the multivariate Gaussian form of $f(\mathbf{r})$ considered previously, which corresponds to $F(R) \propto R^{n-1}\exp(-R^2/2)$, yields $\int_0^\infty R^k F(R)\,\mathrm{d}R = 2^{k/2}\Gamma((n+k)/2)/\Gamma(n/2)$, where $\Gamma(\bullet)$ is Euler's gamma function (Abramowitz and Stegun, 1970) and this last result has precisely the property of Eq. (12) when $n \gg 1$. Thus the set of functions satisfying Eq. (12) includes reasonable forms for $F(\bullet)$.

We shall proceed, assuming Eq. (12) applies, and make the additional approximations of (i) neglecting deviations of all powers of R from their mean value (by replacing any power of R by its expected value) and (ii) discarding terms of relative order n^{-1}. For example, the term $R^4/(n(n+2))$, which appears in $v(R)$, is replaced by its expected value $\int_0^\infty R^4 F(R)\,\mathrm{d}R/(n(n+2)) = n^2 \times (1 + O(n^{-1}))/(n(n+2))$. This simplifies to $1 + O(n^{-1})$ and is then approximated by unity. This approximation scheme leads to Eq. (6) reducing to the simple, explicitly normal form

$$\psi(q) \simeq \sqrt{\frac{1}{2\pi v}}\exp\left(-\frac{(q-\mu)^2}{2v}\right), \tag{13}$$

where

$$\mu = -(2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \mathbf{b}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \mathrm{Tr}(\mathbf{CS})), \tag{14}$$

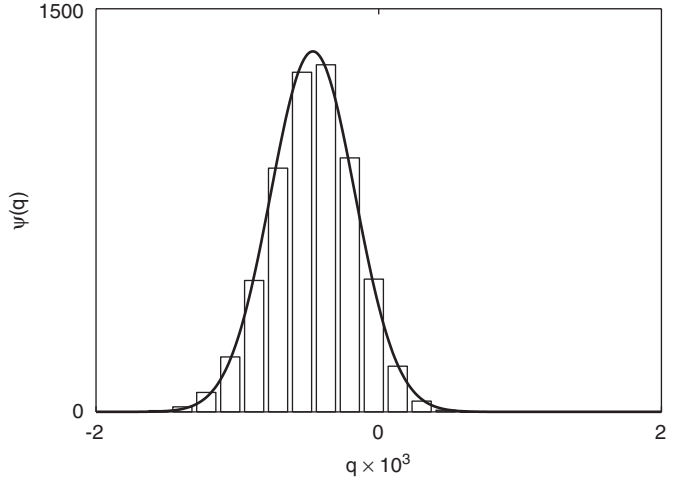

Fig. 4. In this figure, we plot the approximation of $\psi(q)$ given in Eq. (13) against q (solid curve). In the same figure a histogram is plotted that illustrates the results of numerical simulation. For $n = 10$ characters, the matrices $\mathbf{C}$ and $\mathbf{S}$ and the vectors $\mathbf{z}$ and $\mathbf{b}$ were independently generated at random and for the figure presented, $\|\mathbf{z}\|/r \simeq 2$. Holding $\mathbf{C}$, $\mathbf{S}$, $\mathbf{z}$ and $\mathbf{b}$ fixed, we generated 10^5 different mutational changes and hence 10^5 different values of Q. The value of μ following from Eq. (14) is -4.6579×10^{-4} while the mean value of Q resulting from the simulations is -4.6577×10^{-4}. The value of v following from Eq. (15) is 8.8443×10^{-8} while the variance of Q resulting from the simulations is 8.8850×10^{-8}.

$$v = 4(\mathbf{z}+\mathbf{b})^{\mathrm{T}}\mathbf{S}\mathbf{C}\mathbf{S}(\mathbf{z}+\mathbf{b}) + 2\left(\mathrm{Tr}(\mathbf{CSCS}) - \frac{[\mathrm{Tr}(\mathbf{CS})]^2}{n}\right). \tag{15}$$

An example of the effectiveness of this approximation for the distribution $\psi(q)$ is given in Fig. 4.

