Evolutionary quantitative genetics of non-linear developmental systems

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Abstract

In quantitative genetics, the effects of developmental relationships among traits on microevolution are generally represented by the contribution of pleiotropy to additive genetic covariances. Pleiotropic additive genetic covariances arise only from the average effects of alleles on multiple traits, and therefore the evolutionary importance of non-linearities in development are generally neglected in quantitative genetic views on evolution. However, non-linearities in relationships among traits at the level of whole organisms are undeniably important to biology in general, and therefore critical to understanding evolution. I outline a system for characterising key quantitative parameters in non-linear developmental systems, which yields expressions for quantities such as trait means and phenotypic and genetic covariance matrices. I then develop a system for quantitative prediction of evolution in non-linear developmental systems. I apply the system to generating a new hypothesis for why direct stabilising selection is rarely observed. Other uses will include separation of purely correlative from direct and indirect causal effects in studying mechanisms of selection, generation of predictions of medium-term evolutionary trajectories rather than immediate predictions of evolutionary change over single generation time-steps, and the development of efficient and biologically-motivated models for separating additive from epistatic genetic variances and covariances.

Introduction

Evolutionary quantitative genetics provides a central conceptual backbone to studies of microevolution because it quantitatively relates genetic variation and natural selection to evolution. Most quantitative genetic theory, and virtually all empirical evolutionary quantitative genetic work, is based on the linear components of relationships among traits and between traits and fitness. The linear components of phenotypic or genetic relationships among traits and between traits and fitness can completely describe some specific aspects of evolutionary dynamics, even if true relationships are not linear (Rice, 2004b). However, in general, non-linear aspects of relationships among traits, and between traits and fitness, can have profound effects on evolutionary outcomes (Hansen, 2014; Rice, 2002, 2004a). While there is increasing interest in evolution in non-linear systems (e.g., Hether and Hohenlohe 2014; Shaw and Shaw 2013), and some theoretical aspects of non-linear systems are known (Charlesworth, 1990; Wright, 1935), the relationships between non-linearities in processes determining genetic and selective patterns and key evolutionary quantitative genetic parameters, such as genetic (co)variance components and selection gradients, are not well established.

A major appeal of the evolutionary quantitative genetic approach is that it defines explicit parameters, such as additive genetic (co)variances and selection gradients, in the specific terms by which they relate to one another and to evolution. These parameters and relationships transcend specific taxa, traits, and ecological circumstances, and therefore place evolutionary quantitative genetics at the centre of many aspects of evolutionary biology. So far, no framework specifically links the available pieces of theory pertaining to non-linear developmental systems in such a way that parameters in one system can be related to others in general ways. Some theory exists for analysis of function-valued traits, including developmental trajectories (Kirkpatrick and Heckman, 1989; Kirkpatrick et al., 1990; Meyer and Kirkpatrick, 2005). These approaches take a predominantely statistical and descriptive approach to the quantitative genetics of development. Approaches based on explanations for covariances among traits, i.e., on understanding the 'genotype-phenotype map', may be most profitably pursued at an organismal level (Travisano and Shaw, 2013). However general quantitative links between arbitrary

developmental systems and parameters summarising selection and genetics are not available. In fact, it has been argued that a separate theory, in contradistinction to quantitative genetics, is needed to link developmental perspectives to a formal quantitative theory of evolution (Rice, 2008). An integration of developmental perspectives into evolutionary quantitative genetic theory may allow better exploitation of information about why covariances occur both among traits, and between traits and fitness; this could alleviate some of the narrow ways in which evolutionary quantitative genetics must often technically be interpreted (Conner, 2012). Ultimately, a developmental approach could link the generation-to-generation scale at which quantitative genetics predicts evolutionary processes to larger scale phenomena such as the evolution of modularity and developmental memory (Watson et al., 2014), canalisation and genetic assimilation (Waddington, 1949, 1953), and the evolution of phenotypic discontinuities and discrete polymorphisms (Chevin and Lande, 2013).

My first goal is to develop general formulae relating non-linear developmental relationships among traits to classical quantitative genetic parameters such as the additive genetic variance. I provide general formulae based on systems where inputs to the developmental system are multivariate normal, and result from many small additive genetic and environmental effects. These formulae allow calculation of quantities such as mean phenotype, and narrow- and broad-sense genetic and phenotypic covariance matrices, for any system that can be conceptualised as a non-linear developmental system with inputs and outputs. My second goal is to develop a framework that can describe evolution in non-linear developmental systems. I develop the idea from the first section of relating aspects of outputs (phenotypes) to distributions of inputs to a developmental system, for the special case of predicting population mean fitness as a function of inputs to a developmental system. Given calculation of mean fitness for an arbitrary developmental system, descriptions of how fitness changes as a function of inputs to the developmental system follow directly, leading to a formal quantitative genetic system for describing selection, genetics, and evolution in arbitrary developmental systems. This approach leads to general expressions for the evolution of arbitrary properties of non-linear developmental systems, whereby the predictive capacity of evolutionary quantitative genetics can be extended to describe, for example, the evolution of phenotypic and genetic (co)variances, full evolutionary trajectories,

evolutionary optima, and evolution of higher (mixed) moments of phenotype.

Model structure and general notation

Throughout, I assume a very general model structure where exogenous inputs to a developmental system are numerous, additive, and small. This is the infinitesimal model of quantitative genetics (Falconer, 1960; Fisher, 1918). Exogenous variables will be denoted by the symbol ϵ. Exogenous inputs may be decomposed into constituent components, for example, into additive genetic and residual effects. As such, the exogenous value of an individual, indexed i, for a given trait, may be represented as $\epsilon_i = \epsilon_{a,i} + \epsilon_{e,i}$, where a and e denote additive genetic and residual effects. Traits will be denoted z. $\boldsymbol{z}_i$, i.e., the vector of trait values in individual i, may depend on one or more exogenous inputs within the vector of exogenous values, $\boldsymbol{\epsilon}_i$, for individual i, and additionally may depend on the values of other traits, and thus on exogenous inputs indirectly through those other traits. Fitness, W, or individual expected fitness $E(W)_i$, can be treated mathematically as a trait, i.e., it can depend on trait values and exogenous inputs of variation that are independent of trait values.

The term 'phenotypic landscape' will refer to the relationships between exogenous inputs and traits, among traits, and potentially also between traits and fitness. The term 'developmental system' will refer collectively to the phenotypic landscape and exogenous inputs, traits, and fitness where applicable. Diagrammatically, a developmental system may be depicted as a path diagram, wherein exogenous inputs, traits and fitness are represented as measured or latent quantities, and arrows represent the phenotypic landscape; several examples are given in figure 1. A phenotypic landscape is then represented as a vector-valued function, giving the multivariate phenotype (and fitness, when applicable) as a function of exogenous inputs to the developmental system. For example, the developmental system in figure 1(a) would be

represented by a vector-valued function of the form

$$\mathbf{z}_i = \begin{bmatrix} z_1 \\ z_2 \\ W \end{bmatrix}_i = \boldsymbol{f}(\boldsymbol{\epsilon})_i = \begin{bmatrix} f^1(\epsilon_1) \\ f^2(z_1, \epsilon_2) \\ f^3(z_2) \end{bmatrix}.$$

For mathematical purposes, fitness will often be treated as just another trait. Fitness will generally be thought of as expected fitness, given trait values.

Several, mostly conventional, notational details are worth summarising. σ is used to denote several aspects of (co)variation. With single subscripts, σ represents the standard deviation, and σ^2 represents variance. σ with two subscripts represents covariance, and upper case sigma, $\boldsymbol{\Sigma}$, represents a covariance matrix. Matrices and vectors are denoted with bold-faced text, as are functions returning vectors or matrices. Integration and differentiation are denoted in standard ways; a gradient matrix or vector is denoted with bold-faced variables, for example, $\frac{\delta \mathbf{z}}{\delta \boldsymbol{\epsilon}}$ represents the gradient matrix of phenotype with respect to exogenous values.

Multi-dimensional integration is used in this article in expressions to obtain the average value of functions integrated over a distribution of inputs; this operation is expressed with the general form $\bar{\boldsymbol{f}}(\boldsymbol{x}) = \int \boldsymbol{f}(\boldsymbol{x}) p(\boldsymbol{x}) d\boldsymbol{x}$, where $f(\boldsymbol{x})$ is a function, potentially vector-valued, determined by $\boldsymbol{x}$, and where $p(\boldsymbol{x})$ is the density function of $\boldsymbol{x}$. I will primarily consider models where inputs to the developmental system (i.e., where $\boldsymbol{\epsilon}$ is the $\boldsymbol{x}$ variable) are multivariate normal, such that $p(\boldsymbol{x})$ is given as $N(\boldsymbol{\epsilon}, \bar{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}})$, i.e., the normal density of $\boldsymbol{\epsilon}$, given the mean vector $\bar{\boldsymbol{\epsilon}}$, and covariance matrix $\boldsymbol{\Sigma}_{\boldsymbol{\epsilon}}$. The parameters of the normal density of exogenous values, i.e., the mean vector and covariance matrix will generally be written explicitly, as they are key parameters in the theory. The key concept is that the product of the function $f(\boldsymbol{x})$ and the probability at which its inputs $\boldsymbol{x}$ occur, given by $p(\boldsymbol{x})$, is integrated over the components of those inputs. Generally, the mean of a variable x is given by $\int x p(x) dx$, essentially a continuous equivalent of a weighted average. In contrast, $\int f(\boldsymbol{x}) p(\boldsymbol{x}) d\boldsymbol{x}$ gives the average value of a function $y = f(x)$, integrating not over y, but rather over x. This method of obtaining moments of arbitrary quantities, e.g., mean fitness, given a phentoype-fitness function and a distribution of phenotype, is used, for

example, in the derivation of the Lande (1979) equation, and by Kimura and Crow (1978) to calculate mutant-specific selection coefficients, given allelic substitution effects, arbitrary trait distributions, and arbitrary trait-fitness functions. Specific notation for each application of this approach is described as it arises, and is summarised in table 1.

