The Evolution of Genetic Architecture

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Abstract

Genetic architecture, the structure of the mapping from genotype to phenotype, determines the variational properties of the phenotype and is instrumental in understanding its evolutionary potential. Throughout most of the history of evolutionary biology, genetic architecture has been treated as a given set of parameters and not as a set of dynamic variables. The past decade has seen renewed interest in incorporating the genotype-phenotype map as a dynamical part of population genetics. This has been aided by several conceptual advances. I review these developments with emphasis on recent theoretical work on the evolution of genetic architecture and evolvability.

INTRODUCTION

Genetic architecture refers to the pattern of genetic effects that build and control a given phenotypic character and its variational properties. A description of genetic architecture may include statements about gene and allele number, the distribution of allelic and mutational effects, and patterns of pleiotropy, dominance, and epistasis. Despite the obvious complexity of the developmental processes that underlie the genetic architecture, the vast majority of evolutionary theory is built around a few very simple models of the genotype-phenotype relationship. These are models of additive unconstrained gene action, including the polygenic models of quantitative genetics, and the simple one-allele, one-trait models used in the study of adaptation. At least for R.A. Fisher, these models were not merely a matter of simplifying convenience. Fisher presented some ingenious arguments to justify his focus on genes in isolation (Fisher 1930). One of these was that in a large, panmictic, recombining population, all combinations of alleles would occur, and the evolutionary effect of an allele could be found by averaging over all the genotype combinations in which it participates. Fisher then defined additive effects in terms of these averages. The underlying assumption is not that the genetic architecture is simple, but rather that complex gene interactions can be averaged and treated like statistical noise. Similarly, he argued that the high dimensionality of biological organisms meant that there would always be a way to achieve a goal and improve the organism. Thus, there is always an advantageous mutation, and if the population is large enough, the advantageous mutation will arise and become fixed. In effect, Fisher used the very complexity of organismal architecture to argue that we could treat genes and gene effects in a manner resembling mass action in statistical mechanics where particulars average out and general laws emerge.

Here I will argue that many of the complexities of genetic architecture are evolutionarily relevant and should not be treated as noise. I will not do this by challenging Fisher's statistical-mechanics philosophy and replacing it with some unsatisfactory listing of particulars, but rather by arguing that many complexities can have systematic influences on evolutionary dynamics, which we should aim to model and measure.

Classical population genetics tends to treat genetic architecture as a set of invariant parameters and not as evolutionary variables. The Neodarwinian paradigm more or less defined evolution as change in allele frequencies and left little room for the evolution of allelic effects. Concepts such as genetic canalization, the evolution of reduced genetic variability (Waddington 1942), and genetic assimilation—evolutionary responses based on environmentally induced variation (Waddington 1953)—were difficult to accommodate into this framework. Work on the subject was pursued by a few people (e.g., Rendel 1967, Schmalhausen 1949, Waddington 1957), and was largely empirical (for review see Moreno 1994; Scharloo 1991). Canalization has, however, finally been given a solid population genetic interpretation in terms of evolution of reduced gene effects through epistatic interactions with an evolving genetic background (Wagner et al. 1997), and is currently the focus of considerable theoretical and empirical interest (de Visser et al. 2003, Dworkin 2005a, Flatt 2005, Gibson & Dworkin 2004, Gibson & Wagner 2000, Rutherford 2000, Wagner 2005).

Indeed, the past one or two decades have seen a renewed interest in incorporating development and more realistic representations of the genotype-phenotype map into population genetics. This interest is evident in a number of recent edited volumes (Hallgrímsson & Hall 2005, Pigliucci & Preston 2004, Schlosser & Wagner 2004, Wagner 2001, Wolf et al. 2000), and may be motivated by advances in evolutionary developmental biology and interest in the evolution of evolvability (Gerhart & Kirschner 1997, Kauffman 1993, Maynard Smith & Szathmáry 1995, Raff 1996, Wagner & Altenberg 1996, Weiss & Buchanan 2004).

Understanding genetic architecture is important for many biological questions, including: speciation, the evolution of sex and recombination, the survival of small populations, inbreeding, understanding diseases, animal and plant breeding, and understanding the processes and genetics of adaptation and population differences. There is, however, one overarching reason why genetic architecture is essential in understanding evolutionary theory, and that is because it describes or determines the variational properties of characters, and thus their evolutionary potential. Understanding the evolution of evolvability requires understanding the evolution of genetic architecture.