The same approximation leads (with the substitution $t = (q-\mu)/\sqrt{v}$) to

$$P_{ben} \simeq \int_\rho^\infty \frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t, \tag{16}$$

$$P_{fix} \simeq \int_\rho^\infty \Pi(\mathrm{e}^{\sqrt{v}(t-\rho)} - 1)\frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t, \tag{17}$$

$$E[\Delta \ln w] \simeq \sqrt{v}\int_\rho^\infty (t-\rho)\Pi(\mathrm{e}^{\sqrt{v}(t-\rho)} - 1) \times \frac{\exp(-t^2/2)}{\sqrt{2\pi}}\,\mathrm{d}t, \tag{18}$$

where ρ is given by

$$\rho = -\mu/\sqrt{v}. \tag{19}$$

We can interpret the value of ρ as a dimensionless measure of the typical size of a mutation that naturally emerges from the model under consideration (cf. Fisher, 1930; Orr, 1998), but there is no guarantee that it is a positive quantity (see later).

3.2. Compatible mutation and selection

The expressions for μ, v and ρ above can be thought of as consisting of geometrical invariants formed from $\mathbf{z}$, $\mathbf{b}$, $\mathbf{S}$ and $\mathbf{C}$ that encapsulate key aspects of the geometry of the problem. These invariant quantities are unchanged by replacements which represent a rotation of coordinate axes. Such replacements can be written as $\mathbf{z} \to \mathbf{z}^* = \mathbf{O}\mathbf{z}$, $\mathbf{b} \to \mathbf{b}^* = \mathbf{O}\mathbf{b}$, $\mathbf{S} \to \mathbf{S}^* = \mathbf{O}\mathbf{S}\mathbf{O}^{\mathrm{T}}$ and $\mathbf{C} \to \mathbf{C}^* = \mathbf{O}\mathbf{C}\mathbf{O}^{\mathrm{T}}$ where $\mathbf{O}$ is a real $n \times n$ orthogonal matrix (which has the property $\mathbf{O}^{\mathrm{T}} = \mathbf{O}^{-1}$).

A particularly simple case occurs when mutation and selection are compatible in the sense that a choice for the orthogonal matrix $\mathbf{O}$ can be found where the above forms for $\mathbf{S}^*$ and $\mathbf{C}^*$ are both diagonal matrices (i.e. both have vanishing elements off the main diagonal). Generally, this is possible only when $\mathbf{SC} = \mathbf{CS}$ (Strang, 1988). Assuming this condition holds, and that the diagonal elements of $\mathbf{S}^*$ and $\mathbf{C}^*$ are σ_i and m_i^2, respectively, for $i = 1, 2, \ldots, n$, it then follows that the fitness function of Eq. (3) takes the form $w(\mathbf{z}) = \exp(-n^{-1}\sum_{i=1}^n \sigma_i z_i^{*2})$. The distribution of mutant effects is a function only of A (Eq. (1)), and setting $\mathbf{r}^* = \mathbf{O}\mathbf{r}$, we have $A = \sum_{i=1}^n m_i^{-2}(r_i^* - b_i^*)^2$.

Since the relation between $\mathbf{z}$ and $\mathbf{z}^*$ means we can write $z_i^* = O_{i1}z_1 + O_{i2}z_2 + \cdots$ the interpretation we can give to z_i^* is as a set of "composite" traits that independently affect fitness and are linear combinations of the original traits. For the special case of compatible mutation and selection,

the quantities μ and v take the forms

$$\mu = -\sum_{i=1}^{n} \sigma_i (2b_i^* z_i^* + b_i^{*2} + m_i^2),$$

$$v = \sum_{i=1}^{n} \left[4\sigma_i^2 m_i^2 (z_i^* + b_i^*)^2 + 2\left(\sigma_i m_i^2 - \frac{1}{n}\sum_{j=1}^{n} \sigma_j m_j^2 \right)^2 \right]$$

and $\rho = -\mu/\sqrt{v}$. From these results we can infer that ρ need not be positive when mutation is biased ($\mathbf{b} \neq \mathbf{0}$). For example, in the special case where $\mathbf{z}^* = -\mathbf{b}^*$, the numerator of ρ, i.e. $-\mu$, is $\sum_{i=1}^{n} \sigma_i (m_i^2 - b_i^{*2})$ and this will be guaranteed negative if $b_i^{*2} > m_i^2$ for all i.

