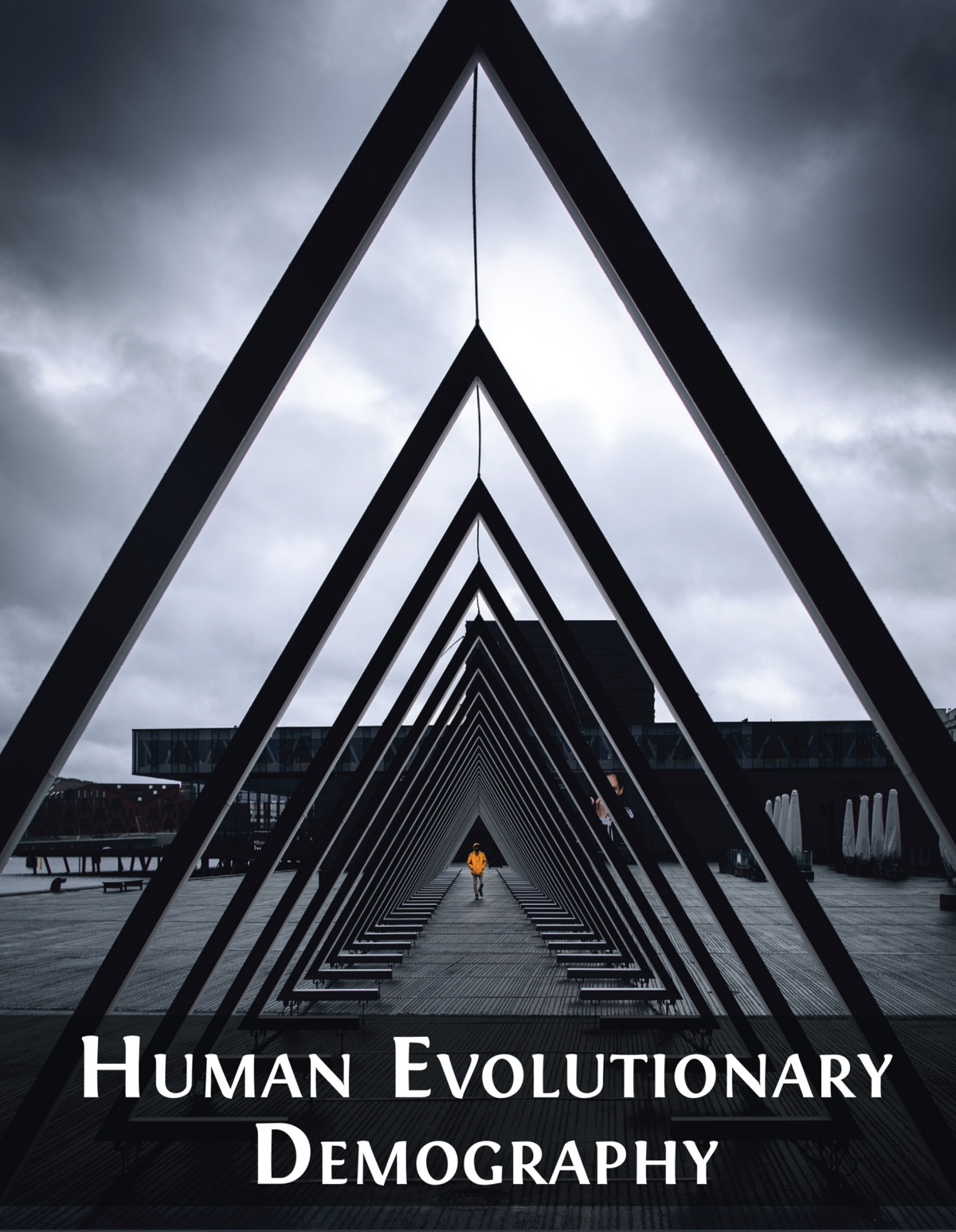

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14. Measuring Selection for Quantitative Traits in Human Populations

Jacob A Moorad

Quantitative genetics offers a powerful suite of statistical approaches designed to describe and predict rates of phenotypic evolution. Its origin lies at the reconciliation of Mendelian and biometrical genetics and Darwin's theory of evolution by natural selection that occurred in the early twentieth century. Quantitative genetics has since played a major role in the science of animal and plant improvement since the mid-twentieth century and in the study of evolution since the 1970s and 80s. The goal of this chapter is to introduce this perspective to demographers, provide guidance on methods intended to characterize natural selection on traits of interest, and to illustrate the flexibility of this approach to deal with complications that are inherent to the study of human populations, such as overlapping generations and social interactions.

An important goal of evolutionary biology is to quantify the rate and direction of phenotypic change occurring in populations and to identify the portion of that change that is caused by natural selection. Understanding this response to selection requires sound measurements of the two elements of phenotypic evolution: (1) phenotypic selection: the association between fitness and the traits of interest, and (2) trait transmission or inheritance: the association between the traits of parents and their offspring. The approaches and data requirements for estimating these components differ, but a complete understanding of the response to selection usually requires estimates of both. Combining these components can describe retrospectively how natural selection caused transmissible genetic change that altered trait means from one generation to the next, and it can provide predictions about how natural selection will contribute to changes in the future. A strength of this approach to understanding evolutionary change is that when the appropriate analytical tools are implemented correctly to estimate one element of the response to selection (e.g. phenotypic selection), it is not necessary to estimate jointly the other (e.g. inheritance). This is important for comparative work because the response to selection can be thought of as a product of both components, and as a result, both can serve as independent indicators of maximal rates of phenotypic evolution. For example, evolution by natural selection can never occur faster than phenotypic selection.