In this review I concentrate on recent theoretical and conceptual developments. There is an enormous empirical literature relevant to genetic architecture, but mostly without good connection to theory; consequently I discuss empirical work only in so far as it connects with or exemplifies conceptual issues. Traditionally, most research on genetic architecture has been concerned with population concepts, such as genetic variances and covariances, but I focus my attention to the biological underpinnings of genetic architecture as embodied in the genotype-phenotype map. This is the most fundamental level, and the "architectures" of population variance or population differences are less clear-cut because they are influenced both by genotype effects and genotype frequencies. The goal is disentangling these and understanding how underlying genetic architecture influences evolution.

GENETIC ARCHITECTURE: DEFINITIONS AND DISTINCTIONS

Genetic architecture can be studied on many different levels. We can ask about the genetic basis for the differences between species or populations, how many genes are involved, whether dominance and epistasis are important, etc. These differences can be studied by line-cross analysis or by quantitative trait loci (QTL) analysis. We can also ask about the architecture of segregating variation in a population. The classical quantitative genetics model, developed by Fisher and others, was based on a decomposition of the phenotype into contributions from different genes and their interactions (Lynch & Walsh 1998). These are defined as regression parameters on the presence of the particular allele combinations, so that the dominance and epistatic effects are interaction terms in the regression. The total phenotypic variance can then be partitioned into contributions from the various terms, including the additive genetic variance, which is the sum of the variances in additive effects, and a series of dominance and epistatic variance components stemming from the interaction terms

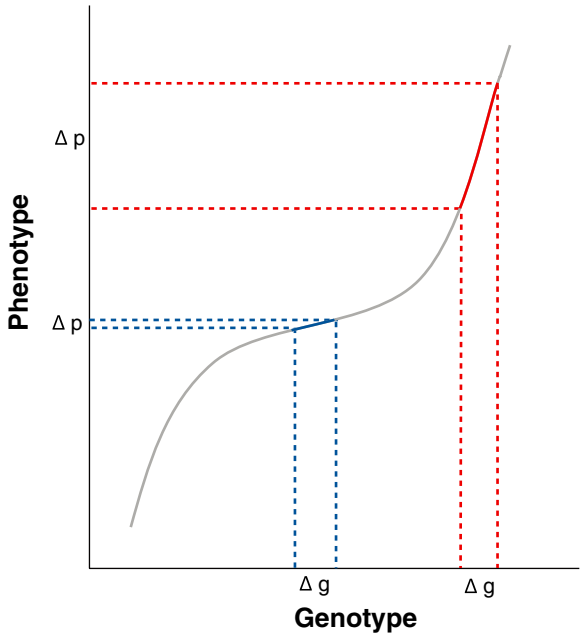

Figure 1

The genotype-phenotype map and canalization: The mapping from genotype to phenotype is a mathematical function that assigns a phenotypic change to each change in genotype. In the flat (canalized) region a given genetic change (Δg) has a small effect (Δp), whereas in the steep (decanalized) region the same change has a large effect. Canalization is evolution toward flat regions, whereas decanalization is evolution toward steep regions.

in the model. This decomposition also generalizes to multiple traits. In this case, the additive genetic variance is replaced with a variance matrix, the G-matrix, which contains the additive genetic variances and covariances between the traits.

We can also study genetic architecture on the level of the genotype-phenotype map, the relationship between individual genotypes and their phenotype (**Figure 1**). It is useful here to recall G.P. Wagner's (1996, Wagner & Altenberg 1996) distinction between variance and variability. Variability has a technical meaning as propensity or disposition to vary. This propensity is conceptually independent of allele frequencies, variances, and other population parameters; it depends on the genotype-phenotype map and mutation rates. The distinction between variation and variability is related to the difference between the G-matrix describing segregating variation, and the mutational M-matrix, describing new (additive) variance and covariance that arise by mutation each generation (e.g., Pigliucci 2004).