The primary goal of this paper is to develop the theoretical framework for quantitative genetic analysis of non-linear developmental systems. Inference of the form and parameters of a phenotypic landscape is not directly treated. It should be noted, though, that the principles are applicable to the analysis of arbitrary phenotypic landscapes, no matter how they are obtained. The parallel to (linear) path analysis, for example in graphical model depictions as in figure 1, should not be taken to indicate that the theory is linked to any particular algorithm or paradigm for analysing observational data. Ideally, inferences about phenotypic landscapes would be obtained via a combination of functional analysis, experimentation, and also regression-based analysis of observational data. Indeed, observational data alone will be insufficient to parameterise some kinds of models of phenotypic landscapes, in particular when they involve simultaneity or recursive loops (Gianola and Sorensen, 2004). In conjunction with the principles and approaches in this paper, use of a wide range of data and approaches would lead to the greatest understanding, and serial improvement of the understanding, of evolution of particular systems, and of non-linear developmental systems in general.

Means and (co)variance components of non-linear systems

In this section, I give general expressions for calculating a number of key parameters of phenotypic distributions and their components. The approach is expandable to descriptions of arbitrary aspects of phenotype: for example, to arbitrary higher mixed moments. I describe the calculation of several key parameters, rather than providing a comprehensive inventory of specific calculations for every parameter that may possibly be of interest. The approach involves integrating aspects of phenotype (expected value, deviation of expected value from the population mean, derivatives of the phenotypic landscape) over the full distribution of exogenous inputs to the developmental system. The integrals are necessary to make the expressions

applicable to any arbitrary developmental system. For conceptually or empirically tractable systems with modest numbers of traits, computations to evaluate any given expression will take between a few seconds and some minutes on a standard desktop computer.

The mean vector of traits, $\bar{\boldsymbol{z}}$, in a non-linear developmental system is

$$\bar{\boldsymbol{z}} = \int \boldsymbol{f}(\boldsymbol{\epsilon}) N(\boldsymbol{\epsilon}, \bar{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}}) \; d\boldsymbol{\epsilon}. \tag{1}$$

Note that in a non-linear developmental system, the mean phenotype given a distribution of exogenous inputs is generally not the same as the phenotype of an individual with the mean of the exogenous inputs to the developmental system, i.e., in general, $\bar{\boldsymbol{z}} \neq \boldsymbol{f}(\bar{\boldsymbol{\epsilon}})$ when $\boldsymbol{f}()$ is non-linear (this is Jensen's 1906 inequality; see also Welsh et al. 1988). Rather, the mean phenotype is obtained by calculating the phenotypic value associated with all possible values of exogenous inputs, i.e., $f(\boldsymbol{\epsilon})$ for all possible values of k exogenous inputs, and integrating all of those values in proportion to the probability that each set of exogenous values occurs, i.e., $N(\boldsymbol{\epsilon}, \boldsymbol{\mu}_{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}})$.

Phenotypic covariances of a non-linear developmental system are given by

$$\boldsymbol{\Sigma}_{\boldsymbol{z}} = \int \left(\boldsymbol{f}(\boldsymbol{\epsilon}) \boldsymbol{f}(\boldsymbol{\epsilon})^T \right) N(\boldsymbol{\epsilon}, \bar{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}}) \; d\boldsymbol{\epsilon} \; - \bar{\boldsymbol{z}} \bar{\boldsymbol{z}}^T. \tag{2}$$

Rice (2004a) also gives a system for calculating arbitrary moments of the distribution of phenotype, given a distribution of inputs to that system, and mathematical functions characterising the system. Rice's 'tensor analysis' approach provides for exact analytical calculations of quantities such as population mean and variance of phenotype, when the phenotypic landscape is finitely differentiable (for example, when the phenotypic landscape is quadratic, as in the examples in Rice 2004a), and otherwise provides (potentially high-order) approximations. The approach that is begun in equations 1 and 2 allows calculation of moments of (and components of) phenotype, which is necessary for material that follows, but does not directly reduce to simple analytical solutions in special cases.

Similarly to calculation of the population mean phenotype, the expected trait value(s) of an individual with a given vector of exogenous breeding values is generally not the phenotype

associated with an individual with the mean exogenous inputs (genetic and environmental) equal to that exogenous breeding value. Rather, the equivalent integration over all of the possible environmental effects that may be experienced by an individual with a particular genetic composition is required; thus the broad-sense genetic value for phenotype, given particular exogenous breeding values $\boldsymbol{\epsilon}_a$ is

$$\boldsymbol{g}(\boldsymbol{\epsilon_a}) = \int f(\boldsymbol{\mu_\epsilon} + \boldsymbol{\epsilon_a} + \boldsymbol{\epsilon_e}) N(\boldsymbol{\epsilon_e}, \mathbf{0}, \boldsymbol{\Sigma_{\epsilon_e}})\ d\boldsymbol{\epsilon_e}. \tag{3}$$

This is equivalent to the un-numbered expression following equation 4 in Lande (1979), which gives the expected fitness conditional on genetic value, given an arbitrary trait-fitness function, by integrating over the distribution of environmental variation. Given equation 3, broad-sense genetic (co)variances are

$$\boldsymbol{\Sigma_g} = \int \left(\boldsymbol{g}(\boldsymbol{\epsilon_a}) \boldsymbol{g}(\boldsymbol{\epsilon_a})^T \right) N(\boldsymbol{\epsilon_a}, \mathbf{0}, \boldsymbol{\Sigma_{\epsilon_a}})\ d\boldsymbol{\epsilon_a}\ - \bar{\boldsymbol{z}}\bar{\boldsymbol{z}}^T. \tag{4}$$

Calculation of additive genetic covariances at the level of the phenotype (as opposed to exogenous inputs) requires a slightly different approach. We must obtain the effect on phenotype of an (infinitesimally small) allelic substitution at the level of exogenous inputs, averaged over all possible phenotypes in which such an allelic substitution may occur. This gives the manifestation of any given component of the input to the developmental system, at the level of phenotype. It is notable here (as in the calculation of broad-sense individual genetic values) that both genetics and environmental effects at the level of inputs to the developmental system influence the manifestation of genetic effects at the level of phenotypes.

Let a_ϵ be the effect on exogenous value of substituting an A_1 allele for an A_2 allele at an additive locus (all notation here follows Falconer 1960). The expected deviation from the population mean in exogenous value for individuals for which an A_1 allele has been so substituted is thus a_ϵ. The average value in a trait, among individuals subjected to the substitution, where the trait value depends on the exogenous value according to $z = f(\epsilon)$, is

$$\bar{z}_{A_1} = \int f(\epsilon + a_\epsilon) p(\epsilon) d\epsilon,$$

where $p(\epsilon)$ is the density of exogenous values of individuals for which the substitution has not been made. Given the Taylor series $f(\epsilon + a_\epsilon) = f(\epsilon) + a_\epsilon \cdot f'(\epsilon)...$, we obtain

$$\bar{z}_{A_1} = \int \left[f(\epsilon) + a_\epsilon \cdot f'(\epsilon) \right] p(\epsilon) d\epsilon$$

in the limit of the infinitesimal model. The allelic substitution effect on z is then

$$a_z = \bar{z}_{A_1} - \bar{z} = \int \left[f(\epsilon) + a_\epsilon \cdot f'(\epsilon) \right] p(\epsilon) d\epsilon - \int f(\epsilon) p(\epsilon) d\epsilon = a_\epsilon \cdot \int f'(\epsilon) p(\epsilon) d\epsilon. \qquad (5)$$

The derivation so far is equivalent in construction to that in Kimura and Crow (1978) for calculation of locus-specific selection coefficients for arbitrary fitness functions and phenotype distributions. Denote the key quantity, the slope of the developmental landscape averaged over inputs to the developmental system, $\int f'(\epsilon) p(\epsilon) d\epsilon = \Phi$, and so, $a_z = \Phi a$. The average excess (Falconer, 1960; Fisher, 1918, 1930) of the A_1 allele in exogenous value is $\alpha_\epsilon = a_\epsilon p(1-p)$, where p is the frequency of the A_1 allele, and the corresponding average excess in the trait is $\alpha_z = a_z p(1-p) = \Phi a_\epsilon p(1-p)$. Thus average excesses for exogenous value and trait are related by $\frac{\alpha_\epsilon}{a_\epsilon} = p(1-p) = \frac{\alpha_z}{\Phi a_\epsilon}$, and so $\alpha_z = \Phi \alpha_\epsilon$. Variance in exogenous value attributable to the locus in question is thus $\sigma^2_{a,\epsilon} = 2p(1-p)\alpha^2_\epsilon$, assuming random mating, and the associated variance in the trait is $\sigma^2_{a,z} = 2p(1-p)\alpha^2_z = 2p(1-p)(\Phi\alpha_\epsilon)^2$. Additive genetic variances for exogenous value and trait are thus related according to $\frac{\sigma^2_{a,z}}{\Phi^2 \alpha^2_\epsilon} = 2p(1-p) = \frac{\sigma^2_{a,\epsilon}}{\alpha^2_\epsilon}$. Additive genetic variance in the trait caused by the projection of exogenous inputs onto trait values via the phenotypic landscape, is

$$\sigma^2_{a,z} = \Phi^2 \sigma^2_{a,\epsilon},$$

if additive genetic exogenous values are normally distributed. Parallel reasoning can be applied to obtain genetic covariances of traits given the genetic variance-covariance matrix of inputs to the developmental system. Compactly, the expressions can be written by first defining a multivariate version of Φ as the matrix of mean gradients of $f(\epsilon)$ integrated over the distribution of ϵ:

$$\boldsymbol{\Phi} = \int \frac{\delta \mathbf{z}}{\delta \boldsymbol{\epsilon}} N(\boldsymbol{\epsilon}, \bar{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}}) \, d\boldsymbol{\epsilon}. \qquad (6)$$

The additive genetic variance or covariance matrix at the level of phenotype is then the projection of the distribution of additive genetic effects at the level of exogenous inputs onto the phenotype, via the average phenotypic effects of infinitesimal inputs. If exogenous breeding values are multivariate normal:

$$\mathbf{G} = \mathbf{\Sigma}_{\boldsymbol{z_a}} = \mathbf{\Phi}\mathbf{\Sigma}_{\boldsymbol{\epsilon_a}}\mathbf{\Phi}^T. \tag{7}$$

More generally, the matrix $\mathbf{\Phi}$ could be obtained as the gradient matrix of population mean phenotype with respect to population mean exogenous values. Such a formulation would allow analysis of phenotypic landscapes that contain discontinuous functions.