In practice, the requirements for quantifying inheritance can be much more demanding than for measuring selection in terms of data quantity and technical know-how. As a result, phenotypic selection is the most often studied of the two components of phenotypic evolution, and the past few decades have brought about a proliferation of plant and animal selection studies performed in natural and artificial environments on a great diversity of traits. Not surprisingly, humans have also been subjects of phenotypic selection analyses, but a greater

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appreciation of the complexities related to these populations demands that special care be taken in the application of analytical methods. The first of these complications involves age structure and overlapping generations. These features characterize many non-human populations, of course, but human data is generally available on time scales far finer than generation time, and age structure is much more difficult to ignore. The second feature involves social interactions. Again, these are certainly not specific to humans, but there are no other species of which we know more about the importance of sociality. Demographers are intimately aware that these are important characteristics of human populations, and including an honest and informed accounting of these features into estimates of natural selection should be a goal of evolutionary studies of humans. This chapter is written with this goal in mind.

The methods discussed here are general to all systems; these have been discussed elsewhere in the primary literature, but it may be useful to collect them in a single overview intended for demographers who are specifically interested in measuring selection on phenotypes in human populations. The perspective taken here follows one of quantitative genetics, an area of study first developed for the purposes of animal improvement (Lush, 1937), but since developed and applied to the study of evolution by natural selection (Lande and Arnold, 1983, Arnold and Wade, 1984a,b). Much of my own work over the past few years has focused upon refining these methods to be useful for understanding evolution in age-structured populations (Moorad et al., 2011; Moorad, 2013a,b; Moorad and Wade, 2013; Moorad, 2014; Moorad and Walling, 2017; Moorad and Ravindran 2022), and here I have applied nearly all the methods discussed in this chapter to study selection in a human population.

I begin this discussion by contextualizing how phenotypic selection fits into the evolution of phenotypes; this is done to make clear the importance of avoiding conflating selection with inheritance (a problem inherent in many studies of selection). As I explain in the next section, selection is defined as a covariance between fitness and the trait(s) of interest (Robertson, 1966; Price, 1970); phenotypic selection does not imply a response to selection. As such, implementing an appropriate definition of fitness is key to appropriate estimates; I demonstrate in the second section (Relative Fitness) how individual reproductive value at birth is our most appropriate definition to be used for this purpose. However, there are many different ways to express phenotypic selection (even using the same measure of fitness). In the third section (Measures of Phenotypic Selection), I discuss what these measures mean, how they are estimated, and how they should be interpreted. Fourthly, I digress into a discussion of social interactions and how the quantitative genetic approach accounts for these (Complications Owing to Social Interactions). Fifthly, I discuss the complication of what to do if some individuals are logically precluded from expressing a trait of interest (age at menarche in males, for example) (Impossible Traits). Finally, I will introduce measuring genotypic selection as an alternative to phenotypic selection for predicting evolutionary responses to selection, and I will discuss the advantages and disadvantages of the two approaches (Genetic Selection for Quantitative Traits).

Phenotypic Selection and Evolutionary Change

As a first step to understanding phenotypic selection, it may be useful to articulate carefully where this fits into how we understand evolution by natural selection. The Price Theorem (Price, 1970, 1972) is often invoked as a fully general expression that formally accomplishes this goal by describing a between-generation change in the mean of some arbitrary trait z.

What is a trait? It can be literally anything that can be attributed in some way to an individual. For the purposes of this discussion, however, I will assume that the trait is observable. The specific shapes of trait distributions do not matter in principle; they can be continuous or discrete, Gaussian or not. Vital rates (age-specific survival and fertility) are traits of obvious importance to many evolutionary demographers. Other human traits of interest might be age at menarche or menopause, total lifetime reproduction, number of years lived past some age of interest, and survival to some age (a dichotomous trait).

Here we imagine an "ancestral" population in which every individual has some trait value z (we begin here with the univariate case where the evolution of one trait is considered without regard to any other, but we will generalize to the multivariate case later). Members of this ancestral population collectively produce offspring that wholly constitute a "descendent" population. The contribution of each ancestor to this new population, relative to the entirety of the ancestral population, is the ancestor's relative fitness, w. By the nature of this definition, w is non-negative with a mean of one. Finally, let us specify that for our purposes here, individuals are organisms, and the "descendents" are the offspring of the "ancestors". Following Price's Theorem, we can express the between-generation change in the mean of the trait as,

$$\Delta\bar{z} = \beta_{wz}\mathrm{cov}(z_d, z) + \delta \qquad [1],$$

where β_{wz} is the coefficient associated with the least-squares regression of relative fitness on trait values, z_d is the value of offspring phenotypes, and δ is the average change in trait values between offspring and their parents *unweighted* by relative fitness.

We can equate the change in the trait mean, $\Delta\bar{z}$, with an evolutionary change, and by doing so, we can identify the role that natural selection plays in this change, but first it is helpful to consider each of the three terms given in the right-hand side of eq. [1] in turn. The meanings of these are as follows.

1. The coefficient β_{wz} is known as the *selection gradient*; this is a slope that tells us how sensitive relative fitness is to changes in z. If we were to multiply this slope by the phenotypic variance of the ancestral population, we would have a *selection coefficient*, $s_z = \beta_{wz}\mathrm{var}(z)$. This is the covariance between relative fitness and ancestral trait values. This is equal to the difference between two trait means in the ancestral population: the first mean is weighted by relative fitness and the second is not.