Until recently, relatively little attention was paid to the distinction between population parameters and parameters describing the genotype-phenotype map. We may suspect that these were often confused or thought to measure similar things. The development of an explicit conceptual distinction between population or statistical notions of genetic architecture on one hand, and functional/physiological/biological

notions on the other was a great step forward. An important contribution was made by Cheverud & Routman (1995), who developed an explicit model of "physiological" epistasis defined without regard to allele frequencies and showed how this physiological epistasis differed from the Fisherian notion of statistical epistasis and even contributed to the additive genetic variance. The Fisherian regression model minimizes the statistical influence of gene interactions (Moreno 1994, Templeton 2000, Whitlock et al. 1995) and, more seriously, the interaction effects in the model miss important distinctions between different types of dominance and epistasis, such as between overdominance and partial dominance, or between positive and negative epistasis (Hansen & Wagner 2001a).

Cheverud & Routman's (1995) model was, however, based on an arbitrary, and not very operational, parameterization of genetic effects. Hansen & Wagner (2001a) generalized this approach by giving an operational definition of a genetic effect as the phenotypic effect of a substitution of an allele (or set of alleles) into a given reference genotype. They then showed how any particular or average genotype could be used as a reference point and how one could translate from one reference genotype to another (see also Barton & Turelli 2004). Genetic effects are not only relative to a reference genotype, but also to a scale of measurement, which will depend on the trait in question. For fitness, which is inherently on a ratio scale, multiplicative interactions are fundamental, and dominance and epistasis are most properly seen as deviances from multiplicative effects (G.P. Wagner, personal communication).

Epistasis occurs when the effect of a gene, or genotype, is different in two different genetic backgrounds (Wagner et al. 1998). The term epistasis hides a vast diversity of complex gene interactions (Rice 2000), and to make progress it is necessary to identify patterns and types of gene interactions that are evolutionarily relevant. One important distinction in this respect is between directional and nondirectional gene interactions (Hansen & Wagner 2001a). Epistasis is said to be directional if genes systematically modify each other in particular patterns or directions in morphospace. Nondirectional epistasis occurs when genes interact, but there are no systematic patterns to the interactions. We can also think of directional epistasis as curvature in the genotype-phenotype map (**Figure 1**; Rice 1998, 2000, 2002). Directional dominance can also occur when allelic effects are systematically altered in relation to the effect of the allele they are combined with. I later show that positive and negative gene interactions can have very different evolutionary consequences. Positive directional gene interactions occur when genes systematically reinforce each other's effects in a particular direction. Negative directional gene interactions occur when genes systematically diminish each other's effect. Directional epistasis for fitness is well recognized in classical population genetics as important in determining the mutation load (e.g., Charlesworth 1990a). Somewhat counterintuitively, negative epistasis for fitness on a multiplicative scale is often known as synergistic epistasis, because it means that deleterious mutations are worse when occurring together. Another important distinction is between epistatic interactions that change the order of effects of a set of alleles (or genotypes), and epistatic interactions that only change the magnitude of effects. Weinreich et al. (2005) referred to the case where the order of fitness effects of a set of alleles is different in different genetic backgrounds as sign epistasis. Obviously, sign epistasis

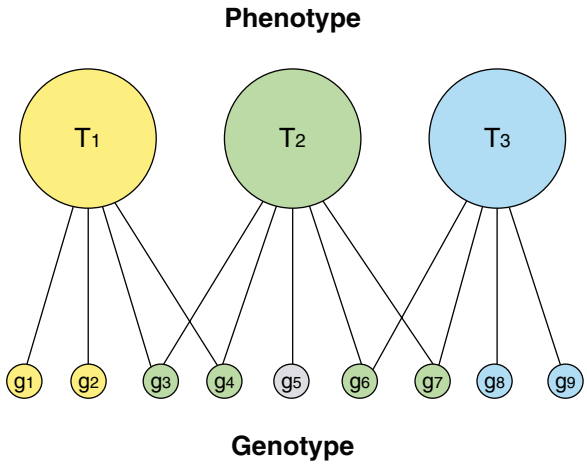

Figure 2

Pleiotropy in the genotype-phenotype map: Nine genes (g_1 to g_9) affect three traits (T_1 to T_3). The genes g_3, g_4, g_6, and g_7 affect more than one character and are said to be pleiotropic. Traits T_1 and T_3 are the most autonomous, as half the genes affecting them have no pleiotropic effects. Trait T_2 is less autonomous with only one fifth of its genes being without pleiotropic effects, but this trait has a larger mutational target size, as it is affected by more genes (five) than the others (four). Traits T_1 and T_3 are independent of each other in that they share no genes. Note, however, that a change in T_1 could affect T_2 through g_3 and g_4, and this could lead to compensatory changes in g_6 and g_7, which would affect T_3.

can lead to dramatic qualitative changes of evolutionary dynamics. Phillips et al. (2000) provide further discussion of epistatic nomenclature.