4. Discussion

In this work we have presented further theoretical developments of Fisher's geometrical model of evolutionary adaptation. In particular, we have extended Fisher's model to incorporate a distribution of mutant effects that includes (i) correlations between mutational effects on different traits, (ii) mutational biases on different traits and (iii) a class of distributions of mutant effects that have the property that surfaces of constant probability density are ellipsoids. This includes a multivariate Gaussian as a special case, but covers more general distributions.

The above was made in the context of fitness functions that were not spherically symmetric.

Making additional assumptions about moments of the distribution of mutant effects and exploiting the large number of traits, n, allowed us to obtain a simple Gaussian form for the distribution of the random variable $Q \equiv \ln(1+s)$, where s is the selection coefficient of a new mutation. Simulations based on a multivariate Gaussian form for the distribution of mutant effects suggest a very reasonable accuracy of the approximation even for values of n as small as $n = 10$ (see Fig. 4).

Out of the analysis, the quantity $\rho = -\mu/\sqrt{v}$ naturally arose (where μ and v are given in Eqs. (14) and (15)). Such a ratio has, for mutations that are spherically symmetric, been interpreted as a dimensionless measure of size of a mutation (Waxman and Welch, 2005). In the presence of mutational bias, the defect with this interpretation was that the quantity ρ may be negative. Exact calculations (not presented) indicate that negative ρ can arise simply from mutational bias ($\mathbf{b} \neq \mathbf{0}$), in the absence of correlations between mutational effects on different traits. A negative value of ρ has very significant implications, since, e.g. by Eq. (16), this implies that the proportion of beneficial mutations can be >0.5 if it occurs; this follows since we can write Eq. (16) as $P_{ben} = \frac{1}{2}\mathrm{erfc}(\rho/\sqrt{2})$ where $\mathrm{erfc}(\bullet)$ is the complementary error function (Abramowitz and Stegun, 1970) and $\frac{1}{2}\mathrm{erfc}(\rho/\sqrt{2}) > 0.5$ for $\rho < 0$. Thus under some circumstances mutational bias may not be a trivial aspect of the problem.

The analysis also leads to explicit result for the distribution of Q that involved a number of different geometrically invariant quantities, indicating the way the differently "orientated" matrices representing selection (**S**) and mutation (**C**) and the various vectors in the problem describing phenotype and mutational bias (**z** and **b**) combine together. It is one of the jobs of theory to focus attention on the important quantities underlying a model, and without the detailed calculations presented here, it would be very hard to predict the combinations of geometrically invariant quantities that are actually present in the final results.

Overall, we view the results obtained here as a step towards a more complete theory of evolutionary adaptation, based on Fisher's geometrical model. Given that Fisher's model has begun to be applied in a variety of contexts of interest to evolutionary biologists (Orr, 1998, 1999, 2000; Hartl and Taubes, 1996, 1998, Burch and Chao, 1999; Peck et al., 1997; Poon and Otto, 2000; Barton, 2001; Welch and Waxman, 2003; Rice, 1990; Whitlock et al., 2003; Waxman and Welch, 2005), it would be interesting to investigate the extent to which empirical data can be used to determine or constrain the values of the quantities appearing in, e.g., Eqs. (15) and (16).