2. The covariance between parent and offspring traits, $\mathrm{cov}(z_d, z)$, represents *transmission fidelity*. This gives us the amount of heritable variation, in absolute terms, associated with this trait in this population. This is often interpreted as *additive genetic variance*, or $\mathrm{var}(G)$. This concept may be expressed differently by restating it as the fraction of phenotypic variance in the ancestral population that is heritable. The covariance given in terms of *narrow-sense heritability* is $\mathrm{cov}(z_d, z) = \mathrm{var}(G) = h^2_z$. Note that h^2_z is also $\beta_{z_d z}$, the slope of the regression of offspring traits upon their parents' trait values, so that one can equivalently write $\mathrm{cov}(z_d, z) = \beta_{z_d z}\mathrm{var}(z)$ following the standard definition of regression coefficients.

3. The last term, δ, is the *transmission bias*. This accounts for all changes in the mean phenotype from one generation to the next that have nothing to do with natural

selection acting to change z. In practice, this is often attributed to changes in the environment or in the genome owing to the influx of new mutations.

From (1), we see that the response to selection, or the portion of the total change attributable to natural selection, is equal to both $\beta_{wz}\text{var}(G)$ and $h_z^2 s_z$. This is known as the "Breeder's Equation" (Lush, 1937). From either formulation, it is clear that both phenotypic selection and inheritance are required for a response to selection, and both independently act as mathematical limits to the potential for evolutionary rates of change owing to the force of selection.

Incidentally, some demographers are accustomed to scaling evolutionary change in terms of the length of time intervals (e.g. years in human studies), and it may seem strange to them to think of evolution expressed on the scale of generations. Because both of those conventional demographic approaches (e.g. Caswell, 2001) and the perspective advocated here assume that vital rates are stable over time, the difference in scaling is a trivial issue. Estimates of selection (or responses to selection) on the generational scale are converted to estimates on the time interval scale by dividing by mean generation time, where $T = \sum_{x=1}^{\infty} x l_x m_x e^{-rx}$ (Lande, 1982; Charlesworth, 1994).

Relative Fitness

As phenotypic selection is a covariance that always involves relative fitness, it is critical to quantify this value carefully. At its essence, relative fitness is simply a weighting factor applied to an individual to express its relative contribution to the next generation. In practice, determining what these weights are does not appear to be straightforward. Indeed, there has been much confusion on this point. Before we go further into a discussion of what relative fitness *is*, it may be illustrating to consider what it *is not*, at least in the context of the quantitative genetics perspective of phenotypic evolution considered here:

Fitness is not a characteristic of groups of individuals, where "group" is defined as belonging to the same population or sharing a common trait value. Groups of individuals can have fitness means, but these do not normally factor directly into expressions describing the response to selection. Fitness is best thought of as an attribute of an individual.

Fitness is not the contribution of some individual to the population at some arbitrary point in the future. As stated before, fitness describes the weighting of ancestral contributions to a descendent population. As such, the concept of fitness depends entirely upon the definitions of these populations. It should be appreciated from the previous section that these definitions are preserved when characterizing both selection and inheritance, and inheritance is always expressed on the scale of single generations (e.g. narrow-sense heritability follows from a parent-offspring regression). One could, in principle, define fitness based upon the number of grandchildren or great-grandchildren, but in these cases, the notion of heritability changes fundamentally to mean something quite different and potentially bizarre, such as the resemblance between great-grandparents and great-grand-offspring. This can potentially conflate the causal processes that we normally understand to be selection and inheritance, and estimates of the response to selection can be rendered invalid (Hadfield and Thomson, 2017).

Fitness is not the number of recruited or adult offspring because pre-adult death is an aspect of the performance of the offspring and not of the parent. Ideally, fitness relates to the number of zygotes produced by zygotes, but, as accounting for the reproductive success all new embryos

in a human population is impractical, using the number of newborns eventually produced by each newborn is a reasonable approximation. In practice, the clearest inferences follow from using the earliest age at which individuals can be observed.

Inclusive fitness is not a concept that is compatible with the modern quantitative genetic perspective taken here. Fitness is measured directly, and its definition need have no relationship to the performance of kin.

Some may object to elements of this list by invoking issues involving social interactions, such as resource transfers and potentially important effects of maternal or grandmaternal care. From a certain perspective, it may seem that these issues must require that the notion of fitness is quite complicated, or even arbitrary. However, if one is willing to accept some assumptions regarding demographic stability, fitness is actually a rather simple concept to understand and one that may be relatively easy to implement. As I discuss in a later section, the manner by which social interactions shape the evolution of phenotypes is accounted for in quantitative genetics not by redefining fitness, but by recognizing how these interactions redefine selection and inheritance in other ways.

In most evolutionary genetic studies, fitness is regarded as the total number of offspring born, R_0, total lifetime reproduction, or total breeding success (the terminology usually depends upon the field that implements it). Relative fitness is then simply this value divided by the mean value for the ancestral population. This is a perfectly adequate approach for populations in which generations do not overlap, but this is certainly not the case for human populations. In these cases, population growth must be considered as part of a satisfactory definition of fitness. While a few different definitions have been suggested, the most satisfactory is the individual's reproductive value at birth. The case for using this measure of fitness is made more explicitly in Moorad (2014), and here I will only discuss how the measure is defined and some of its implications and limitations.

Let us assume that the population has a constant Malthusian growth rate r, and every individual has some known number of new offspring that may vary with its age. For any individual i, its individual reproductive value at birth is,

$$w_i = \sum_{x=1}^{\infty} e^{-rx} B_{ix} \qquad [2],$$

where B_{ix} is the number of offspring alive at the first age class that are produced by individual, i, at age x. Demographers will be familiar with the notion of a reproductive value at birth from Fisher (1930), but it should be emphasised that Fisher defined it as the *average* of eq. [2] taken over all individuals at birth. For systems in which all offspring must have exactly two parents, then this measure must be discounted by half. Eq. [2] has a couple of obvious features that are worth pointing out:

1. The average of B_{ix} taken over all individuals i is equal to the product of: (1) the cumulative rate of survival to x and (2) the mean fecundity rate at x conditional upon survival to that age. Substituting this average into the right-hand side of eq. [2] recovers the Euler-Lotka relationship $1 = \sum_{x=1}^{\infty} l_x F_x e^{-rx}$. It follows that the mean of individual reproductive values at birth is one.