Pleiotropy is the other main factor in the genotype-phenotype relationship (**Figure 2**). A gene is said to be pleiotropic if it affects more than one character. Together with linkage disequilibrium—the statistical associations between alleles at different loci–pleiotropy is the underlying cause of genetic covariation between characters on the population level. There is, however, no simple relationship between genetic covariance and pleiotropy. Typically there will be a variety of different pleiotropic effects that may cancel or overwhelm each other, as when variation in acquisition of resources hides variation in the allocation of resources (Charlesworth 1990b; Houle 1991). Thus, even mutational covariances cannot fully describe pleiotropy. It is also important to remember that the pattern of pleiotropy depends entirely upon the delineation of characters, and from the theoretical point of view it may be more precise to investigate the dimensionality of mutations and alleles (Wagner & Mezey 2000).

GENETIC ARCHITECTURE AND EVOLVABILITY

What is Evolvability?

Literally, evolvability means ability to evolve. As reviewed by Schlichting & Murren (2004), numerous more formal definitions of evolvability have been put forward. In

my opinion, none of these captures the, admittedly varied, usage of the term very well. Hence, I venture a new formulation:

Evolvability is the ability of the genetic system to produce and maintain potentially adaptive genetic variants.

There are three things I emphasize with this definition. First, I follow Wagner & Altenberg (1996) in defining evolvability as a property of the genotype-phenotype map (the genetic system) and not as a population property. Evolvability is a disposition and thus related to variability more than to variation. Often we measure evolvability on the population level, for example, by using mean-scaled additive genetic variances (Hansen et al. 2003b, Houle 1992), but this should be seen as a measure or instantiation of evolvability and not as a definition. For clarity we may use the term population evolvability in these cases. Second, not only the production of variation is important, but also the ability to maintain variation. We want to include the capability for storing and transmitting genetic variation as a part of what makes a system evolvable. Finally, and contrary to Schlichting & Murren (2004), I view the literature on evolvability as almost exclusively concerned with the potential for adaptive evolution, and I suggest that we do not want to include the capacity for producing unconditionally deleterious mutations as a part of a system's evolvability.

With this definition in mind, I review the main aspects of genetic architecture that are important in determining the ability to produce and maintain potentially adaptive variants.

Autonomy

The existence of quasi-independent characters with the potential for evolutionary autonomy is one of the core assumptions of evolutionary biology (Lewontin 1978, Wagner 2001). In their influential review of evolvability, Wagner & Altenberg (1996) drew attention to structural features of the genotype-phenotype map that facilitate autonomy. They argued that the evolvability of a complex system depends on solving the problem of unbounded pleiotropy. If every part depends on every other part, it becomes more and more difficult to find potential advantageous changes when the number of parts is increasing. This is the essence of Fisher's (1930) geometric model of evolution, where he showed that the probability that a new mutation would bring the genotype closer to a given optimum was a decreasing function of the number of traits affected by the mutation. Wagner & Altenberg suggested that this problem could be solved through modularity of the genotype-phenotype map. If the map was divided into modules with relatively few genes having pleiotropic effects across modules, then each module would have evolutionary autonomy (**Figure 2**).

The evolutionary autonomy of a character can be quantified as a conditional evolvability, its evolvability (however defined) when other aspects of the organism are kept fixed (Hansen 2003; Hansen et al. 2003a). The conditional evolvability of a character may be only a fraction of its unconditional evolvability, as a lot of the variation and variability may stem from alleles and mutations with severe pleiotropic constraints, raising the possibility that the apparent evolvability of most quantitative characters may be illusory (Hansen & Houle 2004). In support of this many studies have found that

most genetic variation is concentrated along a few axes in morphospace (Björklund 1996; Blows & Hoffmann 2005). On the other hand, although genetic correlations are generally prevalent, they rarely equal one (Roff 1996). There are examples of large responses to artificial selection with relatively small fitness costs (Weber 1996), and one very careful study showed that there exist a very large number of underlying genetic dimensions for *Drosophila* wing morphology (Mezey & Houle 2005).