After submission of the original version of this paper, I became aware of some very recent work that has taken some interesting steps in this direction. In this work, which addressed the implications of general trends in the distribution of fitness effects, an unbiased Gaussian distribution of mutant effects was adopted. Furthermore, mathematical approximations were made, including a key one of averaging over the various matrices, assuming they were random. One key biological assumption was also made, that gene number of an organism has an appreciable positive correlation with the number of quantitative traits, n (Martin and Lenormand, submitted for publication).

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Appendix A

In this work we have assumed that the distribution of mutant effects, $f(\mathbf{r})$, depends on $\mathbf{r}$ in only a specific combination $A = (\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b})$, with $\mathbf{C}$ a positive definite matrix. In this appendix, we establish that when only a single requirement on the A dependence of $f(\mathbf{r})$ is made (beyond that of normalization), the matrix $\mathbf{C}$ is the variance–covariance matrix of mutational changes.

To proceed, we introduce a non-negative function $F(R)$ that satisfies just two conditions:

$$\int_0^\infty F(R)\,\mathrm{d}R = 1, \tag{A.1}$$

$$\frac{1}{n}\int_0^\infty R^2 F(R)\,\mathrm{d}R = 1, \tag{A.2}$$

but is otherwise arbitrary. With hindsight, we write the distribution of mutant effects in terms of the somewhat arbitrary function $F(\bullet)$ as

$$f(\mathbf{r}) = \frac{1}{\sqrt{\mathrm{Det}(\mathbf{C})}}\,\frac{F(\sqrt{A})}{N_n A^{(n-1)/2}}, \tag{A.3}$$

where Det (...) denotes the determinant of a matrix, $N_n = 2\pi^{n/2}/\Gamma(n/2)$ is the surface area of a unit radius sphere in n dimensions and $\Gamma(\bullet)$ denotes Euler's Gamma function (Abramowitz and Stegun, 1970).

With all integrals with unspecified limits covering the full, $-\infty$ to ∞, range of all integration variables, normalization of $f(\mathbf{r})$, i.e. $\int f(\mathbf{r})\,\mathrm{d}^n r = 1$, automatically follows from Eq. (A.1) when the following change of variables from $\mathbf{r}$ to $\mathbf{R}$ is made: $\mathbf{R} = \mathbf{C}^{-1/2}(\mathbf{r}-\mathbf{b})$. The same change of variables in $\int \mathbf{r} f(\mathbf{r})\,\mathrm{d}^n r$ yields a mean mutational change of $\mathbf{b}$.

The variance–covariance matrix can then be written as $\int(\mathbf{r}-\mathbf{b})(\mathbf{r}-\mathbf{b})^{\mathrm{T}} f(\mathbf{r})\,\mathrm{d}^n r$ and with the same change of variables becomes $\mathbf{C}^{1/2}(\int \mathbf{R}\mathbf{R}^{\mathrm{T}}(F(\|\mathbf{R}\|)/N_n\|\mathbf{R}\|^{n-1})\,\mathrm{d}^n R)\mathbf{C}^{1/2}$. By symmetry, the bracketed quantity has the value $\mathbf{I}\times\kappa$ where $\mathbf{I}$ is the $n\times n$ identity matrix and κ equals $n^{-1}\int_0^1 R^2 F(R)\,\mathrm{d}R$, which equals unity by Eq. (A.2). Hence, when $F(\bullet)$ is subject to Eq. (A.2), the variance–covariance matrix is $\mathbf{C}^{1/2}\times\mathbf{I}\times\mathbf{C}^{1/2}\equiv\mathbf{C}$. The imposition of Eq. (A.2) on $F(\bullet)$ is thus sufficient to give $\mathbf{C}$ the unique identification as the variance–covariance matrix of mutational changes.

Appendix B

In this appendix we present arguments for probability density of Q, namely $\psi(q)$, having the approximate weighted Gaussian form given in Eq. (6).

For the purposes of this appendix, we shall initially write the distribution of mutant effects as $G((\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b}))$ for some non-negative function $G(\bullet)$ that leads to an $f(\mathbf{r})$ that is normalized: $\int f(\mathbf{r})\,\mathrm{d}^n r = 1$.