2. If the population size is stable, then $r = 0$, and relative fitness is equal to lifetime reproductive success. In these cases, nothing is lost if generational overlap is neglected, and $w = R_0/\bar{R}_0$

While the structure of eq. [2] explicitly demonstrates how population growth rates affect the determination of fitness, very little is known about the consequences of ignoring this feature in real populations (as is often the practice). Population growth modifies how realized fertility contributes to fitness, but this influence is amplified in late life when compared to its effect early in life. From this, a reasonable inference could be that estimates of selection for late-acting traits may be particularly sensitive to incorrect estimates or implementation of population growth rates (including using R_0 for fitness when $r \neq 0$). To my knowledge, only two studies have actually measured the association between w and R_0, and these two estimates of the correlations were not independent as they were applied to the same human population over overlapping time ranges. Moorad (2013a) reported correlations between 0.978 and 0.992 (depending upon birth year) for the female population of Utahns born between 1830 and 1894. For both sexes combined, and for the birth years 1860–1889 in the same population, Moorad and Walling (2017) reported a combined correlation of 0.986. Malthusian growth rates for this population were high (between 0.025 and 0.039), and this fact, coupled with extremely high correlations between w and R_0, might suggest that the consequences for ignoring age structure (and thereby assuming that $r = 0$) might be minimal in the general case. As noted before, however, estimates of selection for traits acting at late ages are expected to be the most sensitive to errors arising from neglecting growth rates. Because late-acting traits are expected to contribute little to the variance in fitness (see next section), very high correlations between w and R_0 may persist even when estimates of late-acting selection are heavily biased by errors in population growth rate. A reasonable recommendation would be to use individual reproductive value at birth instead of R_0 whenever possible. Provided that population growth rates can be determined from the data, then there seems no reason to prefer R_0. For cases where data are not adequate for estimating population growth rates, then one should question whether these data are sufficient to make evolutionary inferences.

By using individual reproductive value rather than R_0 as a definition of fitness, one effectively relaxes the, often implicit, assumption that population sizes remain constant over time. This assumption is replaced with the less restrictive requirement that population growth rates are temporally stable (r doesn't change over time). However, this assumption is also likely to be violated in most populations. Unfortunately, there is no clear definition of individual fitness that relaxes this assumption further. When growth rates are free to vary over time, the answer to the question, "What do you mean by fitness?" is, as always, dependent entirely upon the answer to the question, "Well, what do you mean by ancestral and descendent populations?" The answer to the latter question may be arbitrary to some degree (or at least sensitive to one's temporal perspectives), and more conceptual work is needed in this area to better understand this issue. One pragmatic approach to this problem that has been adopted in the past (e.g. Moorad, 2013a) has been to evaluate fitness using the population growth rate determined by individuals that share a common birth time. While this is not an ideal solution, this method does account for some complications arising from age-structure, and it represents an improvement over the alternative R_0 in this respect.

Measures of Phenotypic Selection

Once equipped with a well-founded definition of relative fitness, we can begin to ask how selection acts on phenotypes. We have already defined selection gradients and coefficients in the univariate case and demonstrated where these measures fit into a simple expression of evolutionary dynamics. However, we are often interested in understanding selection at a deeper level. For example, we may want to know something more about the causal relationships between fitness and phenotypes, or we may want to know how two or more traits evolve when they share some genes in common. In these cases, we need to consider multivariate phenotypic selection, and we must refine our definitions accordingly.

Let us now imagine that we have a suite of traits, represented algebraically by a vertical vector $\mathbf{z}$ of degree n. We can regress simultaneously relative fitness on these traits, and this will yield a vector of partial regression coefficients $\mathbf{b}$. Collectively, these comprise the *multivariate directional selection gradient*. Each element b_i expresses the sensitivity of relative fitness to changes in trait z_i holding all other traits $j \neq i$ constant. We can contextualize this gradient into expressions that define and predict multivariate phenotypic evolution by also imagining a $n \times n$ matrix $\mathbf{G}$ that contains the additive genetic variance along the diagonal elements and the genetic covariances in the off-diagonal elements (the genetic covariance is the product of the genetic correlation and the square-root of the product of the two additive genetic variances for the appropriate trait combination). This genetic covariance matrix, or "G-matrix", contains all of the genetic constraints that enable and shape how natural selection ($\mathbf{b}$) affects evolutionary changes over a single generation. This relationship between evolution, selection, and genetic constraint is made explicit in what is known as the *Multivariate Breeder's Equation* (Lande, 1979), which quantifies the multivariate response to selection. If we consider transmission bias specific to all traits $\mathbf{z}$, we can incorporate this response into a generalized version of the Price Theorem given in eq. [1],

$$\Delta\bar{\mathbf{z}} = \mathbf{Gb} + \boldsymbol{\delta} \qquad [3],$$

where $\Delta\bar{\mathbf{z}}$ is the change in trait means for all n traits; $\boldsymbol{\delta}$ is the difference between the phenotypes of the offspring and their parents (averaged over all offspring and unweighted by fitness) for all traits; and $\mathbf{Gb}$ is the multivariate response to selection.

