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COMMENTARY

Developmental Phenotypic Landscapes

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Polly (2008) points out that some evolutionary biologists believe that the additive genetic covariance matrix **G**, and the vector of selection coefficients are sufficient to predict the rate and direction of phenotypic evolution, at least in the short term. He also notes that long-term evolution, saltatory evolution, and the origin of novelty can typically not be predicted by current statistical genetic methods. Polly (2008) expresses the hope that information about the developmental-genetic processes that give rise to the phenotype would make it possible to develop an integrated theory for the phenotypic evolution that could predict long-term and discontinuous evolution.

An important reason for the inability of quantitative genetics to predict long-term evolution is that the relationship between genetic and phenotypic variation is non-linear. Understanding the causes and consequences of this nonlinearity is important for understanding how developmental information could be usefully adapted to evolutionary biology.

Perhaps the most general reason for non-linearity is that the relationships between cause and effect (e.g. transcriptional activator concentration and transcription rate, signaling ligand concentration and downstream signaling pathway activation, substrate concentration and reaction rate) are always saturating and have a hyperbolic or sigmoid form. Regulatory processes inevitably have non-linear effects: the effect of an inhibitor is non-linear (it is proportional to 1/inhibitor); negative feedback, like inhibition, is non-linear; positive feedback is a non-linear process (it is proportional to K^n); cooperativity, like positive feedback, is described by a (non-linear) power function. Any process that depends on diffusion of one or more of its components, and is not at steady state, is a non-linear function of time and space. Finally, the system properties of interacting causal factors can produce highly non-linear relationships between cause and effect even when the independent effect of each cause is perfectly linear (Kacser and Burns 1981; Gilchrist and Nijhout 2001).

What effect do these non-linearities have on the shapes of phenotypic landscapes and evolution on those landscapes? In order to answer this we need to consider what a phenotypic landscape actually depicts. There are basically four different kinds of phenotypic landscapes (admitting that they could be parsed differently than I do here), that represent very different things. In the adaptive landscapes of population genetics, the fitness can be described as a function of gene frequencies, and each point on the surface of such a landscape represents a population mean. In quantitative genetics fitness is described as landscape that is a function of trait values, and the population is represented by a dispersed distribution (hopefully multivariate normal) on the surface. Insofar as selection acts only on phenotypes, a fitness landscape is also a phenotypic landscape where fitness is proportional to phenotypic value. Morphometric landscapes, by contrast, describe the relationship among the measured phenotypes. These are essentially descriptions of how different traits covary in a population. Developmental landscapes describe the relationship between the phenotype and the underlying determinants of the phenotype (e.g. genes, environments, processes, antecedent traits). Each point on the landscape describes an individual of a particular genotype in a particular environment. It is this latter kind of landscape that Rice (1998, 2002) had in mind and that has the potential of

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linking developmental and evolutionary processes. We'll refer to this kind as a developmental phenotypic landscape.

In a developmental phenotypic landscape the independent variable axes are the determinants of the phenotype, and the dependent variable axis is the phenotype (Fig. 1). Most biologically interesting landscapes will be multidimensional with n orthogonal axes of causal variables and m additional orthogonal axes for the different phenotypes controlled by those causal variables (Fig. 2 gives an example for $n = 2$ and $m = 2$).

In a developmental phenotypic landscape a population is represented as a cloud of points (individuals) on the surface, and evolution alters the position and dispersion of those points. If selection is on the plotted phenotype, such landscapes are also fitness landscapes for directional selection. The landscape in effect predicts how the values of the underlying developmental causal variables will change when the phenotype changes due to selection or drift.

If the axes of causal variables represent genotypes (Fig. 1), then values on the axes are restricted to known allelic variation, which is discontinuous, so phenotypes can only take on discrete positions on the landscape. But if the axes represent polygenic developmental or physiological processes, variation along an axis is likely to be continuous (perhaps even normally distributed around a mean). If there are no genetic, demographic nor developmental constraints, then evolution on such a phenotypic landscape is predicted by the Lande–Arnold theory (Lande 1979; Lande and Arnold 1983), which, in pictorial terms, says that under directional section the phenotype will move up the steepest slope of the fitness landscape (see also Rice 2004; Gilchrist and Kingsolver 2001; Steppan et al. 2002).

Real systems are never free of such constraints, and in such cases phenotypic evolution can be predicted by iteration of the multivariate breeder's equation, $\mathbf{R} = \mathbf{G}\mathbf{P}^{-1}\mathbf{S}$, where $\mathbf{R}$ is the vector of phenotypic responses (changes in trait means), $\mathbf{G}$ is additive genetic variance–covariance matrix, $\mathbf{P}$ is the phenotypic covariance matrix and $\mathbf{S}$ is the vector of selection differentials (Lande and Arnold 1983).