Using the fitness function of Eq. (3), the quantity Q of Eq. (5) takes the form $Q = -2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{r} - \mathbf{r}^{\mathrm{T}}\mathbf{S}\mathbf{r}$. The probability density of Q is given by $\psi(q) = E[\delta(q-Q)]$ where $\delta(\bullet)$ denotes a Dirac delta function and the expectation $E[\ldots]$ is taken over all mutations, i.e.

$$\psi(q) = \int \delta(q + 2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{r} + \mathbf{r}^{\mathrm{T}}\mathbf{S}\mathbf{r}) G((\mathbf{r}-\mathbf{b})^{\mathrm{T}}\mathbf{C}^{-1}(\mathbf{r}-\mathbf{b}))\,\mathrm{d}^n r.$$

We simplify this result by expressing it in terms of a linearly transformed mutational change, $\mathbf{R}$, defined by $\mathbf{R} = \mathbf{C}^{-1/2}(\mathbf{r}-\mathbf{b})$. This leads to

$$\psi(q) = \int \delta(q + \Delta + \boldsymbol{\alpha}^{\mathrm{T}}\mathbf{R} + \mathbf{R}^{\mathrm{T}}\mathbf{M}\mathbf{R}) G(\|\mathbf{R}\|^2)\sqrt{\mathrm{Det}(\mathbf{C})}\,\mathrm{d}^n R, \tag{B.1}$$

where Det(...) denotes the determinant of a matrix and

$$\Delta = 2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \mathbf{b}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \frac{\|\mathbf{R}\|^2}{n}\,\mathrm{Tr}(\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2}), \tag{B.2}$$

$$\boldsymbol{\alpha} = 2\mathbf{C}^{1/2}\mathbf{S}(\mathbf{z}+\mathbf{b}), \tag{B.3}$$

$$\mathbf{M} = \mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2} - \frac{\mathbf{I}}{n}\,\mathrm{Tr}(\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2}). \tag{B.4}$$

The integral in Eq. (B.1) can be written as

$$\psi(q) = \int_0^\infty \phi(q) F(R)\,\mathrm{d}R, \tag{B.5}$$

where

$$\phi(q) = \langle \delta(q + \Delta + \boldsymbol{\alpha}^{\mathrm{T}}\mathbf{R} + \mathbf{R}^{\mathrm{T}}\mathbf{M}\mathbf{R})\rangle, \tag{B.6}$$

and the angular bracket, $\langle\ldots\rangle$, denotes isotropic averaging over all directions of $\mathbf{R}$ with its magnitude fixed at R and the function $F(R)\propto R^{n-1}G(R^2)$ coincides with the function $F(R)$ of Appendix A. In particular, it is defined so that $\int_0^\infty F(R)\,\mathrm{d}R = 1$.

We shall concentrate, here, on the function $\phi(q)$ and establish an approximate Gaussian dependence upon q. Since we shall go further than the work of Waxman and Welch (2005), we give independent and slightly extended arguments for the reason for this dependence.

We note that $\phi(q)$ is the probability density for the random variable

$$Y = -(\Delta + \boldsymbol{\alpha}^{\mathrm{T}}\mathbf{R} + \mathbf{R}^{\mathrm{T}}\mathbf{M}\mathbf{R}), \tag{B.7}$$

where the direction of $\mathbf{R}$ is random, but its magnitude is fixed at R. We can write $Y = -\Delta - \sum_{i=1}^n \alpha_i R_i - \sum_{i,j=1}^n M_{ij}R_iR_j$ and as such, it is a sum of random variables which are not all independent, since $\sum_{i=1}^n R_i^2$ has the fixed value of R^2. If, despite this non-independence a central limit sort of behaviour is operating, so that the distribution of Y is near normal, then

$$\langle\delta(q-Y)\rangle \simeq \sqrt{\frac{1}{2\pi v(R)}}\exp\left(-\frac{(q-\mu(R))^2}{2v(R)}\right), \tag{B.8}$$

where $\mu(R)$ and $v(R)$ are the mean and the variance of Y and are obtained by averaging over all directions of $\mathbf{R}$ when $\|\mathbf{R}\|$ is held fixed at R.

