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Characters as the units of evolutionary change

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Abstract

In order to understand evolution we must simplify the enormous phenotypic and genetic complexity of organisms to an understandable, yet hopefully still predictive, level. Life history theory provides a convenient summary of phenotypic complexity, sufficient to approximate fitness of individuals. I argue that it is the nature of the pathways connecting genotype and phenotype are the units which change during evolution, and that properties of these pathways can be used to summarize the immense complexity of the genetic system. I term such units evolutionary characters. Evolutionary characters matter because they determine both the opportunities for evolutionary change, and the constraints on evolution. I review two traditional whole-organism approaches to identifying the nature of evolutionary characters: quantitative genetics, and model building and testing. Quantitative genetic methods are valuable because of their exploratory nature, but have serious practical obstacles to their use. Selection experiments are a powerful genetic technique for exploring issues of constraint and opportunity in the limited range of species where they may be applied to large populations. Model building and testing is also powerful and informative in well-understood systems. These approaches are now being supplemented by comprehensive genomic approaches to the identification of characters. Evolutionary biologists should exploit this new information to build a comprehensive understanding of the characters which underlie evolutionary transitions. This process of understanding the evolutionary implications of functional architecture is the capstone of genomic studies. I suggest that it should be referred to as phenomics to emphasize its importance. Evolutionary biologists should embrace the study of the phenome as a task they are uniquely positioned to undertake.

As evolutionary biologists, we would like to understand the history and predict the course of evolution. This is a difficult task, as the complexity of biological entities is staggeringly high. The phenotype of an organism can be described as a collection of many traits — limb length, bristle number, enzyme activity, hormone levels, etc. Furthermore, each of these traits will change through the life of an individual, making the task of describing the phenotype one of infinite complexity. Clearly, if we need to consider an infinite number of phenotypes to understand evolution, we can make no progress.

Turning to the genetic basis of the phenotype seems hardly better. The genotype of a multicellular organism consists of 10^4 or more genes. Although the number of genes is at least finite, it is small improvement to argue that if only we knew the states of 10,000 genes in a population we could understand evolution. Two major complicating features of the genetic system are that it is polygenic and pleiotropic. Pleiotropy describes the fact that each gene influences many phenotypic traits; it tells us that the fitness of genotypes at each locus will be difficult to predict, as it will depend on its effects on many phenotypes. Polygenic inheritance refers to the fact that many genes influence each phenotypic trait; it tells us that the genetic basis of each phenotype may be difficult to decipher.

To understand evolution, we need to reduce the level of complexity of the problem at both the phenotypic and genotypic levels to one that is both sufficiently precise for our purposes and simple enough to understand and test. This then is the character problem I will consider: what are the entities which need to be studied in order to provide a description of the evolutionary process? I will call these entities evolutionary characters. This paper is concerned with the nature of these evolutionary characters. Why do they matter? How do we identify what the characters are? How many do we need to study to decipher the riddles which fascinate us?

I will explore these ideas through the lens of life history theory. Life history theory is a natural point to begin a search for evolutionary characters because it is a widely accepted method for reducing the phenotypic complexity of the evolutionary problem. A life history is most economically defined as the age-specific schedule of reproduction and mortality of a population of individuals. Reproduction and mortality are the events which influence fitness, so a description of a life history defines its fitness.

I begin by describing the two whole-organism approaches which have been employed to identify the nature of evolutionary characters underlying life histories. These are quantitative genetics, which is a data-driven method for summing up the relationship between genotypes and phenotypes (Lande, 1982). It requires no a priori assumptions about the nature of evolutionary characters. The second method in wide use, which I link to optimality models (Parker and Maynard Smith, 1990), is to make an assumption about the nature of the evolutionary characters which underlie the traits of interest. These assumptions are then tested either by comparing the predictions of models which assume the nature of the characters against observational data, or by experimental tests of their existence. These types of studies are both implicitly directed towards an understanding of the *functional architecture*, the set of pathways which connect genotypes to phenotypes. Genomic studies are currently directed towards the same goal. We can anticipate that merging of genomic and phenotypic approaches to this problem will be come increasingly fruitful; I suggest the term phenomics for this area of inquiry.

Functional architecture and evolutionary characters

Many evolutionary biologists have pointed out the importance of a more thorough understanding of the pathways between genotypes to phenotypes (Lewontin, 1974; Wright, 1977; Schlichting and Pigliucci, 1998), what I have called the functional architecture (Houle, 1991). I start with the intuition that we can begin to understand the tangled mass of genetic relationships with three well-known facts. First, each gene has a very specific set of functions in the organism. Second, these functions are often organized into pathways, which themselves also carry out specific functions, such as production of metabolites, internal signaling, gathering information about the external world, etc. Third, these pathways then are coordinately regulated, for example through the actions of hormones.

These elementary facts from development, biochemistry and physiology suggest several things. First, rather than paying attention to all the genes in an organism, we may be able consider evolution of the pathways, rather than all of the genes that underlie them, at an enormous simplification in the dimensionality of the system. In our terms, the evolutionary characters we are seeking are the properties of the functional pathways themselves. Second, the pleiotropic effects of variation in a pathway will be restricted to phenotypes to which it is functionally connected. We need not consider the effects of each pathway on all of the arbitrarily large number of phenotypes. Finally, the hierarchical nature of some functional architecture suggests that some pathways may be more important than others, to the point where perhaps focusing on a few simple pathways may capture the essential nature of some evolutionary transitions.

This intuition about the organization of biological complexity is represented in Figure 1. At the

top, in the genome domain, we have the DNA sequence and the proteins and RNA molecules that the genome directs the synthesis of. In the second domain, that of the proteome (Kahn, 1995), each of the proteins is recognized for its specific biological function, and these functions are organized into the pathways which perform more general functions, such as aspects of metabolism and development. The domain at the bottom, labeled the phenome, is the organization and regulation of the pathways into the functional architecture, which lays out the relationships between biological function and fitness. In order to understand evolution we must ultimately understand the phenome as well as the genome and the proteome.

This sort of reasoning is the implicit biological justification for many models which consider the optimization of only one or a few evolutionary characters. There are now a fair number of architectural models of evolution (Riska, 1986; Slatkin, 1987; Wagner, 1989; Houle, 1991; de Jong and van Noordwijk, 1992). Wagner's (1989) model is particularly helpful for understanding the implications of this way of thinking. Wagner assumed that there are a set of loci which each determine one 'physiological' property of the organism. These physiological variables are then 'mapped' onto the phenotypes with a 'developmental' function which gives the effects of each physiological state on each of the phenotypic traits. Wagner restricted his analysis to a linear form of this model where the developmental function could be represented as a matrix of linear coefficients, the **B** matrix, which represent the effects of each physiological variable on each of the phenotypes, with all the other physiological variables held constant. While this linear form is mathematically convenient, Wagner noted that in general the developmental function need not be linear, and can involve interactions between the physiological variables. In addition, I suggest that we can relax the assumption that each

physiological variable is controlled by only one locus, and consider it to be a function of all of the genes in a particular pathway. All of these genes that interact to determine one physiological property, such as the flux of material through the pathway, can be treated together when we are concerned with the evolution of particular phenotypic traits, such as life histories.