In the univariate case described in the first section, the selection coefficients differed from the selection gradients only in the sense that they were weighted by phenotypic variances. This is not the case in the multivariate case, as selection gradients follow from partial regression coefficients while the simple covariance definition of selection coefficients remain unchanged. The relationship between the two can be succinctly expressed by imagining an $n \times n$ matrix $\mathbf{P}$ containing phenotypic variances on the diagonal elements and phenotypic covariances on the off-diagonal elements,

$$\mathbf{b} = \mathbf{P}^{-1}\mathbf{s} \qquad [4],$$

where $\mathbf{s}$ is a vector of selection coefficients (Lande and Arnold, 1983). It may be noticed from these definitions that any selection coefficient chosen from within $\mathbf{s}$ will be entirely unaffected by the decision of whether or not to include some other trait in the selection analysis (remember that each of these is a simple covariance). However, because some traits may be phenotypically

correlated with others, selection gradients do not share this context-free nature. The value of each selection gradient b_i is understood to be conditional upon the set of other traits included in the analysis. This implies that unless a suite of traits can be assessed that explain all of the fitness variance in the population, the estimates of selection gradients may be flawed reflections of the true selective forces acting on the population. This is because potentially important traits may be missed that correlate with both fitness and the traits considered in the analysis. In practice, this suggests that an emphasis should always be placed on collecting and analysing the greatest number of informative traits possible, as causal inferences made from these relationships between fitness and traits are expected to become more reliable as the proportions of fitness variance explained increase.

In fact, there are two situations in which all fitness variance is explained by a set of phenotypes, and selection gradients can be interpreted as perfectly reliable indicators of the causal relationships between traits and fitness. The first case is when the trait of interest is relative fitness. This is trivial (the selection gradient for relative fitness is always equal to exactly one) and warrants no further discussion. The second case is when $\mathbf{z}$ is comprised of all vital rates up to the last age of realized fertility. In this case, and for each vital rate, we are asking how individual fitness changes with a change in this vital rate (and with all other vital rates held constant). Eq. [2] defines fitness as a linear function of these traits, and this means that vital rates collectively describe all fitness. One can go through the exercise of actually performing the multiple regression of relative fitness, defined as in [2], upon all vital rates simultaneously. This has been done using human data (Moorad, 2013a) and in an analytical proof (Moorad, 2014), and in both cases, the estimated selection gradients agreed with vital rate "sensitivities" derived by Hamilton (1966) using a completely different method and interpreted elsewhere as selection gradients (Charlesworth, 1994). This equivalency must hold true if eq. [2] provides a valid definition of relative fitness and Hamilton's selection model for the evolution of ageing is sound.

Selection gradients and selection coefficients describe in slightly different ways the strength of associations between fitness and traits, and, as such, play an obvious role in the evolutionary dynamics of trait evolution. Accordingly, selection is most frequently quantified in these terms. Perhaps the most profound measure of selection, however, is the variance in relative fitness, because it provides a population-specific upper limit to the amount of adaptive change that population can experience as a result of selection for *all* traits. In practice, however, it is often interpreted as an upper limit to selection for *any* one trait in the population. In any case, the variance, often called the *opportunity for selection*, has emerged as a popular comparative metric in human studies to evaluate the potential for evolutionary change. It has long been appreciated that this total opportunity for selection, or simply I, can be partitioned into one component arising from fitness variation from pre-reproductive survival and another arising from fitness variation among adults (Crow, 1958). These components are identified as I(survival) and I(fertility); in reality, these are misnomers, as variation in adult survival contributes entirely to I(fertility). For this reason, Crow's method for partitioning I is crude and misleading, but it is still quite commonly implemented. A far better alternative leverages multivariate selection theory in order to provide finer scaled and more readily interpretable results.

Recall our suite of traits **z**. Given an appropriate vector of selection coefficients **s** and a phenotypic variance-covariance matrix **P**, it must be the case that the opportunity for selection generated independently by each trait is given by the vertical vector **i**, where

$$\mathbf{i} = \mathbf{s}\mathbf{P}^{-1}\mathbf{s} \qquad [4]$$

(Moorad and Wade, 2013). The sum of all elements within **i**, divided by I, is the multiple coefficient of determination, or $\mathbf{R}^2$, of the regression of relative fitness on traits **z**. To this point, the expression is perfectly general to all possible **z**. Studies of ageing can use this approach to improve on Crow's method by asking how much variation in fitness is generated by each vital rate independently of all others (e.g. Moorad, 2013a). Because all fitness variation is explained by all vital rates up to the last age of reproduction, the sum of **i**-elements is equal to I (and $\mathbf{R}^2 = 1$). The value of this approach is that it helps identify which traits at which ages have the greatest potential to drive adaptive change in the population. Incidentally, one can use the definition of selection gradients to rewrite [4] as $\mathbf{i} = \mathbf{sb}$. Putting this expression together with a sensible interpretation of Hamilton's finding that the strength of selection for an age-specific trait tends to decline as the age of its expression increases (1966), it appears that, all else being equal, late-acting traits (low b) will tend to contribute less towards the variance in relative fitness than early acting traits (high b). This provides some justification for the warning given in the section on relative fitness that the high correlations between w and R_0 should not be taken to mean that the two measures are interchangeable when considering phenotypic selection for late-acting traits.