Dominance variance is negligible in the general model that is considered here; as allelic substitution effects approach zero (the limit defining the infinitesimal model), so too do the dominance effects arising from non-linearities in the developmental system. Consider the regression of genotypic values on genotype at a given locus (see, for example, figure 7.2 in Falconer 1960). The deviations of genetic values from this regression, averaged over all background genetic and environmental conditions, determine the dominance variance. Thus, in any developmental system where genetic value for phenotype is a continuous function of exogenous genetic values (this can occur if a phenotypic landscape is non-continuous but where exogenous inputs include environmental effects), this regression will become approximately linear, over the range of effects generated by genotypic variation at a single locus, as the limiting conditions of the infinitesimal model are approached. Wright (1935) gives expressions for additive, dominance, and epistatic variances for a quadratic phenotypic landscape, or for a quadratic approximation to a phenotypic landscape, for arbitrary allelic substitution effects and allele frequencies. The additive and epistatic components are proportional to the square of the additive exogenous allelic substitution effect (Wright's 1935 equations 20 and 27), while the dominance variance is proportional to the fourth power of the allelic substitution effect (Wright's equation 22), and so dominance variance arising from developmental relationships among traits becomes negligible relative to additive and epistatic variances in the limit of the infinitesimal model.

Non-linearities in the developmental system do manifest as epistatic (co)variances. The non-additive genetic component of phenotypic (co)variances will generally be a mix of additive

by additive, and typically higher-order, epistatic covariances. The total epistatic effects, however, can be summarised compactly. For arbitrary developmental systems the total epistatic covariances are

$$\boldsymbol{\Sigma}_{\boldsymbol{z},\boldsymbol{E}} = \boldsymbol{\Sigma}_{\boldsymbol{z},\boldsymbol{g}} - \mathbf{G}, \tag{8}$$

where $\boldsymbol{\Sigma}_{\boldsymbol{g}}$ and $\mathbf{G}$ are obtained via equations 4 and 7, respectively. The total environmental covariances (additive and interactive) are obtainable similarly to the broad-sense genetic covariances, and the total plasticity could be obtained by subtracting the broad-sense genetic covariances, and the total environmental covariances, from the total phenotypic covariances.

Selection and evolution of non-linear developmental systems

Consider now that the phenotype $\mathbf{z}_i$ may influence an individual's expected fitness $E(W)_i$, potentially non-linearly. Motivated by the Lande equation (Lande, 1979), $\Delta\bar{\boldsymbol{z}} = \mathbf{G}\boldsymbol{\beta}$, the two key pieces of information that are considered necessary for characterising the microevolutionary process are the $\mathbf{G}$ matrix and the selection gradient $\boldsymbol{\beta}$, the partial derivatives of mean relative fitness with respect to mean phenotype. However, these parameters will not entirely describe the dynamics of systems with non-linear phenotypic landscapes. The Lande equation holds for arbitrary trait-fitness relationships when the offspring-parent regression is linear. However, the parent-offspring regression will not typically be linear in non-linear developmental systems, which can lead to quantitative and qualitative deviation of predictions of the Lande equation from actual evolutionary trajectories (Heywood 2005; see also examples in Rice 2004a, especially the example associated with his figures 7 and 8, and Rice 2011). Theorematic approaches can provide exact descriptions of the dynamics of phenotype (Heywood, 2005; Price, 1970; Rice, 2011), but without necessarily providing insight into why a given evolutionary trajectory occurs. A quantitative genetic approach can potentially yield a system for describing a population's evolutionary trajectory and how it is shaped by development.

Morrissey (2014) describes the "extended selection gradient" as the total effects of traits on (relative) fitness, denoted $\boldsymbol{\eta}$, as opposed to the direct effects of traits on fitness, $\boldsymbol{\beta}$. A key feature of $\boldsymbol{\eta}$ is that it represents the selective meaning of variation in traits, i.e., Sober's (1984,

see also Endler 1986) concept of "selection for". $\boldsymbol{\beta}$ represents "selection for" traits only when all covariances among traits are (or are assumed to be) irrelevant to the mechanism of selection. Another way of describing the extended selection gradient is that it is the vector of partial derivatives of mean relative fitness, not with respect to the traits, as is $\boldsymbol{\beta}$, but rather with respect to the exogenous inputs of variance to each trait. To see this, consider developmental system such as that in figure 1a, with linear effects only; let the system be defined by the developmental system

$$\boldsymbol{f}(\boldsymbol{\epsilon})_i = \begin{bmatrix} E(w)_i \\ z_{2,i} \\ z_{1,i} \end{bmatrix} = \begin{bmatrix} 1 + b_2 z_2 \\ a_2 + b_1 z_1 + \epsilon_{2,i} \\ a_1 + \epsilon_{1,i} \end{bmatrix}.$$

The selection gradients of such a system are $\beta_{z_1} = 0$ and $\beta_{z_2} = b_2$, while the rules of path analysis, applicable to a strictly linear system, give the extended selection gradients as $\eta_{z_1} = b_1 b_2$ and $\eta_{z_2} = b_2$ (Morrissey, 2014). It can be seen that the derivatives of relative fitness with respect to exogenous values also give $\boldsymbol{\eta}$. Expected relative fitness in terms of $\boldsymbol{\epsilon}_i$ is $E(w)_i = 1 + b_2(a_2 + b_1 a_1 + \epsilon_{1,i} + \epsilon_{2,i})$. The derivatives of relative fitness with respect to exogenous values are $\frac{dE(w)}{d\epsilon_2} = b_2 = \eta_2$ and $\frac{dE(w)}{d\epsilon_1} = b_1 b_2 = \eta_1$. Given a strategy to calculate $\boldsymbol{\eta}$ in non-linear phenotypic landscapes, essentially a system of non-linear path analysis, we can use this kind of characterisation of natural selection to describe the evolution of inputs to developmental systems, which in turn can describe evolution of the phenotype.

Take a characterisation of a developmental system, denoted here as a vector-valued function $\mathbf{z}_i = \boldsymbol{f}(\boldsymbol{\epsilon}_i)$, where expected (relative or absolute) fitness is one of the traits predicted from $\boldsymbol{\epsilon}$. That vector-valued function can be re-arranged so as to predict fitness from inputs to the developmental system, $W_i = W(\boldsymbol{\epsilon}_i)$. Population mean fitness can then be calculated just as any trait that depends on inputs to development, as in equation 1, i.e.,

$$\bar{W}(\bar{\boldsymbol{\epsilon}}) = \int W(\boldsymbol{\epsilon}) N(\boldsymbol{\epsilon}, \bar{\boldsymbol{\epsilon}}, \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}})\, d\boldsymbol{\epsilon}. \tag{9}$$

Extended directional and quadratic selection gradients are then obtainable (generally by nu-

merical methods) as

$$\eta_j = \frac{\delta \bar{W}(\bar{\boldsymbol{\epsilon}})}{\delta \bar{\epsilon}_j} \bar{W}^{-1}, \tag{10}$$

and

$$\theta_{jk} = \frac{\delta^2 \bar{W}(\bar{\boldsymbol{\epsilon}})}{\delta \bar{\epsilon}_j \delta \bar{\epsilon}_k} \bar{W}^{-1}, \tag{11}$$

where $\bar{\epsilon}_j$ is the mean of the exogenous inputs to variable j.

If the phenotypic landscape $f(\boldsymbol{\epsilon})$, and the associated mean fitness function $\bar{W}(\bar{\boldsymbol{\epsilon}})$, include one-to-one effects of exogenous variance on each trait, then the extended selection gradients as applied here are the extended selection gradients of both the traits and the exogenous values. If each exogenous value affects the associated trait by any other function than a 1:1 regression, $\boldsymbol{\eta}$ and $\boldsymbol{\theta}$ as defined in equations 10 and 11 will be the extended selection gradients of the exogenous values; they will be extended selection gradients of the traits on an underlying scale, equivalent to the linear predictor scale in a generalised regression model. For example, if some trait z_i within $f(\boldsymbol{\epsilon})$ takes the form $z_i = e^{f(z_1 \ldots z_{i-1})} + \epsilon_i$, then extended selection gradients calculated based on that $f(\boldsymbol{\epsilon})$ function will apply both at the level of the traits $\boldsymbol{z}$ and at the level of exogenous values $\boldsymbol{\epsilon}$. Alternatively, if z_i were defined as $z_i = e^{f(z_1 \ldots z_{i-1} + \epsilon_i)}$, then extended selection gradients calculated using equations 10 and 11 would apply only to the exogenous values.

The per-generation evolution of the mean vector of inputs to the developmental system is

$$\Delta \bar{\boldsymbol{\epsilon}} = \mathbf{G}_{\epsilon} \boldsymbol{\eta}, \tag{12}$$

where $\mathbf{G}_{\epsilon}$ is the additive genetic variance-covariance matrix of exogenous values. Equation 12 is simply an application of the Lande (1979) equation to multivariate normal inputs of additive genetic variation to the developmental system. The Lande equation may be applied in this way because $\mathbf{G}_{\epsilon}$ describes the relationships among the traits before the developmental system is taken into account, and the extended selection gradient vector $\boldsymbol{\eta}$ represents the effects of traits on fitness, accounting for the developmental system. The influence of development on covariance among traits is simply shifted from the genetical inferences to the part of the system that

characterises selection. After selection, but before recombination and segregation, the change in $\mathbf{G}_\epsilon$ due to selection is $\mathbf{G}_\epsilon(\boldsymbol{\theta}-\boldsymbol{\eta}\boldsymbol{\eta}^T)\mathbf{G}_\epsilon$, which follows directly from Lande and Arnold's (1983) expression for the within-generation change in $\mathbf{G}$ as a function of direct selection gradients.