A very simple example of this type of model is the Y model of a life history, shown in Figure 2 (van Noordwijk and de Jong, 1986; Houle, 1991; de Jong and van Noordwijk, 1992). It assumes that the organism acquires some resources, R, from the environment, which it can then allocate to either of two traits, z_1 or z_2. For example, we can assume that z_1 represents somatic function enhancing survival, while z_2 represents reproductive functions. The proportion of all resources allocated to z_2 is P, which leaves fraction 1-P for z_1. In general, the level of expression of z_1 and z_2 may be nonlinear functions of resources allocated. Let us further assume that the values of R and P are determined by separate functional pathways, each containing independent sets of genes. R and P are then evolutionary characters, as they are assumed to be capable of responding to selection independently. However, the biologist studying this life history can observe survival and reproduction, but knows neither the actual allocation hierarchy, nor the gain functions which express the relationship between resources spent and the life history traits.

The bottom panel of Figure 1 represents a somewhat more realistic view of the Y-model. Here the three arrows of Figure 2 are given biological names, and allocation is assumed to be regulated by a hormone. In addition, Figure 1 shows the possibility that the simple Y-model may not be sufficient to describe the real situation. For example, it is usually true that the same morphological form which is necessary for resource acquisition will also influence survival directly, as shown by the dotted line. For

example, plant leaves carry out photosynthesis and gas exchange, which directly affect acquisition; while the resistance of those same leaves to herbivory can also directly influence survival.

In summary, I propose that evolutionary characters are functional pathways. This suggests that evolutionary characters are free to take on values which are to a large degree independent of those of other evolutionary characters, although the pathways will interact with each other to determine fitness. Identification of these characters would allow a description of a population sufficient both to predict its evolutionary dynamics and the eventual equilibrium state. The question then is, How best can we go about identifying these evolutionary characters?

Life history theory

Life history theory concerns the evolution of the schedule of reproduction and mortality through the life of an organism (Roff, 1992; Stearns, 1992; Charlesworth, 1994). The appeal of life history theory is that when one has specified the life history of a population of genetically identical organisms, then one has also specified that genotype's fitness. Every real population of organisms is a collection of genotypes which may differ in their age-specific schedule of birth and death. If we could describe the life history of every genotype in a population, we could predict its evolutionary trajectory. Many persistent problems in evolutionary biology would be soluble if it were easy to measure the fitness of a genotype.

Sadly this is not the case. There are a few organisms where it is convenient to measure something close to fitness under special circumstances - clonal growth in microorganisms (Paquin and

Adams, 1983), seed output of asexual plants (Stratton, 1992), or the competitive ability of Drosophila genotypes (Fowler et al., 1997). However, the special circumstances necessary to obtain these relatively comprehensive measures compromise their generality. In the vast majority of organisms, we can only capture fragmentary glimpses of their fitness through the trees of their normal environment.

For most organisms some parts of the life cycle are readily studied. Therefore, we can fill in some parts of the schedule of age-specific mortality and reproduction, the life table, of most organisms. Life history theory provides a framework with which to interpret these fragmentary pieces of fitness. For example, the fitness of a life-history is usually acutely sensitive to the age at which reproduction commences, because of its correlation with generation time and the size and fecundity of adult organisms. This justifies the study of organisms where timing of reproduction and the size of breeding individuals is known, even when much of the rest of the life-history is obscure.

The origins of the study of the evolution of life histories lie in demography. The necessary information for making demographic predictions are the rate at which new offspring are produced and the rate at which individuals die. The most common representation of a life history is that of the discrete life table (Charlesworth, 1994). To make a life-table, the potential life-cycle of an organism is split up into a series of stages defined by a measurable variable such as age, developmental stage or size. For each of these stages, we measure the probability of survival through that stage, transformation to other stages, and the reproductive rate of individuals in that stage. Demography and fitness follow from these parameters. The life-table representation suggests a finite set of parameters to be estimated - at most the square of the number of stages defined. The choice of the nature and number of stages is subject to conflicting goals of those which are practical to measure, and those adequate to capture the current

state of the population we want to represent.

Clearly a life-table is only an approximation of a real life history. One important aspect of this approximation is the assumption that the set of transition probabilities can accurately capture the fate of individuals. For example, transition probabilities may depend not just on the current state of an individual in the model, but also on that individual's history, which would be expected to affect the state of variables, such as energy reserves, which are outside the purview of the model. Another major approximation is the implicit assumption that the parameters of a life table will not change. This will be violated by changes in the environment, including density and frequency of genotypes in the population.

One way to proceed is simply to add more parameters to this discrete model, including information about the environment, subdividing the stages more finely, etc. Practically speaking, this is not a very promising solution, as our ability to estimate parameters is soon outstripped by such complexity. In the limit, a life history will have infinitely many such parameters. An attractive alternative is to postulate a continuous version of a life table, where survival and reproductive rates are continuous functions of variables such as age or size and the state of the environment. Perhaps relatively simple equations with a small number of parameters can sum up a life history where a life-table is a poor approximation to reality. Roff (1992) reviews many such models. The goal of any life history representation is the same: we want sufficient complexity that the state of the population is captured, without requiring us to estimate an unrealistic number of parameters.

While the demographically focused approach can adequately describe the state of the population, it is clearly not adequate for understanding the evolutionary reasons for that state, nor to make evolutionary predictions. To see this, one has only to consider what sort of life history would be

predicted based on the above representations. Fitness will clearly be maximized by increasing survivorship and reproduction at all ages. This should lead to the evolution of a single population of "Darwinian demons," which live forever, and produce an infinite number of offspring. Since Darwinian demons do not exist, there must be some set of factors which prevent this state. These are the evolutionary constraints on life-histories.

Constraints, tradeoffs and characters

I define a constraint as something which prevents a population from evolving to a naturally selected optimum. One kind of constraint would be the existence of some absolute limit to a life history trait. For example, many sources of mortality are completely beyond the capacity of evolution to alleviate, so it is unrealistic to imagine perfect survivorship. If assuming a limit to each life table parameter made it possible to predict life histories, there would be no need to understand the nature of evolutionary characters, as we would be assuming that each character can be optimized independently. We need to know what the evolutionary characters are to understand the constraints on the joint distribution of sets of life-history traits. These multivariate constraints arise due to the nature of the evolutionary characters which underlie them, and the pattern of pleiotropic effects which are necessary consequences of changes to the characters. For example, in the Y-model in Figure 2, there will be a negative relationship between the degree to which an individual commits resources to survival versus reproduction if all other things are equal. This idea that there are limits on the joint expression of life-history traits is usually referred to as the tradeoff problem. Tradeoffs provide the backbone around which life histories must evolve, and so deciphering their nature has long been an important goal of

experimental work in life history evolution (Reznick, 1985; Bell and Koufopanou, 1986; Partridge and Harvey, 1988; Sinervo and Basolo, 1996). Four of the eight chapters in Stearns (1992) book on life history evolution concern either the concept of trade-offs, or the joint evolution of particular pairs of traits which are likely to be traded off against one another, such as age and size at maturity.

There are two basic sorts of reasons for trade-offs among life history parameters. The first is resource limitation, as in the Y-model. Second, a single phenotype must serve all the needs of the organism. For example, a morphology, or behavior, or physiology which maximizes survival may not maximize reproduction (Schluter et al., 1991). In either case, tradeoffs result from the necessary pleiotropic effects of the evolutionary characters.