The multivariate breeder's equation deals only with empirically measurable phenotypic means and variances and is agnostic about the underlying developmental-genetic mechanism that gives rise to the phenotype. This is because the trait axes of a typical fitness landscape are chosen for their hypothesized correlation with fitness, not because they bear a known causal relationship to the phenotype under selection. In a developmental phenotypic landscape the trait axes *are* the causes of the phenotype, and the developmental mechanism generates the shape of the phenotypic landscape. Analysis of the evolution on a developmental phenotypic landscape may thus allow us to understand how developmental processes change when the phenotype changes under selection.

The multivariate breeder's equation can also be written as $\mathbf{R} = \mathbf{G}\boldsymbol{\beta}$, where $\boldsymbol{\beta}$ vector of partial regression coefficient of the phenotype on the underlying traits, which is (approximately) equivalent to the slopes of the phenotypic landscape in the direction of each axis (for a nice treatment of the precise definition of $\boldsymbol{\beta}$ and its dependence on the nature of the fitness landscape and the population distribution see Walsh (2003)). The important point for our

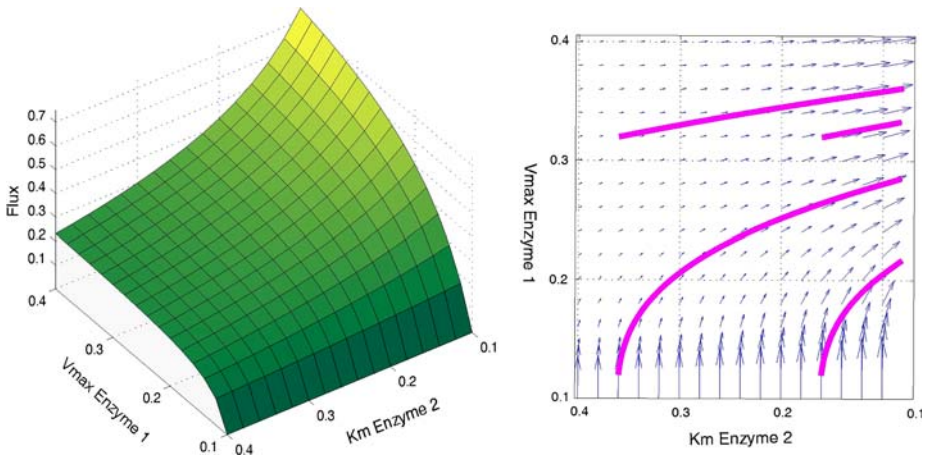

Fig. 1 A, phenotypic landscape for a simple metabolic chain of three sequential enzymatic reactions, plotting the flux trough the system as a function of variation in the V_{max} of one enzyme and the K_m of another, using the equations of Kacser and Burns (1981). All other parameters, including those of the third enzyme are set to 1. In terms of molecular genetics, variation in V_{max} can be interpreted as cis-regulatory variation, and variation in the K_m can be interpreted as coding region variation. (**b**) Vector field showing the gradient of the landscape in (**a**), where the direction and length of the arrows indicate the slope and steepness of gradient, respectively. Predicted trajectories from four different starting points are illustrated, assuming that selection is directional upward (to larger flux) and that there are no genetic or demographic constraints

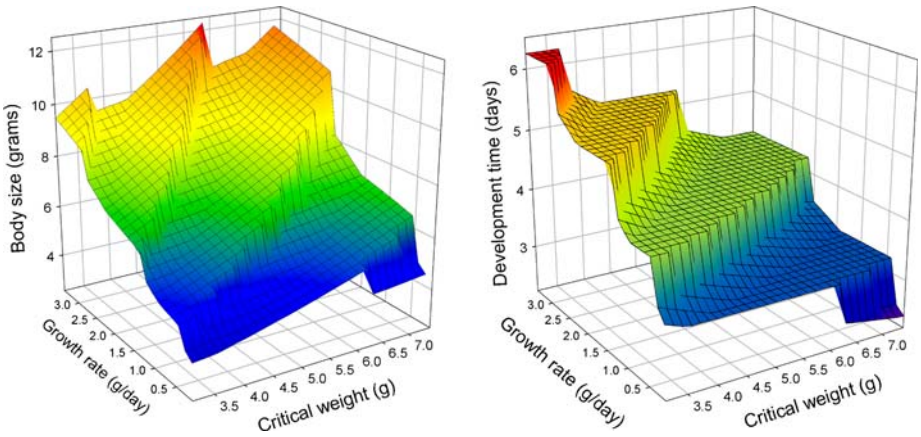

Fig. 2 Developmental phenotypic landscape for body size (**a**) and development time (**b**) in *Manduca sexta*, as a function of two of the developmental determinants of body size: growth rate and critical weight. After Nijhout et al. 2006

purpose is that when evolution moves a population to a location of a phenotypic landscape with a different slope, the variances and covariances among the underlying causal traits will change, which changes **G**, as will the partial regressions, which changes $\boldsymbol{\beta}$. In addition, if selection changes the dispersion of a population on the phenotypic landscape, this will also affect both **G** and $\boldsymbol{\beta}$. In a fundamentally non-linear phenotypic landscape it is inevitable that evolution will take a population to a region where the slopes are different than the one from whence it came. This is why the breeder's equation only predicts evolution in the short term (or, rather, over short distances on the phenotypic landscape) and why **G** and $\boldsymbol{\beta}$ need to be recalculated for each new position on the phenotypic landscape.