We use results for spherical averages, such as $E[R_i]=0$ and $E[R_iR_j] = R^2\delta_{ij}/n$, etc., where δ_{ij} is a Kronecker delta that equals 1 when $i=j$ and is zero otherwise, and obtain

$$\mu(R) = \langle Y\rangle = -\Delta = -\left(2\mathbf{z}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \mathbf{b}^{\mathrm{T}}\mathbf{S}\mathbf{b} + \frac{R^2}{n}\,\mathrm{Tr}(\mathbf{C}\mathbf{S})\right).$$

Similarly,

$$v(R) = \langle Y^2\rangle - \langle Y\rangle^2 = \langle(\boldsymbol{\alpha}^{\mathrm{T}}\mathbf{R})^2\rangle + \langle(\mathbf{R}^{\mathrm{T}}\mathbf{M}\mathbf{R})^2\rangle$$
$$= \frac{R^2}{n}\boldsymbol{\alpha}^{\mathrm{T}}\boldsymbol{\alpha} + \frac{2R^4}{n(n+2)}\,\mathrm{Tr}(\mathbf{M}^2)$$
$$= \frac{4R^2}{n}(\mathbf{z}+\mathbf{b})^{\mathrm{T}}\mathbf{S}\mathbf{C}\mathbf{S}(\mathbf{z}+\mathbf{b}) + \frac{2R^4}{n(n+2)}\left(\mathrm{Tr}(\mathbf{C}\mathbf{S}\mathbf{C}\mathbf{S}) - \frac{[\mathrm{Tr}(\mathbf{C}\mathbf{S})]^2}{n}\right).$$

Defining $\mu_j = \langle(Y-\mu(R))^j\rangle$, we note that approximate normality also implies $\mu_3^2/[v(R)]^3 \ll 1$ and $\mu_4/[v(R)]^2 - 3 \ll 1$, and these inequalities should hold for a range of R. Exact analytical expressions for the ratios $\mu_3^2/[v(R)]^3$ and $\mu_4/[v(R)]^2$ (results not shown) are expressible in terms of a single vector, $\boldsymbol{\alpha} = 2\mathbf{C}^{1/2}\mathbf{S}(\mathbf{z}+\mathbf{b})$, and a single matrix, $\mathbf{M} = \mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2} - (\mathbf{I}/n)\,\mathrm{Tr}(\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2})$. These expressions allow investigation of $\mu_3^2/[v(R)]^3$ and $\mu_4/[v(R)]^2 - 3$,and in the absence of detailed information about $\mathbf{S}$ and $\mathbf{C}$, we have carried out this investigation using randomly generated values of $\boldsymbol{\alpha}$ and $\mathbf{M}$. We took elements of $\boldsymbol{\alpha}$ to be independent and identically distributed standard normal random variables (i.e. with mean zero and variance unity). Furthermore, to determine $\mathbf{M}$ we set $\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2} = \mathbf{A}^{\mathrm{T}}\mathbf{A}$ where $\mathbf{A}$ is an $n \times n$ matrix whose elements are also independent and identically distributed standard normal random variables. Writing $\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2}$ in terms of the matrix $\mathbf{A}$, in the form shown, is consistent with the positive definiteness of $\mathbf{C}^{1/2}\mathbf{S}\mathbf{C}^{1/2}$. We find, for $n = 50$ (100) and R in the range $(0, \sqrt{n})$, that typically $\mu_3^2/[v(R)]^3$ and $\mu_4/[v(R)]^2 - 3$ are $\lesssim 0.2(0.1)$. It is thus plausible that large enough n leads to an approximately normal distribution of q, Eq. (B.6), and hence to Eq. (6) of the main body of this paper.

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