Constraints may be operative over a range of time scales. It is sometimes useful to regard any factor which prevents evolution from increasing fitness at the maximum rate as a constraint (Clark, 1987). This is a quantitative constraint. At the other extreme, constraints may be regarded as those factors which completely prevent the attainment of some optimal state (Houle, 1991), such as the Darwinian demon. This is an absolute constraint. These two kinds of constraints form the endpoints of a continuum connected by variance in the environment. If the selective environment of a population stays constant, then the population will overcome any quantitative constraints, and the equilibrium achieved will be only a function of the absolute constraints. However, when the environment is changing, and therefore the selected optimum is not constant, then a quantitative constraint can dictate whether the population ever reaches an optimum state, how far behind the optimum the population will lag (Maynard Smith, 1976), and even whether the population can evolve fast enough to avoid extinction (Lynch and Lande, 1992; Gomulkiewicz and Holt, 1995).

The relationship of quantitative and absolute constraints to the underlying evolutionary characters is quite different. Absolute constraints imply that the biological system is incapable of evolving some combination of phenotypic traits. If we conceive of the phenotype of an organism as defining a multidimensional space, with each axis representing the value of a particular life history trait, then at equilibrium it will be impossible to proceed in certain directions in that space. At this equilibrium point, there would be fewer evolutionary characters than there are phenotypic dimensions to the organism. For example, in the Y-model, evolution is expected to maximize R, the rate of acquisition of resources rather quickly, after which time only shifts in P, the allocation of resources between somatic and reproductive functions, will be possible. In Wagner's B model, we would find that the number of physiological characters which are capable of responding to selection is less than the number of traits we are considering. An absolute constraint can therefore in theory be detected by determining whether the dimensionality of the evolutionary characters is less than the dimensionality of one's description of the phenotype. I discuss how one might do this in more detail below.

To detect quantitative constraints, we must examine both the amount and nature of the genetic variation for each trait. The amount of genetic variation will set an upper limit to the rate of evolution of each trait. The nature of the pleiotropic effects of each of the evolutionary characters which underlie a trait will determine the correlated response to selection. If selection on one trait drags other traits away from their optima, progress towards the optimum will be slowed. To predict a quantitative constraint we need to identify evolutionary characters, and measure the variance caused by each of them. This is a more difficult task than in detecting an absolute constraint, as it is easier to identify an absence of variation in some dimensions than to understand the nature of all the variation which is present.

Quantitative genetics

One potential solution to the character problem is to use quantitative genetics to search them out (Lande, 1982). The quantitative genetic formulation of the evolutionary process uses information both on natural selection, and on the phenotypic and genetic covariances among traits to make a numerical prediction of the future course of evolution. The primary advantage of this approach is that it requires no a priori assumptions about the nature of the evolutionary characters. An obvious disadvantage is that it is often difficult to obtain the necessary estimates of genetic relatedness of individuals while they are in a natural environment. Marker based techniques promise to alleviate such difficulties in the future (Ritland and Ritland, 1996).

In the quantitative genetic model, if we construct a vector of mean trait values, $\bar{\mathbf{z}}$, the change in this vector due to a single generation of selection, $\Delta\bar{\mathbf{z}}$ is predicted to be

$$\Delta\bar{\mathbf{z}} = \mathbf{G}\mathbf{P}^{-1}\mathbf{S} \qquad \textbf{(3)}$$

where **S** is the vector of covariances between each trait and fitness; **G** is the genetic and **P** the phenotypic variance-covariance matrix of the traits (Lande, 1979). This equation is known as the breeder's equation, from its usefulness in artificial selection programs. The variance and covariance matrices contain information both on how variable the traits are, in the variances (found along the matrix diagonal), and how the expression of each trait is related to that of the other traits, the covariances (the off-diagonal elements). Recall that correlations are just covariances standardized so that they lie between -1 and +1. Thus covariances summarize the linear relationships between pairs of traits.

A given amount of selection, **S,** affects the traits **z** through the filter of phenotypic and genotypic covariances. A covariance between z_1 and fitness (S_1) reflects both directional forces directly on z_1, but also selection on all traits phenotypically correlated with z_1 (Lande and Arnold, 1983). If z_1 and z_2 are positively correlated and z_1 is being selected to increase, then z_2 will also show a correlation with fitness, even if it is not directly selected. As usual with correlational data, the observed covariance with fitness (**S**) does not imply anything about the cause of the covariance. However the term $\boldsymbol{\beta}=\mathbf{P}^{-1}\mathbf{S}$ gives the standardized regression of each trait on fitness, that is the strength of the covariance between the trait and fitness, holding all other traits in the analysis constant.

A difficult challenge in quantitative genetic studies of natural selection is to include all selected traits which are correlated with the traits of interest (Lande and Arnold, 1983; Mitchell-Olds and Shaw, 1987). Inclusion of traits capturing an adequate representation of the life history and therefore fitness in the study alleviates this problem, as the correlated effects on fitness through the focal traits will be captured.

There is a second step to the filtering process, which is determining the genetically mediated effects of selection on phenotypes of offspring. One part of this is straightforward: for a given value of β_i, the larger the value of G_{ii}, the genetic variance in z_i, the larger the response to selection will be. In addition to this, selected alleles which influence one trait will likely have effects on other traits as well. For example, if we assume that there is also a positive genetic covariance between z_1 and z_2 ($G_{12}>0$), then a genetic response in z_1 will lead to a correlated response in z_2 . The same is true for alleles influencing every trait in the organism. Selection on one trait may affect a wide variety of traits in ways which would be unpredictable without information on the variances and covariances of all selected

traits. Thus multiplication of the selection gradient by **G** in equation 1 sums up all these direct and indirect genetic responses to give the net effect of selection on **z**.

In principle, the quantitative genetic formulation of life history evolution is an empiricist's dream come true. It provides a blueprint for future research by enumerating precisely a set of quantities (**S**, **G** and **P**) which when measured will provide a prediction of evolutionary responses. In addition, this approach places difficult interpretational issues aside, such as why natural selection favors particular combinations of phenotypes, or why some traits are more highly correlated than others. One apparently does not have to understand how the system works to predict or even to shape its behavior. Furthermore it has been suggested that the **G** matrix can reveal both absolute and quantitative constraints on evolution (Lande, 1979; Cheverud, 1984). Absolute constraints are indicated by a low degree of dimensionality. Quantitative constraints can be quantified by the directions of maximum variance and covariance of **G**.

Part of the attraction of quantitative genetics is that it could provide an empirically sufficient dynamic model, which would hold over periods of many generations, perhaps long enough to include the differentiation of species, genera, or higher taxa (Lande, 1979, 1980, 1982; Arnold, 1981b). If so, it would allow both retrospective analyses of the history of selection and predictions of the future course of evolution under novel environments. Unfortunately, it is now clear that quantitative genetics is unlikely to be suitable for such a task (Mitchell-Olds and Rutledge, 1986; Turelli, 1988; Roff, 1997). There are a number of conceptual, statistical and practical pitfalls which lead to this conclusion. Chief among these is the requirement that the **G** matrix must remain constant over the relevant evolutionary time frame. This requires a host of restrictive subsidiary assumptions that selection be weak and

constant in form, the number of loci influencing each trait be large, the average effects of alleles be small, and that genotype-environment interactions are not large enough to be troublesome (Lande, 1979, 1982; Mitchell-Olds and Rutledge, 1986; Turelli, 1988). Some of these assumptions are particularly problematic for life history traits. For example it is difficult to see how selection on life history traits can be weak, as life history determines fitness, and there are many examples of alleles with large effects on life histories (Roff, 1986; Templeton et al., 1993).