A landscape whose shape has been determined empirical, by sampling along all axes of variation, can be used to predict evolution within the range of sampling. But because of the non-linearities it is not possible to extrapolate beyond that range with any confidence. This is where developmental information may come in handy, because if the underlying developmental/physiological mechanism that gives rise to the phenotype is known, then a phenotypic landscape can be predicted for parameter values that have not been measured.

But to do this you need a lot of information about the mechanism that gives rise to the trait, and that is as yet unavailable for most traits, except purely biochemical ones and handful of molecular-genetic mechanisms. In order to construct a developmental phenotypic landscape one needs sufficient mechanistic and quantitative information to build an accurate mathematical model for the ontogeny of the trait, so that the trait can be plotted as a function of the underlying parameter values. Because the processes that give rise to the trait are non-linear, it is impossible in most cases to derive a closed-form solution that gives the phenotype value as an explicit function of the parameters (i.e. the underlying causal traits). Thus, numerical simulation of the phenotype is typically required.

An example of two developmental phenotypic landscapes whose underlying developmental physiology is well-understood is shown in Fig. 2. These are the depictions of the mechanism that controls body size and development time in the tobacco hornworm, *Manduca sexta*. In *Manduca*, as in other insects, the adult does not grow, and adult body size is determined by the size at which a larva stops feeding and enters metamorphosis. The developmental physiological mechanism that controls the cessation of growth in *Manduca* has been analyzed quantitatively (Nijhout et al. 2006), and the underlying processes can be described by a set of mathematical equations that describe the underlying developmental mechanisms and that allows us to compute the predicted body size and development time given only three empirically measurable parameters: (1) the growth rate, (2) the critical weight which is the body size at which the endocrine events that will lead to metamorphosis are initiated, and (3) the period required for the decay of juvenile hormone, which acts as an inhibitor for the secretion of ecdysone. The model predicts body size and development time of a variety of genetic strains with a 3-fold range in body sizes with 98% accuracy (for development of the model see Nijhout et al. 2006). The model can be used to calculate developmental phenotypic landscapes as function of the three parameters. Two such landscapes, using only growth rate and critical weight as variables and keeping the third parameter constant, are shown in Fig. 2. The two landscapes use the identical ranges for the two underlying developmental parameters, which are plotted within their normal physiological ranges. The sawtooth pattern arises from the fact that one of the developmental hormones that controls the cessation of growth is photoperiodically gated.

The landscapes in Fig. 2 are "individual landscapes" in the sense that each point on the surface represents a specific and unique combination of parameters that represents an individual organism. Such a landscape can be turned into a "population" landscape" if the population distribution is known. For instance, if the population is multivariate normal for the underlying parameters and panmictic, then

that distribution could be used as a smoothing kernel to calculate a new landscape where each point represents a population mean.

It should be clear that sampling the small region of either phenotypic landscape where a population happens to reside would be nearly useless in deducing its overall shape. Understanding the developmental-physiological mechanism, however, allows one to calculate the entire landscape that is physiologically accessible. And if new variation arises it is a simple matter to calculate the extension of the landscape in that direction. Abrupt non-linearities in the phenotypic landscape, like those shown in Fig. 2, may lead to apparent saltatory phenotypic evolution, even though changes in the underlying developmental processes are gradual and continuous. Thus, one way in which understanding development could aid evolution is by "predicting" the pattern of non-linear regressions that should be used when a population moves to a new region of phenotypic space. The laborious process of having to empirically determine **G** every few generations would be replaced by measuring the population distribution of values of the underlying developmental parameters, which can be used to compute the shape of the developmental phenotypic landscape occupied by the population.

Finally, if the effects of environment (such as temperature, photoperiod, nutrition, etc.) on a developmental process are known, then those effects can be incorporated into a mathematical model for the phenotype. Each environmental variable can then be plotted as an additional orthogonal axis of variation. The developmental phenotypic landscape parallel to an environmental axis represents a (multidimensional) reaction norm. A simple example would be in a biochemical system like that shown in Fig. 1 where the V_{max} of one reaction is affected by temperature: the axis of variation of that V_{max} could then be interpreted as representing either cis-regulatory variation, or temperature variation. The developmental phenotypic landscape then provides a graphical way of examining phenotypic plasticity and the interaction of genetic and environmental variation.

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