Non-directional Selection

In this discussion of multivariate selection, I have qualified the selection gradient as *directional*. This means that the function that relates fitness to phenotypes is assumed to be linear. Differently put, the fitness benefit (or cost) associated with phenotypic deviation from its mean is in proportion to the magnitude of the deviation. Depending upon the questions being asked or the traits being investigated, this constraint placed upon the fitness function may be undesirable. For example, fitness may be a quadratic function of some phenotype, or phenotypic value for one trait may interact with values for another trait to cause fitness effects that are not captured properly by a first-order linear regression. In these cases, we can expand our expressions of phenotypic selection to capture these second-order polynomial (quadratic) effects. Before discussing how to do this, it may be helpful to review some of the common nomenclature used in this area:

Stabilising selection is a negative association between fitness and the squared deviations from the trait mean. If this is sufficiently strong, then fitness may favour intermediate values. Human birth weight in the mid-twentieth-century population is the classic example of this phenomenon, as infant mortality is minimized at seven pounds but increases in smaller and larger infants (Karn and Penrose, 1951).

Disruptive selection is a positive association between fitness and the squared deviations from the trait means. If this is sufficiently strong, then fitness may favour extreme values.

Interaction selection is any association between fitness and the product of the deviation of two trait values from their respective means. Here, combinations of trait values can have emergent properties that help determine fitness.

It's important to note that these forms of what we can collectively term *quadratic selection* can co-occur with directional selection. For example, stabilising and positive directional selection together could suggest that fitness increases as a trait value increases, but fitness gains diminish as the trait value become more extreme. Finally, note that some biologists use slightly different definitions of stabilising and disruptive selection that effectively combine the linear and quadratic effects of the phenotype on fitness. In this usage, stabilising selection refers only to the case where fitness is maximized at an intermediate phenotypic value and disruptive selection is found where fitness is minimized at intermediate phenotypic values. The different definitions can create some confusion, but the exact meaning of the terms should be clear (or at least decipherable) from the context. To be clear, I will use the former definitions (as described in points 1–2 above) in what follows.

Estimating quadratic selection for some collection of traits $\mathbf{z}$ involves first defining *quadratic selection coefficients*. These are the multivariate extensions of the univariate selection coefficients discusses above. For n traits, we define an $n \times n$ matrix $\mathbf{C}$ with any element c_{ij} defined as the covariance between relative fitness and the product of deviations from means for traits ij,

$$c_{ij} = \text{cov}\big(w, (z_i - \bar{z}_i)(z_j - \bar{z}_j)\big) \qquad [5].$$

From here, we can take two different approaches to estimating *quadratic selection gradients*, which are, of course, the quadratic analogues to directional selection gradients. If we are comfortable with the assumption that the traits $\mathbf{z}$ are multivariate normal before selection, then the matrix $\boldsymbol{\gamma}$ defines a matrix of quadratic selection gradients (Lande and Arnold, 1983),

$$\boldsymbol{\gamma} = \mathbf{P}^{-1}\mathbf{C}\mathbf{P}^{-1} \qquad [6]$$

where $\mathbf{P}$ is the phenotypic covariance matrix discussed earlier. For any trait i, $\gamma_{ii} < 0$ favours stabilising selection and $\gamma_{ii} > 0$ favours disruptive selection. For any trait pair ij, $\gamma_{ij} < 0$ indicates negative interaction selection and $\gamma_{ij} > 0$ indicates positive interaction selection.

Unfortunately, we can seldom count on $\mathbf{z}$ being multivariate normal. In these cases, we cannot estimate $\mathbf{b}$ and $\boldsymbol{\gamma}$ independent of each other, because these may become statistically intertwined owing to the emergence of mean-variance or mean-covariance relationships. The solution here is similar to the strategy that we adopted to deal with estimating multivariate directional selection for correlated traits: we use multivariate regression on all traits simultaneously, except we now define some traits to be the products of deviations from their means. To do so, we construct an $n \times n$ matrix $\mathbf{A}$ that resembles $\mathbf{C}$, except that instead of covariances between relative fitness and products of deviations from trait means, the elements are simply the deviations from trait means,

$$a_{ij} = (z_i - \bar{z}_i)(z_j - \bar{z}_j) \qquad [7].$$

We then vectorise $\mathbf{A}$ and append this to $\mathbf{z}$ to construct a new trait vector $\mathbf{z}'$, such that $\mathbf{z}' = \begin{bmatrix} \mathbf{z} \\ vec(\mathbf{A}) \end{bmatrix}$. Using this trait vector, we construct a new phenotypic covariance matrix . $\mathbf{P}' = \begin{bmatrix} \mathbf{P} & \text{cov}(\mathbf{z}, vec(\mathbf{A})) \\ \text{cov}(vec(\mathbf{A}), \mathbf{z}) & \text{cov}(vec(\mathbf{A})) \end{bmatrix}$. Finally, we define a new selection coefficient vector

$\mathbf{s'}$ by appending the first-order trait selection coefficients to the vectorised $\mathbf{C}$, such that $\mathbf{s'} = \begin{bmatrix} \mathbf{s} \\ vec(\mathbf{C}) \end{bmatrix}$. Following eq. [4], the new selection gradient that follows is

$$\mathbf{b'} = (\mathbf{P'})^{-1}\mathbf{s'} = \begin{bmatrix} \mathbf{P} & \text{cov}(\mathbf{z}, vec(\mathbf{A})) \\ \text{cov}(vec(\mathbf{A}), \mathbf{z}) & \text{cov}(vec(\mathbf{A})) \end{bmatrix} \begin{bmatrix} \mathbf{s} \\ vec(\mathbf{C}) \end{bmatrix} \quad [8].$$

The resulting selection gradient $\mathbf{b'}$ has $n \times (n + 1)$ elements. The first n elements are directional selection gradients. The remainder are transformed by de-vectorization into an $n \times n$ matrix that defines quadratic selection gradients corresponding to the traits $\mathbf{z}$. Note that the off-diagonal elements of this matrix should be equivalent to one-half $\boldsymbol{\gamma}$, as derived by the Lande-Arnold method, if all elements in the covariance matrix $\text{cov}(\mathbf{z}, vec(\mathbf{A}))$ are zero[1]. Otherwise, $\boldsymbol{\gamma}$ cannot be taken as a reliable indicator of quadratic selection gradients.