Despite this consensus, one recent study suggests that the primary axis along which populations evolve is similar to the major axis of variation in **G** in several species (Schluter, 1996). However, Schluter notes these observation can be explained either by **G** playing a dominant role in constraining evolution, or as natural selection reshaping **G** to fit the prevailing selective environment.

Detecting constraints with quantitative genetics

In response to these problems, practitioners are now suggesting quantitative genetics be employed to detect whether a population is at a local fitness optimum, and to supply hypotheses about why a population might deviate from the optimum if it is not. This sort of goal is much easier to justify, as there is ample evidence that the quantitative genetic approach is capable of rather accurate predictions in the short term (Falconer, 1989; Roff, 1997). This more limited program is most clearly laid out by Kirkpatrick (Kirkpatrick et al., 1990; Gomulkiewicz and Kirkpatrick, 1992; Kirkpatrick and Lofsvold, 1992), who suggests a three step process. First, the selection gradient is estimated to determine whether a population is already at a local optimum. At an optimum, all of the selection gradients will equal 0. If this condition is not met, then selection favors a different combination of phenotypes than the

population mean. In this case, the second step is to estimate whether the **G** matrix has variation to allow response to selection in all directions, or reflects some genetic constraint which would prevent progress in one or more directions. If the matrix lacks variation in some dimensions, examination of the pattern of variation would provide hypotheses about the nature of the constraint present. Finally, it would be necessary to compare the nature of the apparent constraint with the selection gradients which remain non-zero, to see whether they correspond.

The first step of this program has rarely been attempted for life history traits. An exception is a small study of size and timing of reproduction in *Arabidopsis* (Mitchell-Olds, 1996). Instead, those studying life histories have depended on having an a priori demographic model of the life history with which to infer selection gradients. If the demographic model is in fact correct, this is an important shortcut to the Kirkpatrick program. A formidable set of difficulties arises in the estimation of the selection gradients (Lande and Arnold, 1983; Mitchell-Olds and Shaw, 1987). However, without experimental tests of the demographic model's validity, there still seems to be substantial opportunity for error in specifying it, for example if biologically important features of life history have been ignored, such as time lags or density dependence.

If the selection gradients suggest that the population is not at a local optimum, then the population is either not at equilibrium, or is genetically constrained from reaching the optimum. The quantitative genetic model predicts that these constraints will leave their mark in **G** (Lande, 1979, 1982). In mathematical terms, a matrix which is lacking variation in some combinations of traits is *singular*, and will have a determinant which is 0. Detection of these singularities is the second step in the Kirkpatrick program. A singularity would indicate that the **G** matrix lacks variation to allow

evolution in one or more directions in phenotype space. Even if we were not confident that **G** would remain constant in the long term, a singular **G** would nevertheless be satisfying evidence for a genetic constraint at the present time.

A non-singular **G** matrix suggests that there are at least as many evolutionary characters as there are traits in the matrix. Furthermore, it suggests that the evolutionary characters have a pattern of effects on the measured traits such that a response is possible in each trait, while holding the others constant. Note that this relationship need not be a simple one. For the Y-model, there are just as many evolutionary characters (R, and P) as there are life history traits (z_1 and z_2), but no life-history trait is a function of only one evolutionary character. If both evolutionary characters have genetic variance, then the **G** matrix will not be singular, and the system is predicted to be able to evolve to any phenotype.

In the Y model, assuming that the population is not perturbed by directional pressures other than selection, the population is predicted to evolve until R reaches a constrained maximum value R_{opt}, where natural selection has fixed alleles which have positive effects on R, and those which reduce R have been eliminated. At that point, R will have no genetic variance, and effectively ceases to exist as evolutionary character. Conversely, the selection on the allocation would be less intense, as the passing of resources between different functions, each of which increases fitness, would be subject to less intense selection (Lande, 1982). This example is a special case of more general reasoning which considers only variation due to tradeoffs, while variation in quantities whose value is maximized by natural selection is assumed to be absent. This assumption is crucial to the use of quantitative genetics as a means of detecting absolute constraints.

There is good reason to doubt this assumption. In addition to the variation due to tradeoffs, we

expect the **G** matrix will contain two other kinds of variation. The first arises from mutation and gene flow, which often perturb populations away from their selected equilibrium states. In these cases, the equilibrium achieved is a function both of these perturbations and of the resulting selection pressures. A large number of experiments have shown that mutation reduces fitness (Mukai et al., 1972; Simmons and Crow, 1977; Shabalina et al., 1997; Keightley and Ohnishi, 1998), and that life history traits seem to receive a substantially larger input of mutational variance than morphological traits (Houle et al., 1996; Houle, 1998). The large amount of variation in fitness correlates implies that such directional perturbations are also important (Houle, 1992; Burt, 1995). Theoretical work has shown that the consequences of such perturbations can have important effects on the equilibrium life history (Charlesworth, 1990), and the form of the variance-covariance matrix (Houle, 1991).

To take this into account, we need to modify the breeder's equation (Equation 1) to account for the vector of perturbations, **D**

$$\Delta\bar{z} = GP^{-1}S + D \qquad \textbf{(4)}$$

At equilibrium, the perturbations would be precisely compensated for by the response to selection, so that

$$-D = GP^{-1}S \qquad \textbf{(5)}$$

Above, I made the assumption that $R=R_{opt}$, and that therefore we might not expect to see variation in R at all. However, either mutation or gene flow may reduce R below R_{opt} through the introduction of deleterious variation. These introduced alleles could, for example, reduce the ability to catch prey, or

photosynthesize at peak efficiency. This then generates additional variance in all of the life history and provides the opportunity for an additional response to selection to recover this new loss in fitness.

The second form of variation in the **G** matrix, other than that due to tradeoffs, is experimental error. The large standard errors of quantitative genetic parameters are legendary. Indeed, it is rare to see a correlation matrix for more than a few traits where all of the correlations fall in the range -1 to +1. This poses statistical problems for analyses of **G** (Hayes and Hill, 1981). More generally, the existence of a constraint can never be conclusively demonstrated, as one can never prove a complete absence of variance in a particular direction.

There is a substantial older literature on the detection of constraints which was uninformed by these issues. The goal of many experiments was to find simple evidence for singular **G** matrices, such as a lack of variation in particular traits, or a perfect negative correlation between traits assumed to be subject to tradeoffs. Single-trait studies have almost always found a good deal of genetic variance in life histories (Lewontin, 1974; Mousseau and Roff, 1987; Roff and Mousseau, 1987), although it can be particularly hard to see against the background of large residual variances that such traits carry (Houle, 1992). On the other hand, a few studies have failed to detect genetic variance for fitness correlates in ecologically important situations (Bradshaw, 1991; Futuyma et al., 1995).

The detection of genetic constraints through examination of genetic correlations has a much more ambiguous experimental history, in part because the expectation is unclear. If two traits vary only due to a perfect tradeoff between them, then we expect a perfect negative correlation (Charnov, 1989), as in the Y model. Unfortunately, constraints are likely to involve more than two traits (Pease and Bull, 1988; Charlesworth, 1990) Even making the assumption that all of the variation is due to

tradeoffs, in the multi-trait case, there is no longer any simple criterion for determining whether **G** values reflect constraints, unless the form of the tradeoffs are precisely known (Charlesworth, 1990). Charlesworth (1990) presents a numerical example of a constrained five trait life table where at equilibrium there are five negative correlations, three positive and two zero correlations. It is not surprising then that the experimental evidence shows a wide diversity of correlations among life history traits, with only about 40% of the estimates being less than 0 (Roff, 1996). Very few estimates fall near -1 or +1, where an absolute pairwise constraint would be indicated. The preponderance of positive correlations may suggest that directional perturbations are an important source of covariance among life history traits.