Morrissey (2014) gives evolution of the mean phenotype, in a linear developmental system, as $\Delta\bar{\boldsymbol{z}} = \boldsymbol{\Phi}\mathbf{G}_\epsilon\boldsymbol{\eta}$. Essentially, $\boldsymbol{\Phi}$ (see equation 6) is a function mapping an infinitesimally small change in exogenous variables, $\boldsymbol{\epsilon}$, onto changes in phenotype, $\boldsymbol{z}$. Thus, $\Delta\bar{\boldsymbol{z}} = \boldsymbol{\Phi}\mathbf{G}_\epsilon\boldsymbol{\eta}$ gives the approximate evolutionary trajectory, when $\Delta\bar{\boldsymbol{\epsilon}}$ is small, in a non-linear system. Non-linear developmental systems will cause the evolutionary trajectory to curve away from this prediction, even in a single time-step (e.g., generation). Evolution of the mean phenotype can simply be obtained as the difference between population mean phenotype before selection in each of two subsequent generations, each of which can be calculated with equation 1. Re-writing equation 1 as a function of population mean exogenous inputs, say $\bar{\boldsymbol{z}} = \boldsymbol{f}^*(\bar{\boldsymbol{\epsilon}})$, evolution of the mean vector of phenotype is

$$\Delta\bar{\boldsymbol{z}} = \boldsymbol{f}^*(\bar{\boldsymbol{\epsilon}} + \mathbf{G}_\epsilon\boldsymbol{\eta}) - \boldsymbol{f}^*(\bar{\boldsymbol{\epsilon}}). \tag{13}$$

Established evolutionary quantitative genetic theory only provides a comprehensive treatment of evolution of population mean phenotype, with only short term predictions. Technically, only $\Delta\bar{\boldsymbol{z}}$ for a single generation is predicted by the breeder's (Lush, 1937) and Lande (1979) equations. Some general theory exists to describe transient changes in genetic (co)variances due to gametic disequilibrium (Bulmer, 1971; Tallis, 1987; Tallis and Leppard, 1988; Turelli and Barton, 1994), but otherwise a general system for understanding the evolution of higher moments of phenotype is lacking. The incorporation of a phenotypic landscape perspective into evolutionary quantitative genetic theory provides a general mechanism for modelling the full joint distribution of phenotype, and of components of phenotypic (co)variation. The evolution of the $\mathbf{G}$ matrix, any other components of $\mathbf{P}$, or higher (mixed) moments of the phenotype, are obtainable equivalently by substituting the appropriate function for $\boldsymbol{f}^*(\bar{\boldsymbol{\epsilon}})$ in equation 13, i.e., using the different expressions given in the section '(Co)variance components in non-linear systems', or straightforward extensions thereof.

Equation 13 can be used to give evolution of moments of phenotype under either of two

assumptions. First, it will hold given gametic phase equilibrium, or assuming that the system being analysed is at a quasi-equilibrium state between the effects of selection and recombination on the gametic phase equilibrium effect on exogenous additive genetic variances and covariances. Alternatively, it can be seen as predicting the permanent component of the change in phenotype, i.e., that which would occur after relaxation of selection and restoration of gametic phase equilibrium. The change in phenotype, accounting for both the permanent evolutionary effects on mean exogenous genetic parameters, and transient changes in $\mathbf{G}_\epsilon$ could be made by allowing for changes in the exogenous (co)variances in the $\boldsymbol{f}^*()$ functions used in the application of equation 13, according to standard theory (Bulmer, 1971).

Selective evolutionary constraints arising from the developmental system

While simple theoretical arguments suggest that stabilising selection should be common (Hansen and Houle, 2004; Lande, 1976), and models of evolutionary divergence with stabilising selection seem to best fit macroevolutionary trends (Estes and Arnold, 2007; Hunt, 2007; Uyeda et al., 2011), stabilising selection is surprisingly rarely directly detected. A large part of the lack of convincing evidence for stabilising selection could arise from the fact that statistical power in most studies is typically insufficient to detect non-linear selection (Haller and Hendry, 2014). However, meta-analyses of (direct) selection gradients (Kingsolver et al., 2001) have revealed that curvature of fitness functions is positive about as often as it is negative, and is typically modest relative to directional selection. Given these two observations, we cannot use low statistical power as the primary explanation for a lack of direct evidence for stabilising selection in nature. Thus, the lack of direct evidence for stabilising selection, relative to the apparent preponderance of evidence for directional selection, remains to be explained.

Stabilising selection, or non-linear selection in general, may arise from the developmental system. Many ecologically-relevant sets of traits will be related to one another by non-linear functions. Wright (1935) analysed a two trait model where z_2 is a quadratic function of z_1, and where z_2 is monotonically related to fitness. The overall structure of this model could be

represented diagrammatically as in figure 1a, and is elaborated in figure 2. Wright's (1935) model could be seen as a gentical version of Arnold's (1983; see also Arnold 2003) 'morphology-performance-fitness' model. z_2 might be a life history trait, narrowly-defined, i.e., a feature of a life table. All life history traits are monotonically directly related to fitness. Additionally, no traits other than life histories directly influence fitness, although they may have statistically direct effects (e.g., non-zero β and/or γ) in analyses that do not include life history traits. Stabilising selection in the Wright-Arnold model, and in reality, can therefore only occur via indirect effects of traits on fitness. The Wright-Arnold model is at equilibrium when the mean value of z_1 is equal to the value that maximises z_2 (this is strictly true if z_1 is symmetrically distributed). Although it is intuitively clear that such a system is dominated by stabilising selection, this selection is not represented in any way by the parameters that are generally used in quantitative genetics, i.e., neither in the **G** matrix, nor in direct multivariate directional or quadratic selection gradients. Such stabilising selection can be modelled and quantified with extended selection gradients.

Example: evolutionary prediction and interpretation of genetics and selection in the Wright-Arnold model

In this section, I present more detailed analyses of the Wright-Arnold model under simple assumptions about the quantitative genetic basis of variation in exogenous values. The first goal is to generate an example of how the various expressions given above can be applied to an arbitrary developmental system. The second goal is to explore how different ways of characterising the genetics and selection of the system, and of predicting its evolutionary trajectory, perform in principle. In particular, I explore the Wright-Arnold model at equilibrium, and in a non-equilibrium state.

In both the equilibrium and non-equilibrium cases, the parameters of the developmental system are assumed to be known. Such parameters could be estimated using mixed modelling techniques. For example, parameters of the phenotypic landscape can be estimated as effects of fixed covariates in mixed models, and exogenous variances can be estimated as variance components, conditioning on fixed covariates. For the equilibrium case, I assume that the

404 developmental system's parameters are

$$f(\boldsymbol{\epsilon}_i) = \begin{bmatrix} z_{1,i} \\ z_{2,i} \\ E[W]_i \end{bmatrix} = \begin{bmatrix} \alpha + \epsilon_{1,i} \\ 10 - z_{1,i}^2 \\ e^{\frac{z_{2,i}}{10}} \end{bmatrix}$$

405 and

$$\mathbf{\Sigma}_{\boldsymbol{\epsilon},\boldsymbol{a}} = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \mathbf{\Sigma}_{\boldsymbol{\epsilon},\boldsymbol{e}} = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \bar{\boldsymbol{\epsilon}} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

406 and for the non-equilibrium case, I assume that the mean exogenous value for z_1, i.e., $\bar{\epsilon}_1$, is
407 -1 or +1. These values are useful for demonstration, but more complicated parameters, e.g.,
408 non-zero exogenous variances of z_2 and expected fitness, are easily accommodated. Note that
409 these quantities pertain to variance in exogenous values, not phenotype. Both phenotypic traits
410 and fitness are variable in this system, and the first steps of our analyses will be to calculate
411 phenotypic means and variances.

412 **The equilibrium scenario**

413 The mean vector of phenotype, $\bar{\mathbf{z}}$, as calculated using equation 1, is

$$\bar{\mathbf{z}} = \begin{bmatrix} \bar{z_1} \\ \bar{z_2} \\ \bar{W} \end{bmatrix} = \begin{bmatrix} 0 \\ 9 \\ 2.48 \end{bmatrix}$$

414 and the phenotypic variance-covariance matrix, calculated using equation 2 is

$$\mathbf{P} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 2 & 0.41 \\ 0 & 0.41 & 0.087 \end{bmatrix}.$$

415 The mechanics of equations 1 and 2 are depicted in figures 3 and 4. The first key to the
416 analysis of non-linear systems, which is apparent in figure 3, is why it is necessary to integrate

over the distribution of all inputs to the developmental system in order to obtain parameters of the distribution of traits. An average individual for z_1, i.e., $z_1 = 0$ has a phenotype for z_2 of 10, which is an extreme phenotype for z_2. Individuals with non-average phenotypes for z_1 produce less than maximal, i.e., < 10 phenotypes for z_2, and so the mean of z_2 is lower than the value of z_2 corresponding to the mean of z_1. The same reasoning applies to the variance: the mean squared difference from the mean of any individual for z_2 is also a function of how the mean and variance of the distribution of z_1 interact with the curved function describing the effect of z_1 on z_2.

The average effects of all traits on each another, calculated using equation 6 are

$$\mathbf{\Phi} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0.25 & 1 \end{bmatrix}.$$

As for the phenotypic covariance of z_1 and z_2, there is no net effect of z_1 and z_2. This does not mean that there is no relationship, just that there is no average effect. The additive genetic covariance matrix of the two traits and absolute fitness is

$$\mathbf{G} = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Since the only source of genetic variance to this system is the exogenous input to z_1, and since z_1 has no average effects on other traits in the equilibrium scenario, there is no additive genetic covariance between z_1 and z_2 or fitness, nor is there any additive genetic covariance of either trait with fitness.

The total genetic (co)variances, calculated using equations 3 and 4, are

$$\mathbf{\Sigma_G} = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0.1 \\ 0 & 0.1 & 0.021 \end{bmatrix}.$$

Interestingly, empirical analysis of a Wright-Arnold system at equilibrium could easily mistake the non-additive genetic variance for z_2 for additive variance. Every pedigree relationship to which additive genetic variance contributes covariance will also have a contribution from epistatic variance (Lynch and Walsh 1998, table 7.2), if epistatic variance occurs in a given population. So any standard analysis of $\sigma_a^2(z_2)$, including parent-offspring regression, sib-analysis, or mixed model (e.g., 'animal model') analysis, would to some extent mistake epistatic variance for additive variance. While pedigree designs exist that can in principle separate epistatic from additive genetic variance components, the task will probably rarely be feasible except in conjunction with a system for explaining why epistasis occurs, such as a model of non-linear development. If epistatic variance in z_2 were mistaken for additive genetic variance in a Wright-Arnold system at equilibrium, an erroneous evolutionary prediction would result.