Complications Owing to Social Interactions

Demographers are well aware that individual humans are social animals, and as such, interactions are fundamental to our biology. These interactions can have evolutionary impacts on phenotypes when between-individual interactions affect either how fitness views phenotypes (natural selection) or how phenotypes emerged from genotypes (inheritance). In the first case, social interactions may cause the fitness of an individual to be sensitive to the phenotypes of social partners. Natural selection generated in this fashion is known as *group-level selection*, which can contribute to a conceptually flexible multivariate perspective of natural selection termed *multi-level selection*. In the second case, the phenotypes of individuals may be determined to some degree by the genes of social partners, and we call these social genetic effects *associative* or *indirect genetic effects* (Griffing, 1968; Moore et al., 1997; Bijma et al., 2007). Phenotypic evolution approaches can quantify and separate the influence of both multi-level selection and social genetic effects on a response to selection, but a useful discussion of the latter is beyond the scope of this chapter. A more detailed description of this concept, as applied to post-reproductive survival in human populations, can be found in Moorad and Walling (2017). Here, I will focus on multi-level selection, or the manner by which social interactions affect phenotypic selection and how we may quantify these influences.

It may be clear by this point that while the phenotypic evolution notion of relative fitness is very rigid, this perspective is actually very flexible in how it defines a trait (for example, we have already seen how directional and quadratic selection is defined using first- and second-order aspects of the same phenotype). In principle, we are free to choose any possible feature that describes an individual and include that in our fitness regression. Using the method of *contextual analysis*, we include aspects of the distribution of social partner phenotypes in our selection analysis (Heisler and Damuth, 1987; Damuth and Heisler, 1988; Goodnight et al., 1992). Perhaps the most useful of such an approach would be to identify for each individual i the mean phenotypic values of the social partners of i and attribute this contextual trait to that individual. Let us refer to this social trait mean z' to distinguish this from the individual's trait z. Using a single trait for the purposes of illustration (but recognizing that multivariate extensions

1 Stinchcombe, J.R., A.F. Agrawal, P.A. Hohenlohe, S.J. Arnold, and M.W. Blows. 2008. *Evolution 62(9)*: 2435–2440.

to this approach are straightforward), we would perform a bivariate regression of relative fitness on both the individual and contextual trait. This regression would yield two partial regression coefficients: b_{wz} and $b_{wz'}$. The first is the slope of the regression of fitness on the individuals' phenotypes, holding the contextual trait constant. This is known as *individual-level selection*. The other aspect of multi-level selection, *group-level selection*, is quantified by the slope of the regression of fitness on the contextual trait, holding the individuals' phenotypes constant. Note that there are no logical constraints on what the values of these selection gradients might be. They can be identical or different in both magnitude and direction. In any case, evolutionary dynamics can become much more interesting when it happens that group-level selection is important. If this component of selection is important, then evolution can occur much faster or slower than would be suggested by a selection analysis that ignored contextual traits. In nineteenth-century Utah, for example, there is weak individual-level selection that favours females to reproduce with more than one male ($b_{wz} = +0.0827$, where z is the individual trait: the number of husbands). This probably reflects increased reproduction in young widows who remarry. However, individuals whose mothers reproduced with more than one male also benefit, and this is reflected in a positive group selection gradient of roughly the same magnitude ($b_{wz'} = +0.0075$; where z' is the contextual trait: the number of the mothers' husbands) (Moorad, 2013b). If there is any genetic variation for this trait in this population (which is not a given), then we could infer that group selection accelerates the evolution of polyandry slightly. In other situations where the selection gradients are in different directions, and group-level selection is much stronger than individual-level selection, a naïve individual-level selection analysis could, in principle, predict evolution in the wrong direction!

We can contextualize how multi-level selection contributes to the response to selection by recognizing that this response has both a direct component acting on selection for z and an indirect component acting through z'. Summing these two together yields to response to selection,

$$\Delta\bar{z} = b_{wz}\mathrm{var}(z) + b_{wz'}\mathrm{cov}(z', z) \qquad [9].$$

Recognizing that the covariance in eq. [9] can be expressed as the product of a slope and a variance, eq. [9] can be restated in a more useful way,

$$\Delta\bar{z} = b_{wz} + b_{z'z}b_{wz'}\mathrm{v})\mathrm{var}(z) \qquad [10],$$

where $b_{z'z}$, the slope of the regression of social partner mean phenotype on the individual phenotype, can be interpreted (in the absence of indirect genetic effects) as the coefficient of genetic relatedness between the social partners and the individuals. In most human populations, this coefficient between full siblings or between offspring and parent will be one-half, and between half siblings and between grandchildren and grandparent this will be one-quarter.

It is important to note that it is up to the investigator to define the group of social partners that interact with the focal individuals (and this choice hopefully reflects some interesting social dynamic), but this definition will affect the interpretation of the multi-level selection gradients. This "group" need not even be a group in the sense that it consists of a plurality of individuals — it can be a single individual, such as a mother, as in the example given above. In this case, the term "group-selection" may appear inappropriate, so *family-level* selection may be more palatable to some. Furthermore, there is no limit to the number of contextual traits

that can be applied to the same phenotypes. For example, it may be appropriate to consider a *trivariate* form of multi-level selection for some phenotype of interest in which maternal and grandmaternal trait values were included as contextual traits. For the purposes of predicting a response to selection, eq. [10] would need to be expanded to include two group selection terms (each weighted appropriately by relatedness of one-half and one-quarter).