Identification of evolutionary characters

A somewhat more promising way to infer the existence of evolutionary characters or constraints from **G** matrices is to examine the structure of the entire matrix through the related multivariate techniques of factor analysis (Gale and Eaves, 1972; Arnold, 1981a) or principal components analysis (Kirkpatrick et al., 1990). Both techniques seek to summarize the entire pattern of variation and covariation expressed in a covariance matrix like **G**, rather than focusing on only a few elements at a time. In principle, each can be used to test the dimensionality of the matrix and the existence of absolute constraints, but they are most useful to suggest hypotheses about the nature of the evolutionary characters which underlie the most important axes of variation in the data, that is quantitative constraints.

Let's assume that we have measured p traits, so the **G** matrix is of dimension $p \times p$. Principal

components analysis decomposes the matrix into a series of linear combinations of the original traits, called principle components or eigenvectors. Associated with each eigenvector is an eigenvalue whose magnitude is related to the amount of variation in the data in the direction of the eigenvector. In effect, this analysis may be thought of as beginning with the question: In which direction relative to the multivariate mean is there the most variation? The direction is the first eigenvector, and the magnitude of the variance is related to the corresponding first eigenvalue. Once this largest direction of variation is removed, the same question is asked of the residual values, subject to the additional constraint that the next direction chosen must be at right angles to, (*orthogonal* to) the first eigenvector. This proceeds for p steps, with the ith eigenvector subject to the constraint that it must be orthogonal to the previous $i-1$ eigenvectors. The result is an analysis which captures the full structure of the original **G** matrix. This is a major disadvantage of principle components, as it means that the error variance of **G** will also be included in all of the eigenvectors, biasing both their direction and the amount of variance they explain.

In contrast, factor analysis begins with the assumption that there are less than p unobserved factors which account for the majority of the correlation structure in **G** (Johnson and Wichern, 1982). As in principal components, a factor is a linear combination of the measured traits. Factor analysis explicitly assumes that some of the apparent 'structure' in **G** is due to error variance. Therefore, the first step in a factor analysis is not to try to explain the maximum amount of variance, but to sequester what are sometimes referred to as 'unique' or 'specific' factors which apply only to a single trait in the analysis. Only after this step, does the analysis proceed in a manner analogous to principal components to ask in which direction would a hypothesized set of factors best explain the remaining data. The underlying assumption is a functional one, that causal, or 'common,' factors exist which can explain the

covariance among traits. This is reminiscent of my assumptions about the nature of evolutionary characters above.

Factor analysis is not a single technique, like principal components, but a complex family of techniques meant to uncover the underlying correlation-causing factors. Versions of factor analysis exist which counter many of the difficulties of principal components, such as the requirement that the principal components be orthogonal to one another, or that the first component be chosen by the narrow criterion of maximizing the explained variance. Among this arsenal of techniques are maximum likelihood models for testing the minimum number of common factors necessary to explain the observed **G** matrix. If one has an a priori notion of what the underlying evolutionary characters are, then related techniques such as path analysis or structural equation models can be used to validate them (Crespi and Bookstein, 1989).

In either analysis, the result is a set of linear combinations of the original variables, along with an estimate of how much variation is associated with each combination. These linear combinations can then be used as the basis for other analyses, such as the detection of selection on the presumed factors. Kirkpatrick et al. (1990) proposed that such techniques could be used to test the dimensionality of the underlying **G** matrix, by constructing confidence limits on each of the eigenvalues in a principal components analysis. The number of those whose confidence limits do not overlap 0 is the inferred dimensionality of the system. Maximum likelihood factor analysis was devised to provides tests of similar hypotheses concerning the minimal number of factors required to explain the data structure (Johnson and Wichern, 1982, pp. 415-423). While these techniques are in theory promising, the large experimental errors in determining **G** suggest that inferences about the least variable dimensions of the

genetic system are likely to be unreliable. Furthermore, the results of such analyses have never been subjected to experimental tests of their reliability.

Selection gradients and tradeoffs

A very different, and relatively unknown method for inferring the existence of constraints is to examine the selection gradients for metric traits with respect to several life history traits (Schluter et al., 1991). If selection of conflicting direction is observed, then this suggests that the metric trait (or a trait it is correlated with) affects fitness through its effects on the life history traits, but that no single value of the metric trait is optimal in all circumstances. For example, Schluter and Smith (Schluter and Smith, 1986) observed that beak length in song sparrows was positively correlated with overwinter survival, but negatively correlated with female reproductive success. This suggests that a tradeoff between fecundity and survivorship must exist such that they cannot simultaneously be maximized. The developmental pathway which leads to the phenotype then is the cause of the tradeoff.

Selection experiments

The goal of evolutionary quantitative genetics is prediction of the outcome of selection. An attractive alternative to the estimation of quantitative genetic parameters, with all the attendant problems, is simply to either apply artificial selection in an interesting direction and observe the response, or set up conditions where the action of natural selection is constrained to a known direction. This latter sort of experiment has recently been reviewed under the name laboratory evolution by Rose et al. (1996), who carefully distinguish between artificial selection and natural selection in the laboratory. However, this

distinction is not as important in our context. The critical issue is that the selection gradient be known.

The first question to be asked with selection experiments is whether the population responds to selection at all. For life histories, the answer seems to depend on the size of the populations used. In many small experiments, sometimes no response is observed (Lints et al., 1979), but when the experiments were later repeated with larger populations spectacular responses were observed (Zwaan et al., 1995a, b; Rose et al., 1996; Chippindale et al., 1997). This contrast suggest that artificial selection is a problematic source of data on evolutionary characters because of the small population sizes usually involved. These results and many others like them suggest that many life history traits have substantial genetic variation, as indicated by the direct measurement of variation. Furthermore, this variation is available for natural selection to bring about a reshaping of the overall life history.

Once a response is observed, the pattern of responses to selection may provide an indication of the nature of the pleiotropic effects of the selected variation. For example, Chippindale, et al. (1996) selected for increased starvation resistance in *Drosophila melanogaster*, and observed a correlated increase in lipid storage, accompanied by decreased larval survival and growth rate. A reasonable hypothesis from these results is that the underlying evolutionary character which has responded to selection is really lipid metabolism, and that the changes in lipid metabolism have costs seen in growth rates and viability.

Selection experiments have the advantage that they compound the effects of selection over many generations, and potentially in very large populations. The within population genetic variance is converted to variation among populations. This increases the range of phenotypes, especially if both high and low selected lines are included, making it far easier to, in effect, detect the variance in the

original population. An important disadvantage is that only a single selection gradient can be applied to each population. Information will only be gained about the variation in this one direction in phenotype space. In contrast, a study of within population variance can be extended to a much wider range of traits simultaneously, and thus may be more suitable for exploratory purposes.