The directional and quadratic direct and extended selection gradients of z_1 and z_2, as calculated using equations 10 and 11, are

$$\boldsymbol{\beta} = \frac{d\bar{W}}{d\bar{\boldsymbol{z}}}\bar{W}^{-1} = \begin{bmatrix} 0 \\ 0.1 \end{bmatrix}, \qquad \boldsymbol{\eta} = \frac{d\bar{W}}{d\bar{\boldsymbol{\epsilon}}}\bar{W}^{-1} = \begin{bmatrix} 0 \\ 0.1 \end{bmatrix},$$

and

$$\boldsymbol{\gamma} = \frac{d^2\bar{W}}{d\bar{\boldsymbol{z}}^2}\bar{W}^{-1} = \begin{bmatrix} 0 & 0 \\ 0 & 0.01 \end{bmatrix}, \qquad \boldsymbol{\theta} = \frac{d^2\bar{W}}{d\bar{\boldsymbol{\epsilon}}^2}\bar{W}^{-1} = \begin{bmatrix} -0.17 & 0 \\ 0 & 0.01 \end{bmatrix}.$$

Selection gradients have been defined for normal traits (Lande and Arnold, 1983). It is therefore not possible to give values of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ for the Wright-Arnold system that are consistent with all expressions given in Lande and Arnold (1983), since the quadratic effect of z_1 on z_2 causes the joint distribution of these traits to be non-normal. The values given here are those that would be obtained by standard regression analysis (e.g., application of equation 16 in Lande and Arnold (1983), and are consistent with the fact that there is no information about fitness in z_1, given values of z_2, and therefore correspond also to the definition of selection gradients as representing the direct effects of traits on relative fitness. Note that the values of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ for z_1 would take the corresponding values of $\boldsymbol{\eta}$ and $\boldsymbol{\theta}$ in a univariate analysis of selection of z_1. This illustrates how (the true values) direct selection gradients a not only parameters of a

given biological system, but their (true) values also depend on the traits included in a given study (Morrissey, 2014). In this case a univariate analysis would recover useful information about the biology of the system. Such a univariate analysis would rarely be conducted when multivariate data are available, as multivariate analyses are generally understood, in principle, to provide the most robust inferences of evolutionary quantitative genetic parameters (Walsh and Blows, 2009). A study using only on univariate selection gradients would have to be motivated by a prior understanding of the non-linear properties of the developmental system – i.e., an understanding of how univariate selection gradients can sometimes provide inferences that extended gradients provide – and its results from such could only be interpreted with that developmental understanding.

The (non)evolution of exogenous inputs in the equilibrium system is given by

$$\Delta\bar{\boldsymbol{\epsilon}} = \mathbf{G}_{\epsilon}\boldsymbol{\eta} = \begin{bmatrix} 0.5 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 0 \\ 0.1 \end{bmatrix} = \mathbf{0},$$

and consequently $\Delta\bar{\boldsymbol{z}}$ would be zero as well.

This calculation gives the permanent component of the response to selection, i.e., that which would occur after several generations of random mating to restore gametic phase disequilibrium. This would be the expected total and immediate change in mean phenotype, if $\mathbf{G}_{\epsilon}$ was at an equilibrium value between selection and recombination. If, on the other hand, selection was applied to a previously unselected randomly mated population, the expected change in $\mathbf{G}_{\epsilon}$ could be calculated, and its effect on $\Delta\bar{\boldsymbol{z}}$ could be obtained as well. The change in $\mathbf{G}_{\epsilon}$ due to selection, but before recombination is

$$\Delta\mathbf{G}_{\epsilon} = \mathbf{G}_{\epsilon}(\boldsymbol{\theta}-\boldsymbol{\eta}\boldsymbol{\eta}')\mathbf{G}_{\epsilon} = \begin{bmatrix} 0.5 & 0 \\ 0 & 0 \end{bmatrix} \left(\begin{bmatrix} -0.17 & 0 \\ 0 & 0.01 \end{bmatrix} - \begin{bmatrix} 0 \\ 0.1 \end{bmatrix} \begin{bmatrix} 0 & 0.1 \end{bmatrix} \right) \begin{bmatrix} 0.5 & 0 \\ 0 & 0 \end{bmatrix} = \begin{bmatrix} -0.04167 & 0 \\ 0 & 0 \end{bmatrix}.$$

If the population was previously unselected and randomly mated, $\mathbf{G}_{\epsilon}$ would be the equilibrium value. In the second generation, after one round of selection in parents, and one round of recombination in the production of offspring, the exogenous additive genetic covariance matrix

will be

$$\mathbf{G}'_\epsilon = \mathbf{G}_\epsilon + \frac{\Delta \mathbf{G}_\epsilon}{2} = \begin{bmatrix} 0.4791 & 0 \\ 0 & 0 \end{bmatrix},$$

assuming many unlinked loci (Bulmer, 1971). This transient evolution of $\mathbf{G}_\epsilon$ can then be used in equation 13 to predict the change in the distribution of phenotype in the next generation. In the Wright-Arnold example at equilibrium, the reduction in exogenous variance for z_1 causes a slight increase in z_2, with $\Delta \bar{z}_2 \approx 0.02$ due to the evolution of gametic phase disequilibrium in ϵ_1.

The key descriptor of the Wright-Arnold system at equilibrium is the extended quadratic selection gradient of z_1, i.e., $\theta_{1,1} = -0.17$. This is the key evolutionary parameter that describes the nature of such a system as being dominated by stabilising selection. In contrast, the direct quadratic selection gradient of z_1 is zero in a model that includes z_2, and is -0.17 in a model that includes z_2. Both these values are correct, and illustrate the fact that the true value of the direct quadratic selection gradient is not merely a descriptor of the biology of multivariate selection, but also a function of the set of traits considered in a given study, as is the direct directional selection gradient (Morrissey, 2014).

Non-equilibrium scenario

Non-equilibrium scenarios in the Wright-Arnold model are instructive for two reasons. First, it is useful to explore the values of the evolutionary parameters of a non-linear system that is expected to evolve. Second, analysis of such a system yields further insights into just what stabilising selection means in the extended sense, generally, and in the equilibrium scenario especially. Note that the only difference between the equilibrium and non-equilibrium scenarios is the mean of the exogenous inputs to z_1. All differences in microevolutionary parameters thus arise from the difference between two populations with genetically-based differences in mean values of inputs to development, but with the same developmental system, and the same direct effects of traits on fitness.

The mean vector and phenotypic covariances when $\bar{\epsilon}_1 = -1$ are

$$\bar{\mathbf{z}} = \begin{bmatrix} \bar{z}_1 \\ \bar{z}_2 \\ \bar{W} \end{bmatrix} = \begin{bmatrix} -1 \\ 8 \\ 2.28 \end{bmatrix} \quad \mathbf{P} = \begin{bmatrix} 1 & 2 & 0.38 \\ 2 & 6 & 1.08 \\ 0.38 & 1.08 & 0.20 \end{bmatrix}.$$

Note that a very similar non-equilibrium scenario exists when $\bar{\epsilon}_1 = +1$. In this alternative scenario (depicted in the right/bottom plots in figure 4), all evolutionary parameters are the same, except those relating to the relationship of z_1 to other traits (i.e., genetic and phenotypic covariances with z_2, and the directional extended sense selection gradient) are opposite in sign.

The effects of all traits on one another are

$$\mathbf{\Phi} = \begin{bmatrix} 1 & 0 & 0 \\ 2 & 1 & 0 \\ 0.38 & 0.23 & 1 \end{bmatrix},$$

and the additive genetic variance-covariance matrix of the traits and fitness is

$$\mathbf{G} = \begin{bmatrix} 0.5 & 1 & 0.19 \\ 1 & 2 & 0.38 \\ 0.19 & 0.38 & 0.072 \end{bmatrix}.$$

We can see that as there is now an average effect of z_1 on z_2, and as in the equilibrium scenario z_2 still has an average effect on fitness, the exogenous genetic variance for z_1 is projected onto z_2, and ultimately onto fitness as well, in a way that does not occur in the equilibrium scenario.

The direct and extended selection gradients are

$$\boldsymbol{\beta} = \frac{d\bar{W}}{d\bar{\boldsymbol{z}}}\bar{W}^{-1} = \begin{bmatrix} 0 \\ 0.1 \end{bmatrix}, \qquad \boldsymbol{\eta} = \frac{d\bar{W}}{d\bar{\boldsymbol{\epsilon}}}\bar{W}^{-1} = \begin{bmatrix} 0.17 \\ 0.1 \end{bmatrix},$$

and

$$\boldsymbol{\gamma} = \frac{d^2\bar{W}}{d\bar{\boldsymbol{z}}^2}\bar{W}^{-1} = \begin{bmatrix} 0 & 0 \\ 0 & 0.01 \end{bmatrix}, \qquad \boldsymbol{\theta} = \frac{d^2\bar{W}}{d\bar{\boldsymbol{\epsilon}}^2}\bar{W}^{-1} = \begin{bmatrix} -0.13 & 0.016 \\ 0.016 & 0.01 \end{bmatrix},$$

and evolution of the mean vector and covariance matrix of the traits, using equation 13 is

$$\Delta\bar{\boldsymbol{z}} = \begin{bmatrix} 0.083 \\ 0.16 \end{bmatrix} \quad \textit{and} \quad \Delta\mathbf{P} = \begin{bmatrix} 0 & -0.15 \\ -0.15 & -0.61 \end{bmatrix}.$$

The non-equilibrium system is expected to evolve toward the parameters of the equilibrium system. Note that although the exogenous input to z_2 does not evolve (in this instructive scenario, there is no exogenous additive genetic variance for z_2), z_2 evolves due to evolution of z_1, combined with the effect of z_1 on z_2.