Impossible Traits

Many demographers are interested in conditional traits, or those traits that are expressed in only certain individuals that meet some specific condition. For example, age of menarche is a trait limited to females, but a formal selection analysis should be applied to all individuals within the investigated population. In fact, all individuals *must* have all trait values included in the analysis to ensure that the **P**-matrix in eq. [4] is invertible. It is clear that these trait values must be imputed in those situations in which some traits are logically precluded from happening in some individuals. The appropriate value to impute is the mean value of the trait taken from the portion of the population that expresses that trait. However, a new trait should be added to the analysis to indicate whether or not a value was imputed (Moorad and Wade, 2013). The multivariate phenotypic selection analysis should include a selection gradient that applies to this indicator, or dummy trait, and one would interpret this to be the strength of selection acting on dichotomous expression of trait.

In the menarche example above, the indicator trait could be "female" (0 for male, 1 for female). For the sake of simplicity, I am ignoring the fact that some females will not live long enough to experience menarche (allowing for this would require a second indicator variable). Provided that we consider no other traits beyond the indicator trait (z_1, female) and the conditional traits (z_2, age at menarche), then our multiple regression that relates relative fitness to the traits of interest takes the form,

$$w = a + \beta_{wz_1} z_1 + \beta_{wz_2} z_2 + \varepsilon \,,$$

and the partial regression coefficients indicate selection gradients. The first coefficient β_{wz_1} represents the strength of selection for being born female. As human populations tend to have slight male bias at birth, one would expect that this term should be slightly positive in most cases. The reason for this is that because all humans have exactly one biological mother and one father, males and females collectively contribute equally to offspring production (the ultimate source of fitness). However, males are more numerous and thus can expect to have slightly less fitness each than the females. The second coefficient β_{wz_2} is selection for age at menarche in females. However, females make up less than half of all individuals at birth, so this partial regression coefficient will need to be weighted by the fraction of females in order to provide a selection gradient fit to be applied to predict a response to selection (Moorad and Wade, 2013).

Genetic Selection for Quantitative Traits

In the multivariate context, selection gradients provide a superior picture of fitness causality than selection coefficients, because the latter will combine both the direct effects of a phenotype on fitness and the indirect effects caused by correlations with all other traits that may have a more direct relationship with fitness. In principle, selection gradients will partition and identify

only the direct contribution, and this will provide a more complete model of causality. As discussed above, however, the causal model suggested by estimated selection gradients may be sensitive to the decision of whether or not to include particular traits in a selection analysis (Rausher, 1992; Morrissey et al., 2010). For this reason, biologists have been cautioned to treat selection gradients as only tentative suggestions for causal relationships between fitness and phenotypes to be tested by experimental manipulations (Wade and Kalisz, 1990). This is not possible for human populations for obvious reasons.

Rather than concern themselves overmuch with identifying causality, however, investigators may wish to know simply how much natural selection changes the mean of one trait in a single generation. To know this, one may independently estimate a selection coefficient (using the covariance between fitness and ancestral trait values) and narrow-sense heritability (using other quantitative genetic methods), and then take the product of these two estimates. However, this is not the most efficient use of data, and estimating the standard errors for this product is not straightforward. Fortunately, one can estimate directly the evolutionary change owing to the effects of natural selection using the genetic covariance between relative fitness and the trait of interest. This genetic covariance is interpreted as genetic selection for the trait. This approach appeals to the "Robertson-Price Identity" (Robertson, 1966; Price, 1970) that identifies the trait of interest to be the *genetic* or *breeding value* for that trait instead of the trait itself. In this way, the univariate Breeder's Equation $\Delta\bar{z} = \beta_{wz}\mathrm{var}(G)$ becomes $\Delta\bar{z} = \mathrm{cov}(G_w G_z)$, where this covariance is estimated directly from the data, usually by implementing a quantitative genetic bivariate "Animal Model" (Lynch and Walsh, 1998; Kruuk, 2004); this is a linear mixed-modelling approach that incorporates pedigree information in conjunction with phenotype data to yield estimates of **G**-matrices. A technical explanation for how Animal Models can be used to estimate genetic covariances is beyond the scope of this chapter, but the interested reader is recommended to read Wilson et al. (2010) for an accessible introduction to the subject intended for ecologists. It may also be useful to read Moorad and Walling (2017); at the time of this writing, this is currently the only Animal Model application of the Robertson-Price Identity used to estimate genetic selection in a human population. However, it should be noted before delving into Animal Models that the data requirements for estimating genotypic selection (in terms of sample size) can be far greater than that needed to estimate phenotypic selection. Information on several thousands of phenotyped and related individuals over multiple generations may be necessary for reasonably precise estimates of genetic covariances.

Final Remarks

The phenotypic evolution approach emphasises the role that the distribution of individual values of phenotypes and relative fitness play in trait evolution. This is, of course, the causal mechanism of evolution by natural selection articulated by Charles Darwin, but it is not a perspective that is shared by other approaches that may be familiar to demographers. For example, population projection matrices can be used to estimate selection gradients correctly in some situations. These approaches do not explicitly consider individual data, except as a means to summarize trait averages associated with shared states (e.g. age or size). As a result, among-individual variation, a property that is at the conceptual heart of natural selection, is not easily dealt with. It is my firm belief that individual-based methods employed by phenotypic evolution and quantitative genetics offer a superior approach to measuring a diversity of metrics

related to natural selection and inheritance in most cases. Some will disagree, but I hope that this chapter makes clear to all readers that these regression-based methods exist, and they are accessible and appropriate tools for demographers interested in understanding evolution in human populations.

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