Optimality studies

The quantitative genetic approaches to the study of life history traits all focus directly or indirectly on evolutionary dynamics, that is the response to selection. It requires few a priori assumptions about the nature of the underlying evolutionary characters. The alternative "optimality" approach is to begin with assumptions about the nature of the evolutionary characters, then test those assumptions with a combination of observations or experiments. I call this the optimality approach, because the implications of the assumptions are usually worked out by constructing a model which predicts the optimum phenotype, given the assumptions. Since we do not wish our models to predict the evolution of non-existent Darwinian demons, it is clear that we must immediately make an assumption about the nature of the constraints and tradeoffs which limit the range of possible phenotypes (Partridge and Harvey, 1988; Parker and Maynard Smith, 1990). In doing so, we essentially reify these hypothetical factors into evolutionary characters. In addition, we assume that all of the other potential evolutionary characters are of lesser importance. The optimality approach therefore assumes that absolute constraints are important, while quantitative constraints are not. Once the functional architecture and the relationships of the phenotypes to fitness are assumed, it is a conceptually straightforward task to

find what the optimal phenotype would be, although it is frequently very difficult to find an analytical solution.

A good set of examples of optimality models are the reproductive effort models, which consider the proportion of available resources which should be allocated to reproduction (Roff, 1992, Chapter 8; Stearns, 1992, Chapter 8; Charlesworth, 1994, pp. 213-223). The Y model is a very simple example of a reproductive effort model. Williams (1966) first proposed this way of looking at life histories. He suggested that both fecundity and survival would be positive functions of reproductive effort. In the terms of this paper, Williams implies that reproductive effort is an evolutionary character with antagonistic effects on mortality and fecundity. This insight has inspired a great deal of theoretical and experimental work, which either assumes the existence of a 'cost of reproduction', or tests for the existence of such costs.

It is important to bear in mind that there may be many potential explanations of an evolutionary pattern; the problem will often be to distinguish among many formally correct models. While it is easy to accept William's basic insight that there is a cost to reproduction, there are many potential ways in which such costs could be manifested. For example, Sibly and Calow (1986, pp. 66-71) discuss a simple life history model which imagines that the life cycle is divided into a juvenile period prior to first breeding, and an adult period in which reproduction takes place periodically. Even in this simple life cycle, fecundity per reproductive bout can be correlated with adult survival rate, with interbreeding interval, juvenile survival of the reproducing individual, the time to maturity of the breeding individual, the quality of the offspring, juvenile survival of the offspring through levels of parental care. Similarly, shortening the adult interbreeding interval may also increase lifetime fecundity, but at a cost in adult

survival or offspring quality of survivorship. Each of these possible tradeoffs is a different assumption about the nature of the evolutionary character reproductive effort.

The result of this is that we can come up with many possible explanations for any pattern. For example, the goal of reproductive effort models is often to explain the evolution of reproductive lifespan, in particular the existence of semelparous (annual, or breed once) and iterparous (perennial, or breed multiple times) life histories. Models have shown us that we can explain differences among populations as being due to differences in mean levels of extrinsic sources of mortality (Charnov and Schaffer, 1973), to the variance in mortality or fecundity (Orzack and Tuljapurkar, 1989), to differences in the relationship between reproductive effort and effective fecundity, between somatic effort and survival (reviewed by Charlesworth, 1994, pp. 213-223), as well as, no doubt, other possibilities we have not thought of yet. This reinforces that observational or experimental tests are an essential component of optimality explanations.

Testing optimality models

Models may be tested either through their predictions, or through their assumptions. As noted above, the predictions of several models may fit the same data, so models whose assumptions are well tested should be preferred. Since the nature of evolutionary characters are usually key assumptions, the identification of these characters is of crucial importance to the optimality approach. For the reproductive effort models, the key assumption is that mortality and reproduction are in some way inversely related, and therefore a huge amount of effort has been devoted to detecting "costs of reproduction." There has been considerable debate on the best ways to make these tests (Reznick,

1985, 1992; Bell and Koufopanou, 1986; Partridge and Harvey, 1988; Leroi et al., 1994b; Sinervo and Basolo, 1996). The three attractive options are experimental manipulations, selection experiments, and quantitative genetics.

Ultimately, we are interested in the evolutionary potential of populations, which argues that quantitative genetic and selection based approaches to these questions are the most useful (Reznick, 1985, 1992). However, as outlined above the pitfalls of the quantitative genetic approach approach are many. These difficulties are not so great when a particular relationship, such as between reproduction and mortality is of a priori interest, in contrast to the exploratory role I emphasized above. If we have a good measure of mortality and of reproduction, and a high negative correlation is observed, we can be fairly confident that we have found a tradeoff. Selection experiments can be a powerful way to test for correlated responses predicted from assumptions about the nature of the evolutionary characters in short-lived model organisms (Rose et al., 1996), as discussed above.

In the experimental approach, the experimenter directly alters a life history trait. The extent and nature of correlated effects on other traits are then used to infer something about the nature of the evolutionary characters underlying the traits (Partridge and Harvey, 1988; Sinervo and Basolo, 1996). Experimental manipulations allows a wider variety of organisms to be investigated, often with less effort. It also can generate a range of variation far greater than that amenable to an observational genetic study. However, the nature of the manipulation needs to be carefully considered, as the observed correlations are not necessarily of evolutionary relevance (Reznick, 1985).

Sinervo and de Nardo (Sinervo and DeNardo, 1996) distinguish between three categories of manipulations with varying relevance. First, the environment of an individual can be altered to affect the

life history. However the resulting plastic response may be different from what an evolutionary response would be, especially if the goal of the manipulation is to extend the range of observed variation beyond that in the population. For example, the response of *Drosophila melanogaster* lines to manipulations of food availability bore little resemblance to their evolutionary response to food limitation (Leroi et al., 1994a).

Second, one can manipulate the value of a trait directly. For example, adding or removing eggs from nests as a means of manipulating reproduction is readily accomplished in birds, and so has been carried out numerous times (Gustafsson and Sutherland, 1988). However, direct manipulations do not necessarily capture all the evolutionary costs of fecundity. The eggs themselves may be metabolically costly to produce (Winkler, 1985), so parents with reduced clutches still pay some costs of offspring they no longer care for, while those with enhanced clutches escape these costs. A more subtle problem is the level of parental care offered to an altered clutch. The assumption of the manipulator is that parent birds would respond with a level of parental care appropriate to the clutch size it finds itself caring for, but as with purely environmental manipulations, the plastic response to altered clutch size may not be appropriate, especially at extreme clutch sizes (Gustafsson and Sutherland, 1988), indicating costs which could be alleviated over evolutionary time, or displacing the costs away from the evolutionarily relevant phenoypes.

The ideal manipulation is to alter the evolutionary character itself in the same way that evolution would do, hence the relevance of selection experiments. However, this precise a manipulation requires that the evolutionary character is already known from independent evidence, and so must be used in conjunction with comparative or genetic approaches. An outstanding example of this type of study is

the ongoing work of Zera on wing-polymorphic crickets (Zera and Denno, 1997). Many insect species have wing polymorphisms, where short-winged flightless, and long-winged flight-capable individuals are found, often in the same populations. Compared to wingless individuals, winged individuals have longer time to reproductive maturity and lower fecundity overall. This is consistent with the idea that flight capability is costly, and competes for resources with reproduction; in other words, the polymorphism captures a classic life-history tradeoff.

Direct evidence for this tradeoff has come from controlled studies demonstrating the two wing morphs in two *Gryllus* cricket species consume and assimilate similar amounts of nutrients, while wingless individuals accumulate about 50% less wing muscle mass and 50% less lipid, an important flight fuel in this group, resulting in whole-organism respiration rates significantly lower than that of winged individuals (Mole and Zera, 1993; Zera et al., 1994, 1998). These energetic and material savings are sufficient to account for the 50% larger ovarian mass of short-winged individuals.