In the alternative non-equilibrium state where $\bar{\epsilon}_1 = +1$, $\eta_1 = -0.17$. This illustrates the principle of stabilising selection in the extended sense: z_1 is positively directionally selected when $\bar{\epsilon}_1$ is below the optimum, and is negatively selected when it is above the optimum. Even though z_2 is directionally-selected, its evolutionary trajectory is dominated by stabilising selection of z_1. It seems that many of the traits commonly studied in nature could be very much like z_2. Most traits measured in field studies of natural selection reflect aspects of organismal performance that are certainly the product of much underlying behaviour and physiology. In many such cases, it is not surprising that directional selection dominates some traits (Kingsolver and Pfennig, 2004). As such, more detailed study of why and how traits that are subject to direction selection vary, i.e., by also studying traits more like z_1, though they may be challenging to measure, may be necessary to test whether the stabilising selection that seems required to explain evolutionary dynamics (Estes and Arnold, 2007; Hunt, 2007; Uyeda et al., 2011) exists in contemporary populations.

Power of the extended selection gradient approach

It may initially seem that inference of extended selection gradients, whether directional or quadratic, is a greater statistical challenge than inference of direct selection gradients. In fact, extended selection gradients may often be estimated with greater precision, conditional on a model of a developmental system. Here I consider one aspect of how knowledge or assumptions about a developmental system may be harnessed to improve inference of selection. I consider that the basic structure of a linear system may be known, i.e., the ordering of effects may

reasonably be assumed, perhaps because of temporal ordering, but the statistical form of the effects may be unknown.

Consider a Wright-Arnold developmental system with true values of

$$f(\boldsymbol{\epsilon}_i) = \begin{bmatrix} z_{1,i} \\ z_{2,i} \\ E[W]_i \end{bmatrix} = \begin{bmatrix} \alpha + \epsilon_{1,i} \\ 1 - 0.3 \cdot z_{1,i}^2 + \epsilon_{2,i} \\ e^{\frac{z_{2,i}}{4}} \end{bmatrix}$$

where realised individual fitness is Poisson-distributed with expectation $E[W]$, and

$$\boldsymbol{\Sigma}_{\boldsymbol{\epsilon}} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \bar{\epsilon} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

This system is very similar to that considered above and in figures 3 and 4, but more realistic (and less amenable to constructing instructive plots) in that there is exogenous variance for z_2, and in that we consider stochastic (Poisson) variation in fitness. Alternatively, consider a pure directional selection model, where $z_2 = 1 + \frac{z_1}{4} + \epsilon_2$ is substituted for the middle equation in the phenotypic landscape. The extended selection gradients of z_1 in these systems are: stabilising (i.e., when $z_{2,i} = 1 - 0.3 \cdot z_{1,i}^2 + \epsilon_{2,i}$)

$$\boldsymbol{\eta}_{z_1} = 0, \quad \boldsymbol{\theta}_{z_1} = -0.13,$$

and directional (i.e., when $z_2 = 1 + \frac{z_1}{4} + \epsilon_{2,i}$)

$$\boldsymbol{\eta}_{z_1} = 0.0625, \quad \boldsymbol{\theta}_{z_1} = 0.004.$$

For studies with sample sizes between 50 and 500, I simulated data according to both developmental systems. I then calculated three sets of measures of the extended selection gradients of z_1. First I calculated the direct selection gradients in a univariate analysis considering only z_1 as a predictor of fitness. This statistical machinery for calculating direct selection gradients is a valid approach to obtaining the extended selection gradients, if mediating traits (i.e., z_2,

in this case) are identified and excluded from the analysis. It works using the same knowledge of the developmental system that is required to obtain extended selection gradients, in that it requires knowledge of what mediating traits need to be excluded in order for direct and extended selection gradients to be equivalent. Second, I calculated extended selection gradients, by modelling the effect of z_1 on z_2 with a linear model with linear and quadratic terms, and the effect of z_2 on fitness as a Poisson generalised linear model with both linear and squared terms. Third, I calculated extended selection gradients, again using a quadratic (i.e., containing linear and squared terms) model of the effect of z_1 on z_2, but using glm of the effect of z_2 on fitness that contained only a (log) linear term. This third model represents a (correct) assumption by the investigator that the direct effect of z_2 on fitness is monotonic and (log) linear.

Explicit inclusion of the developmental system in inference of selection of z_1 greatly improves statistical power in the simulated scenarios (figure 5). Direct selection gradient estimates (excluding the mediating trait in order to render direct and extended selection gradients equivalent) does not produce estimates that are sufficiently precise to allow robust inference of selection, even with appreciable sample sizes, despite the simplicity of the analysis (figure 5a,d,g,j). This corroborates Haller and Hendry's (2014) finding that typical sample sizes are inadequate to characterise (direct) quadratic selection gradients. However, for the same directional and quadratic selection scenarios of z_1, and indeed for the same simulated datasets, both versions of the explicit extended selection gradient analysis yield much more precise estimates, with the potential to distinguish between zero, and modest but non-trivial, selection gradients with reasonable certainty, and given reasonable sample sizes (figure 5).

Discussion

Integration of information about the developmental system into evolutionary quantitative genetics provides many advantages. These advantages ultimately come from shifting the emphasis from documenting the existence of phenotypic and genetic patterns of covariation among traits, to explaining why covariance occurs among traits and between traits and fitness. In the examples here, I have focused on one possible benefit of a quantitative genetic developmental

584 approach, i.e., that it provides a new hypothesis to explain the lack of direct evidence for
585 stabilising selection in nature. Other key benefits of this more mechanistic approach to quanti-
586 tative genetic parameters may include efficient model-based procedures for separating additive
587 and epistatic variance components, and ways to model the evolution of any arbitrary aspect
588 of phenotype. Ultimately, these benefits require different kinds of information than do more
589 descriptive common approaches to evolutionary quantitative genetics. However, this need for
590 additional information should be seen primarily as an opportunity, where expressions such as
591 those presented here could be seen as an insertion point into quantitative genetics for perspec-
592 tives from environmental physiology and functional ecology.

593 A great deal is known about many phenotypic landscapes. Many sub-fields of biology,
594 in particular, functional ecology and environmental physiology, generate this information. For
595 example, optimal foraging theory generates simple predictions about foraging phenotypes based
596 on simple inherent trade-offs (Pyke et al., 1977). Similarly, ideas about energy and time budgets
597 provide a variety of relatively simple ways to bring organismal biology views on relationships
598 among traits into a quantitative framework (Zera and Harshman, 2001), and the phenotypic
599 landscapes systems of some morphological characters are understood in fine detail (e.g., Salazar-
600 Ciudad and Jernval 2010; Salazar-Ciudad and Marin-Riera 2013). Even when the specific form
601 of the phenotypic landscape is unknown, informed decisions about the direct and indirect causal
602 structures relating different aspects of phenotype to one another and to fitness will often be
603 possible using common sense; for a start, subscription to a linear understanding of time and
604 causality can go a long way.

605 Estimation of the parameters of non-linear developmental systems will often be possible
606 using standard statistical tools. Phenotypic landscapes composed of polynomial functions are
607 generally estimable using multiple regression models. Simultaneous estimation of coefficients
608 of phenotypic landscapes, and of exogenous (co)variance components, would require multiple
609 regression mixed models of the sort commonly applied in quantitative genetic analysis of ex-
610 perimental data and of natural populations. The main difference is that exogenous variance
611 components are estimated by conditioning on endogenous effects, which is accomplished by
612 including traits (or functions of traits) as fixed effects (see Morrissey 2014 for linear exam-

613 ples, from which extensions to polynomial effects of traits on one another is straightforward).
614 Parameters of plastic phenotypic landscapes are similarly estimable using random regression
615 mixed models (Meyer, 1998; Wilson et al., 2005; Zuur et al., 2009). It will generally be possi-
616 ble as well to estimate parameters of non-linear phenotypic landscapes with functional forms
617 that cannot be expressed as polynomial functions. For simple pedigree structures, for example,
618 where (exogenous) genetic variances might be calculated from sire effects, parameters could be
619 estimated using existing tools such the function `nlme` in the `R` package `nlme` (Pinheiro et al.,
620 2013). Parameters of (non-polynomial) non-linear developmental systems can in principle be
621 estimated using general pedigrees using Bayesian approaches and tools (e.g., using tools such
622 as the BUGS language, Plummer 2010; Spiegelhalter et al. 2003).

623 Evolutionary quantitative genetic studies typically treat genetic influences on phenotype, and
624 selective consequences of phenotype, i.e., effects of traits on fitness, as separate components
625 of the microevolutionary process. However, it is a narrow perspective to view the causes of
626 relationships among traits (a) in a primarily statistical framework to be tackled with **P** and
627 **G** matrix estimation, and (b) as a matter of only genetics, not selection. In the Wright-
628 Arnold model at equilibrium (figures 3 and 4), it is correct to say that z_1 is not directly
629 selected, nor is it genetically correlated with a directly selected trait, and therefore it will
630 not evolve. However, it is equally correct to say that it is not expected to evolve because it
631 is subject to stabilising selection (and is at the optimum). In either interpretation, studying
632 constraint via the developmental system brings explanatory power that is not typically exploited
633 in quantitative genetic studies that are motivated by the Lande equation.

634 It seems probable that many traits of interest to evolutionary biologists could have a devel-
635 opmental basis similar to that of z_2 in the Wright-Arnold model. Indeed, while z_2 is termed
636 "performance" in Arnold's (1983; 2003) works, any kind of trait, including morphology, could
637 occupy the position of z_2 in a developmental system. In particular, traits such as overall body
638 size, or the size of sexual ornaments, may be determined not by maximisation, but rather by
639 optimisation, of other traits. Individuals that grow the largest may do so, not by foraging very
640 little, nor by foraging wildly and inefficiency, but by behaving in some optimal manner. In a
641 population where foraging rate (z_1) was optimised for maximal growth and body size (z_2), and

where size was positively related to fitness, as is commonly observed (Kingsolver and Pfennig, 2004), an explicitly developmental view may be useful for understanding the system. In such a system, any additive genetic variance in behaviour would be manifested entirely as epistatic variance for body size. Epistatic variance contributes to phenotypic covariances among all classes of relatives. Models that do not explicitly model epistatic genetic variance would interpret this covariance of body size among relatives as evidence for heritability, as is common (Postma, 2014). The observation of sub-optimal body size, or an observation of its failure to evolve larger values, would be a case of the common paradox of stasis. A developmental view could motivate a researcher to solve this problem, either by seeking to separate additive genetic and epistatic variance components for body size, a difficult but not an impossible task (Lynch and Walsh, 1998), or by seeking to hypothesise, measure, and model those traits that may be optimised by selection for large size.