The proximal basis for the switch between wing morphs has long been supposed to be juvenile hormone (JH) levels (Roff, 1986), and there is now reasonably convincing evidence that this is true for *G. rubens* (Zera and Denno, 1997). While JH biosynthesis itself does not differ between morphs, juvenile hormone esterase, an enzyme which degrades JH in order to trigger molt to an adult form in insects, does. Remarkably, direct application of JH to *Gryllus assimilis* individuals, a species of cricket which is monomorphic for long wings, resulted in short-winged individuals extremely similar to naturally occurring short-winged individuals in other *Gryllus* species (Zera et al., 1998). This similarity extended to a host of correlated features: flight muscle mass, enzyme activities, muscle respiration, ovarian mass, lipid and triglyceride levels. This strongly suggests that the JH levels are the key element

of an evolutionary character which affects all these aspects of the life history.

It is useful to contrast these studies of JH in wing-polymorphisms where there is a rich set of background information, with the technically more sophisticated studies of mice genetically engineered to express rat growth hormone (Kajiura and Rollo, 1996; Rollo et al., 1997). We would like to be able to manipulate one aspect of the life history in an evolutionarily relevant manner to decipher the "costs of growth," and the fact that creation of transgenic lines yield genetic changes make them an attractive model for evolutionary changes. However, in the mouse there is no indication from comparative or other evidence that this is an evolutionarily relevant manipulation.

Transformed mice constitutively are 50% larger than control mice, and yet they consume less food than control mice when body size is controlled for (Kajiura and Rollo, 1996). There are also pleiotropic effects on reproduction, which is postponed until 25% later in life, and ultimately yields only 1/3 the number of offspring per female relative to controls (Rollo et al., 1997). There are many possible interpretations of these results. This manipulation may reveal necessary costs of increasing growth rates or size, but this is difficult to accept given that other rodents have much larger body sizes. Stepping down a level of generality, it may be telling us about the necessary costs of one particular way of becoming large - increased expression of growth hormone. This is the interpretation favored by Rollo and his colleagues, who attribute the maladaptive aspects of this manipulation to energy stress. They suggest that the mice do not appropriately relieve this energy stress through ad libitum feeding because feeding is regulated to meet growth and protein needs, and is insensitive to energy demands per se (Webster, 1993). Given this scenario, the evolutionary implications of the observed costs of growth are not so clear. For example, a population of mice subject to increased energy stress could be

expected to evolve a new and more appropriate feeding strategy, which might relieve the observed costs of growth. There might also be other mechanisms for increased size which are less evolutionarily costly, such as postponing reproduction without affecting early growth rates. A final interpretation is that the costs observed are due to peculiarities of the manipulation itself. As Rollo et al. (1997) point out, the normal circadian rhythm of GH expression is suppressed in the manipulated mice, and the level of other hormones altered due to regulatory interactions. We need a more complete understanding of the functional basis of growth to determine what the implications of this manipulation are.

New functional alternatives

As evolutionary biologists, we have long been concerned with the evolutionary character problem by other names - in particular as constraints or trade-offs. We have been hopeful that the evolutionary character problem could be solved by whole organism approaches, such as those I have discussed above. While these approaches can be informative, they have many pitfalls which can only be avoided by thorough, multidisciplinary approaches such as those being taken with wing-polymporphic insects (Zera and Denno, 1997). This suggests the desirability of exploiting technical advances which will simplify the process of indentifying the functional wiring underlying evolution.

Most efforts by evolutionary biologists to understand evolutionary characters have been directed at the important but crude question of whether there is a pleiotropic relationship between a pair of traits. However, theory makes clear that it is not simply the existence of a tradeoff which is important to validate a particular evolutionary scenario, but the precise quantitative nature of the

tradeoff. For example, current modeling efforts on the reproductive effort problem seek to incorporate growth and age and size at maturity into the reproductive effort model in a more general way (Sibly et al., 1985; Kozlowski, 1992; Bernardo, 1993). All such models assume that age and size at maturity are in effect one trait, with a strong positive relationship between them, while reproductive fitness is enhanced both by being early, and by being large. Two different growth curves have been used to model deterministic growers. One set of models takes a von Bertalanffy growth equation as an assumption (Roff, 1984; Stearns and Koella, 1986; Berrigan and Koella, 1994, reviewed by Day and Taylor, 1997). The von Bertalanffy model assumes that there is a maximum possible size that an organism can achieve, and that growth rates diminish as this asymptotic size is approached. An alternative is to model growth as a power function of mass (Roff, 1983; Kozlowski and Weigert, 1987; Kozlowski and Weiner, 1996). Here there is no maximum size, so additional growth always results in larger size. Cessation of growth is assumed to be due to the shunting of resources to reproduction, away from growth. In each case, there is a tight tradeoff-driven relationship between age and size at maturity, dictated by the growth model. Only the shape of this relationship differs between the models. Day and Taylor (1997) showed that even with such similar models, the effect of a change in growth rate on the optimal age at maturity differs between them. When juvenile and adult mortality are held constant, the von Bertalanffy-based models will predict that an increase in growth rate will usually lead to a decrease in age at maturity, as an individual will simply approach its maximum size more rapidly. The power function based models predict that a fast growing individual should always mature later, as it would be more willing to pay the mortality costs of additional growth.

As evolutionary biologists we really need to know the precise nature of the evolutionary

characters which underlie life history transitions. To get this information, we will have to depend more heavily on studies of gene function and interrelationships. Genomic analyses ultimately hold the promise of a complete understanding of the functional wiring of organisms. QTL mapping holds the promise of identifying which loci out of all the ones in the functional wiring actually vary within and among populations. Explicitly evolutionary studies will ultimately be necessary to tell us which of the loci that vary are important in effecting evolutionary transitions.

Genomics

A fundamentally new tool which will ultimately prove the key to developing the detailed wiring diagram underlying potential life history transitions are the complete descriptions of gene sequences which the various genome projects have produced (e.g. Fleischmann et al., 1995; Clayton et al., 1997; *C. elegans* Sequencing Consortium, 1998). Just how much we have to understand is emphasized by the high proportion of protein coding sequences found which have no known function. For example 56% of the over 6400 proteins coded for by the yeast genome had no known function at the time the sequence was completed (Clayton et al., 1997). Substantial efforts are now being directed at understanding the functions of these unknown proteins (James, 1997). Evolutionary studies which make use of whole genomes are in their infancy, but already yield some intriguing results relevant to our study of evolutionary characters. For example, comparisons of the genome complements of pathogenic and non-pathogenic species suggests hypotheses about which pathways are necessary for a pathogenic life history (Huynen and Bork, 1998). In the longer term, application of comparative genomic methods to suites of taxa differing in life histories will prove a powerful source of hypotheses concerning the

characters responsible for evolutionary transitions.

A complementary approach which nibbles at the edges of this ignorance are mutagenesis screens which have been used in model systems to identify large numbers of genes with particular classes of mutant phenotypes. For example, mutant screens in the nematode worm *Caenorhabditis elegans* have led to the discovery of at least eight genes which are capable of affecting mortality rates (Hekimi et al., 1998). Consideration of what we have learned from these mutations highlights both the possibilities and the limitations of this approach. These genes seem to fall into two categories with independent effects on mortality (Lakowski and Hekimi, 1996), and so identify two evolutionary characters which can affect lifespan. One set of genes affects the entry of worms into a resting stage, known as a dauer larva. Lifespan of a dauer larva can be up to six months, compared to a normal life span of 15 days. The genes identified seem to be part of the signalling pathway that turns on the dauer phenotype when conditions deteriorate. The existence of these genes is predictable from the natural history of the organism, the fact that it has an inducible resting stage. However, when the constitutively dauer genotypes are placed at a temperature too high for induction of the morphological dauer larva phenotype, lifespan is still lengthened considerably. This has revealed unexpected complexity to the basis of the phenotype which would otherwise have been difficult to find. Otherwise, these loci are not very informative, since they do not help identify the physiological basis of the alterations to lifespan.