While it is conceptually useful to think of the developmental system as composed of three parts: exogenous inputs, the phenotypic landscape, and phenotypic outputs; they are not necessarily distinct. For example, because the phenotypic landscape may take any form, there is no reason why exogenous inputs cannot modulate the phenotypic landscape itself. For example, a phenotypic landscape taking the form $f\left(\begin{bmatrix}\epsilon_1 \\ \epsilon_2\end{bmatrix}\right) = f^1(\epsilon_1 \cdot \epsilon_2)$ could be thought of as any arbitrary kind of interaction between the two inputs. Depending on the nature of the inputs, one may be considered a reaction norm, in which case a general model of the genetics, selection, and evolution of plasticity would result. Such an approach may be particularly useful in quantitative genetic studies of plasticity; reaction norms are often discussed as the 'true targets of selection', but of course reaction norms are only selected in the sense of extended selection gradients, i.e., indirectly via the manifest phenotypes they shape. Analysis of phenotypic landscapes that are themselves functions of exogenous inputs, would lead to general models that cover different mechanisms of genetic assimilation and canalisation (Waddington, 1949, 1953) and evolution of disjunct phenotypic distributions (Chevin and Lande, 2013). Rice (2002; 2004a; 2008) provides a general theory of non-linear developmental relationships among traits. His theory is adaptable to evolutionary prediction by way of approximating the covariance of genetic factors in the

developmental system with relative fitness. This directly provides comprehensive evolutionary prediction for additive, normally-distributed, factors, but could be extended by predicting non-additive inheritance, in much the same way as Heywood (2005) obtained an exact form of the univariate breeder's equation. The statistical genetic mechanics outlined here resolve the need for an extended view of how general developmental relationships influence evolution with the useful concept of the selection gradient. These mechanics assume that there is some level at which inputs to the developmental system can be considered additive. Such models will not necessarily always be appropriate, but given any knowledge (or suspicion) of non-linear developmental relationships, the assumption of normal inputs to a non-linear developmental system can at least be viewed as consistent with knowledge of development, where assumptions of breeder's and Lande equations may be inconsistent.

Conclusion

Several attempts have already been made to show how developmental perspectives will elucidate aspects of the microevolutionary process that are likely to be trivialised by established quantitative genetic approaches. Here, I have attempted to devise a general theory that retains the desirable and highly general perspective of evolutionary quantitative genetics, while providing a flexible way of incorporating information about development into broadly meaningful ways of characterising genetic variation and natural selection. In this way it will be possible for quantitative genetic studies of evolution to more directly benefit from the wider biological study of how organisms work.

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Table 1: Summary of notation.

symbol or expression	description
(a) general labels	
ϵ	exogenous inputs to the developmental system
z	traits, i.e., outputs of the developmental system
W	absolute fitness, herein generally conceptualised as expected absolute fitness
w	relative fitness, i.e., $w_i = \frac{W_i}{\bar{W}}$
a	denotes additive genetic (co)variance components
e	denotes residual or environmental (co)variance components
(b) quantities	
ϵ_i, $\mathbf{z}_i$	the vectors of exogenous inputs experience by individual i and of individual phenotype
$\bar{\epsilon}$, $\bar{\mathbf{z}}$	population mean of exogenous inputs to the developmental system, and of phenotype
$\boldsymbol{\Sigma_\epsilon}$	variance-covariance matrix of exogenous inputs
$\boldsymbol{\Sigma_{\epsilon,a}}$	additive genetic variance-covariance matrix of exogenous inputs
$\boldsymbol{\Sigma_{\epsilon,e}}$	environmental variance-covariance matrix of exogenous inputs
$\mathbf{P} = \boldsymbol{\Sigma_z}$	phenotypic covariance matrix
$\mathbf{G} = \boldsymbol{\Sigma_{z,a}}$	additive genetic covariance matrix
$\boldsymbol{\Sigma_{z,E}}$	epistatic covariance matrix
$\boldsymbol{\Sigma_{z,g}}$	broad-sense genetic covariance matrix
$\boldsymbol{\Phi}$	the matrix of average first partial derivatives of traits with respect to exogenous inputs
$\boldsymbol{\beta}$	the vector of direct directional selection gradients
$\boldsymbol{\gamma}$	the matrix of direct quadratic selection gradients
$\boldsymbol{\eta}$	the vector of extended directional selection gradients
$\boldsymbol{\theta}$	the matrix of extended quadratic selection gradients
(c) functions	
$\boldsymbol{f}(\boldsymbol{\epsilon})$	the 'phenotypic landscape': the vector-valued function returning individual phenotype as a function of individual exogenous inputs to the developmental system
$N(\boldsymbol{x}, \boldsymbol{\mu}, \boldsymbol{\Sigma})$	the normal probability density function at vector x, given mean vector μ and variance-covariance matrix σ
$\boldsymbol{g}(\boldsymbol{\epsilon}_a)$	the broad-sense genetic value: expected phenotype of an individual with additive genetic exogenous values $\boldsymbol{\epsilon}_a$, integrating over the distribution of environmental effects
$W(\boldsymbol{\epsilon})_i$	scalar-valued function describing individual expected fitness as a function of exogenous inputs to the developmental system, obtained from re-arrangement of $\boldsymbol{f}(\boldsymbol{\epsilon})$
$\bar{W}(\bar{\boldsymbol{\epsilon}})$	scalar-valued function describing population mean expected fitness as a function of population mean exogenous inputs to the developmental system
$\boldsymbol{f}^*(\bar{\boldsymbol{\epsilon}})$	arbitrary moment of phenotype (e.g., mean phenotype) as a function of population mean exogenous inputs (assuming a particular value of $\boldsymbol{\Sigma_\epsilon}$)

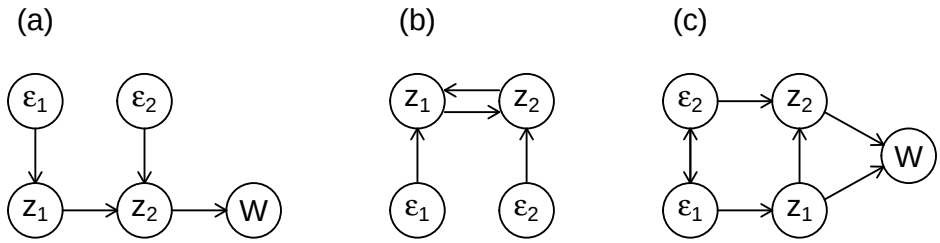

Figure 1: Examples of the basic model structures encompassed by the approach outlined in this paper. Each structure could be referred to generally as a 'developmental system'. Within each developmental system, there are inputs of variation, denoted by ϵ, traits, denoted z, where fitness, W, may be treated as any trait. These specific models are motivated by (a) the Wright-Arnold (Arnold, 1983, 2003; Wright, 1935) morphology-performance-fitness model, (b) binodal regulatory motifs such as those recently investigated by Hether and Hohenlohe (2014), and (c) a general set of relationships among exogenous inputs, traits, and fitness, such as that often used in path analyses of natural selection. Values of functions comprising phenotypic landscapes may be obtained in any way. Ideally, such models would be approached with a combination of theoretical and functional analysis, experimental results, and observational data.

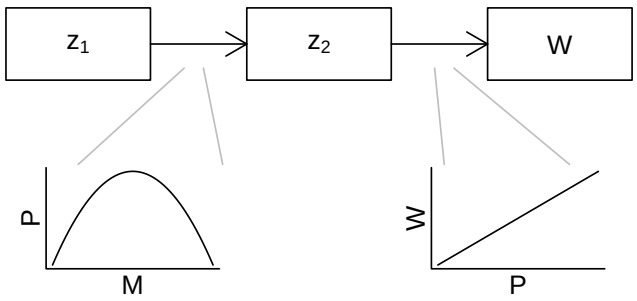

Figure 2: Depiction of Sewall Wright's (1935) developmental model. A 'primary scale' trait, z_1, equivalent to 'morphology' in Steven Arnold's (1983, 2003) morphology-performance-fitness model, influences a 'secondary scale' trait, z_2, (equivalent to Arnold's 'performance') via a non-linear function, depicted here as a quadratic function with a maximum within the range of phenotype in the population. z_2 influences fitness (W) monotonically. Such a system is dominated by stabilising selection. However, this stabilising selection is neither represented by standard representations of the genetics of the system, i.e., elements of the $\mathbf{G}$ matrix, nor descriptions of selection, such as direct selection gradients, β and γ.

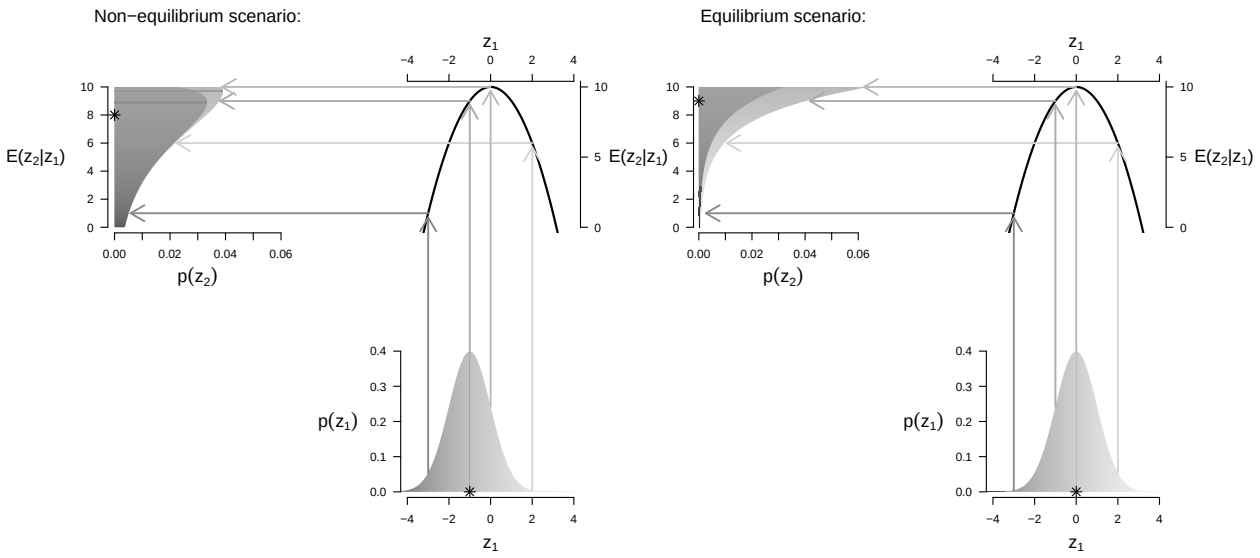

Figure 3: The distribution of phenotype in a simple non-linear developmental system. If one trait, z_1, influences another, z_2, via a non-linear function, then a complex distribution of the z_2 results. For two traits in the Wright-Arnold model (Wright's and Arnold's terminologies for a system as in figure 2 are, Wright: z_1 = "primary scale", z_2 = "secondary scale", Arnold: z_1 = "morphology", z_2 = "performance") with a quadratic phenotypic landscape, $z_2 = 10 - z_1^2$, the distribution of z_2 results from a projection of z_1 onto z_2. This example plots the expected value of z_2, under the general model presented here (i.e., developmental systems that may be described according to a vector-valued function and analysed using equations such as 1 to 13). Additional variance may occur in a trait such as z_2 over and above that which is associated with a traits such as z_1; this is not depicted in the example here, in order to make the plot simpler and instructive, although all associated theory can accommodate such variance. Assuming that increased values of z_2 are selected, the system is at an equilibrium when the distribution of z_1 maximises z_2 (as on the right-hand set of panels). A key feature of non-linear developmental systems is that the mean phenotype may be a complex function of the distribution of inputs and the shape of the phenotypic landscape. Even in the simple scenario depicted here, the mean (means indicated by asterisks) value of z_2 does not directly relate to the value of z_2 that results from the mean value of z_1, and so strategies are necessary that integrate over the full distribution of inputs to the developmental system (in this case, the z_1 is the 'input' in terms of creating the distribution of z_2; see text).

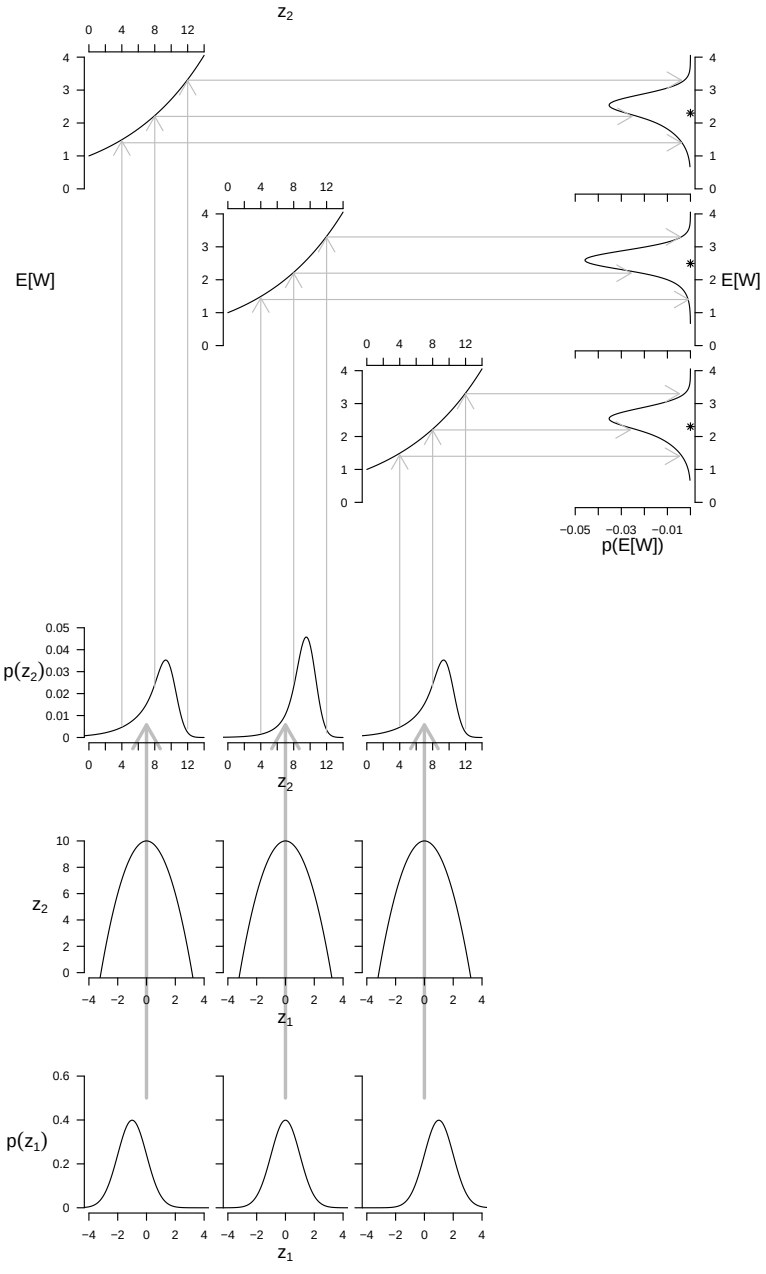

Figure 4: The full developmental system in the Wright-Arnold model (figure 2) of stabilising selection. The lower panels depict the development of the second trait's distribution, $p(z_2)$, as a function of its quadratic dependence on the first trait, z_1, which briefly depict the scheme given in more detail in figure 3. The upper panels depict the developmental dependence of the distribution of expected fitness $p(E[W])$ on $p(z_2)$ and so ultimately on $p(z_1)$. Together, the three distributions of multivariate phenotype and fitness depict non-linear selection in the extended sense. Whereas the direct effects of traits on fitness are either null (for z_1) or monotonic (for z_2), the total effect of z_1 on fitness indicates stabilising selection. Either increasing the mean of z_1 (bottom & right plots), or decreasing the mean of z_1 (top & left plots) leads to decreases in population mean fitness, holding the developmental system constant.

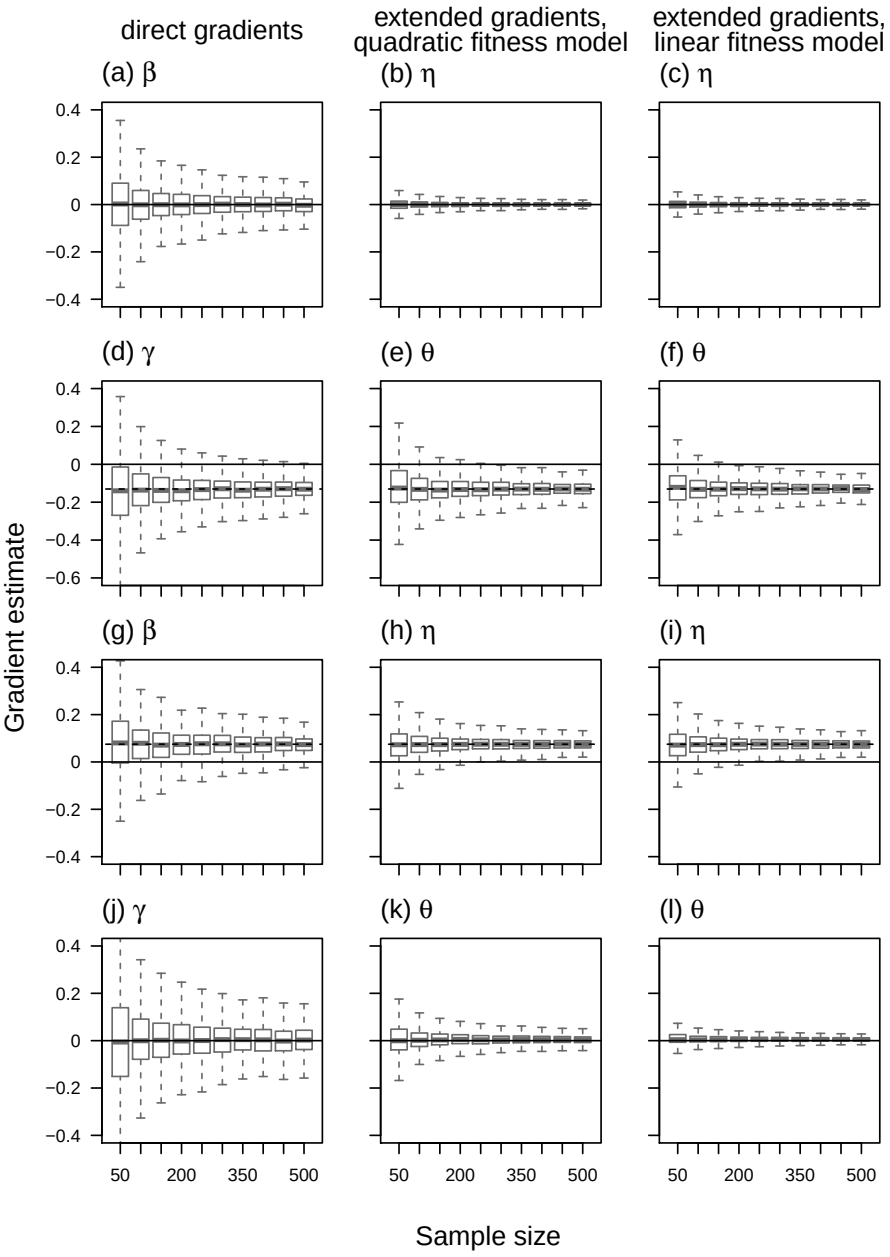

Figure 5: Simulated distributions of estimated selection gradients. True values of selection gradients for each scenario are plotted in grey lines (in all cases, analyses are unbiased, so this grey line overlaps closely on the mean estimated values). Panels (a-f) show a scenario where there is stabilising selection, but no directional selection, and panels (g-l) show a scenario where there is directional selection with no non-linear selection. The left shows analyses of direct selection gradients, but where knowledge of the developmental system has been used to omit moderating traits, such that the direct selection gradients are equivalent to the extended selection gradients. The middle and right columns show analyses of extended selection gradients, assuming that trait-fitness relationships are quadratic, and (log) linear, respectively.