The second class of genes affecting mortality rates are the clock genes, so called because they seem to affect a host of traits that have a temporal component (Hekimi et al., 1998). The effects on lifespan seem to be highly correlated with effects on development rate. The genes act maternally, suggesting that they are involved in setting the rate of living of worms early in life, and that this rate is

difficult to change later. One of the clock genes has been cloned, and shows extensive homology with a yeast gene which is involved in regulating the switch from growth on glucose to growth on nonfermentable carbon sources. The implication is that in the worm, the clock genes are involved in activating a fundamental energetic pathway, with mutants depriving worms of the energy the pathway supplies, with the pleiotropic effect of slowing the rate of living, and decreasing mortality rate. This suggests that the clock genotype is a classic example of an antagonistically pleiotropic one, where the fitness advantages of increased metabolism on fitness early in life more than compensates for the gain in fitness late in life.

Possession of the entire sequence of the *C. elegans* genome will catalyze the identification of the missing elements of these known pathways. What is known is tantalizing rather than conclusive, but clearly reveals the power of the genomic approach to the identification of evolutionary characters.

QTL mapping

Quantitative trait locus (QTL) mapping seeks to find the genetic location of segregating variation, usually in artificially constructed populations. To do the mapping, the population is first constructed by crossing stocks which differ in the phenotype of interest. In addition, the two stocks are characterized for genetic markers at previously mapped marker loci. The QTL mapping is then carried out by looking for correlations between the markers and the phenotype in the descendants of the original cross. The technique is beginning to be widely applied to life history traits by evolutionary biologists (Mitchell-Olds, 1995) and plant (Stuber, 1995) and animal breeders (Haley, 1995).

While ultimately the goal is to identify the specific loci responsible for the mapped variation, this

is rarely possible today using QTL mapping alone, given the large numbers of unknown loci in the genome, and the small numbers of markers employed in QTL mapping (Mackay and Fry, 1996). A related problem is that a single QTL containing region may harbor several loci affecting the trait. Successes in identifying the specific loci involved have only come by comparing QTL maps with previously mapped loci which are known to influence the trait of interest, which are called candidate genes (Doebley et al., 1995, 1997; Long et al., 1995; Mackay and Fry, 1996). Presumably the information necessary to resolve these issues will increase in model organisms as the genomic data increase.

Even without knowledge of the function of a QTL, its identification can delineate the existence of evolutionary characters. For example, Mitchell-Olds (1996) mapped two genes controlling flowering time in *Arabidopsis thaliana*. Both gene regions also had correlated effects on plant size, such that late flowering plants were large. This reflects a classic time vs. size tradeoff as postulated in many life history theories. Interestingly, the strains crossed to initiate mapping did not vary in flowering time, but each carried one early and one late allele whose effects approximately canceled out.

A second example of the usefulness of QTL mapping for the identification of evolutionary characters are maps of the differences between primitive cultivars of maize, and its wild progenitor teosinte (Doebley and Stec, 1993; Doebley et al., 1995). The two strains are extremely different in large numbers of traits, so different that they were originally classified as different genera (Iltis, 1983). Most of the morphological differences reflect increased reproductive effort and harvestability in the cultivar, both of great practical value to agriculturalists. The list of major changes includes at least a dozen traits in the ear and the overall architecture of the plant. Remarkably, only five regions of the

genome seem to control the lion's share of the differences in all of these traits. In some cases, the correlated effects of a single locus seem sensibly related to each other. For example, the seed of teosinte is protected by a hard outer glume, covering the opening of the thick cupule in which the seed sits. A mutation at a single locus, *tga1*, withdraws the protective cupule and softens the glume to the edible form found in maize (Dorweiler et al., 1993). However, two other loci jointly determine a bewildering variety of seemingly unrelated traits, including the conversion of the long lateral branches of teosinte to the short ones of maize, the conversion of the terminal inflorescence on the lateral branches from male to female, an increase in the number of seeds/ear, rearrangement of the seeds along the ear, increase in seed size, and for increasing the tendency of ears to stay intact during handling (Doebley et al., 1995). One of these, *tb1*, has been identified and cloned (Doebley et al., 1995, 1997). All of this evidence suggests the presence of a functional pathway whose nature could never have been predicted a priori.

The conservation of gene order in the grasses enables the comparison of QTL positions between maize, rice and sorghum, and remarkably these two gene regions also have effects on mass per seed in crosses between wild and cultivated strains in all three species (Paterson et al., 1995). Correspondence of regions influencing other traits, such as day-length response is also apparent, suggesting that the same evolutionary characters have been involved in independent domestication events.

Phenomics

Very soon, we will have a catalog of all of the genes in a wide sample of model multicellular organisms.

This has already lead to a shift in attention away from genomics, to the decipherment of the biological roles of the proteins a genome is capable of constructing. The set of proteins in an organism has been dubbed its proteome (Kahn, 1995). Understanding the proteome will occupy more reductionist scientists such as biochemists and developmental biologists for some time. Within a few years or decades at the most we can anticipate that the proteome too will be deciphered, that is we will know what all the genes do, and which biochemical or developmental pathways they are organized into.

There is another domain which we need to understand, and that is the potential effects of variation in the proteome on the phenotype (see Figure 1). This is the same task I have suggested we need to pursue to promote our understanding of evolution, the decipherment of evolutionary characters. I suggest the term *phenomics* for this task, to suggest that this is ultimately as important as the genome projects themselves. The task of phenomics is to understand the implications of functional architecture for biology. Some pathways are likely to be important for evolution, while others rarely are. The ones which underlie major evolutionary transitions, or respond to phenotypic selection most readily, or cause the most genetic load should receive the most attention from all sorts of biologists. Other pathways may be ignored as a first approximation. These are crucial tasks which evolutionary biologists should embrace as one for which their conceptual training makes them uniquely suited.

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Figure 1. Three different representations of biological complexity: the genome, the proteome, and the phenome. The genome is the DNA sequence, and the molecules which it directs the synthesis of. Genomics is the study of the DNA sequence. The proteome consists of all the interacting biomolecules created by the genome. Proteomics is the study of the functions of these proteins (and nucleic acids), and the networks of relationships among these molecules. The phenome is the relationship between the pathways which make up the proteome and the phenotype, and especially fitness. In this representation, the morphology of the organism is dictated by development. This, in combination with basic metabolism determines the amount of resources (R) which the organism can acquire. These resources are then spent to enhance fitness by increasing both fecundity (here represented as a function of gametogenesis), and viability (represented as some costly defensive function). The relative amount of resource allocated to these two functions is assumed to be regulated by a hormone. In addition to affecting resource acquisition, morphology and development may influence other aspects of the phenome, as shown by the dotted line between development and viability.

Figure 2. The Y model of a pair of life history traits. The organism acquires resources, R, and allocates proportion P of them to trait z_2 , leaving proportion 1-P for trait z_1.

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