Variational autonomy is not just a question of presence or absence of pleiotropy. It depends on patterns of variability of the pleiotropic effects (**Figure 2**). If two characters are affected by the same genes in the same way, they have no evolutionary autonomy, but if the genes vary in their pleiotropic effects, for example, if one set of genes have positive effects on both characters, while another set of genes have positive effects on one character and negative effects on the other, then the two characters are largely autonomous despite all genes being pleiotropic. In fact, the two characters may have higher conditional evolvabilities in this situation because they each have a larger mutational target size. Hansen (2003) found that conditional evolvability was typically maximized at intermediate degrees of pleiotropy in several different classes of models and hypothesized that evolvability was generally maximized by genetic architectures with maximal variation in pleiotropic effects. Welch & Waxman (2003) also found that increased modularity does not necessarily increase the rate of adaptation. Baatz & Wagner (1997), however, found that hidden pleiotropic effects (i.e., pleiotropic effects that cancel to generate zero genetic correlation) could reduce the long-term conditional evolvability of a character, presumably through the evolution of covariance or higher cross moments between the traits owing to gene-frequency changes.

Pleiotropy also affects the maintenance of genetic variation in mutation-selection balance (e.g., Wagner 1989). Although less genetic variance is maintained when the genes underlying a character have pleiotropic effects, the pleiotropy also increases the mutational target size per character so as to maintain more variation per character (Hansen 2003). Still, individual genes with many pleiotropic effects will show less molecular variation (Waxman & Peck 1998).

Mutability

Mutation is the ultimate source of variation and thus sets a fundamental upper limit to evolvability. Many large-scale mutation-accumulation experiments have revealed, however, that surprisingly large amounts of phenotypic variation are generated each generation for most quantitative characters (Houle et al. 1996, Lynch et al. 1999). Combined with the general observation of abundant segregating genetic variation (e.g., Houle 1992), this observation has led to the notion that high evolvability is the rule, and that populations are rarely mutation limited. As discussed above, however, the focus on variation in individual characters ignores pleiotropic constraints, leaving levels of conditional evolvability poorly understood (e.g., Blows & Hoffmann 2005, Hansen & Houle 2004, Galis 1999). The degree of pleiotropic constraints on mutational variation is little explored and also likely to be more severe than pleiotropic constraints on standing variation because mutational variation is not yet filtered by selection.

In interpreting mutational variability we must distinguish between rates and effects. Traits may differ in their mutational variability owing to differences in the effects of the mutations that occur (i.e., reflecting different degrees of canalization), or because of the rate at which the mutations appear. Although the molecular mutation rate differs between different organisms and different regions of the genome (Drake et al. 1998), the most important determinant of the rate of mutation affecting a phenotypic trait is the mutational target size, the number, size, and mutability of the genes and regulatory elements that affect a trait (Houle 1998). Houle (1992, 1998) has argued that mutational target size can explain the generally higher population evolvability of life-history traits and fitness components as compared to morphological traits.

Experimental evidence for the importance of mutation rates for evolvability comes from de Visser et al. (1999), who compared rates of adaptation in different mutator strains of *Escherichia coli* with orders-of-magnitude different mutation rates, and found evidence of mutation limitation on evolvability in small, poorly adapted populations, but not in large or well-adapted populations.

Coordination

The evolvability of a complex system depends crucially on its potential for coordinated variability (Riedl 1977). Such coordination arises through development, or through the functional coordination of the organism. The general principle is that simple, nonobstructive changes in developmental processes can lead to large changes in phenotype, which may have a higher likelihood of being advantageous because they are structured by the developmental process. Examples include changes in time or rate of development as in classical cases of heterochronic and allometric change (e.g., Gould 2002).

Developmental modularity is one source of coordinated change through co-option. Co-option consists of employing or expressing one part of the organism—a gene, a gene network, a developmental program, an organ, a physiological response, or a behavior—in a new context. Evidence of evolution by co-option is well documented (e.g., Gerhart & Kirschner 1997, Raff 1996). For example, the widespread observation of genetic programs or modules expressed in different tissues and at different stages of development is evidence of co-option (von Dassow & Munro 1999).

Gene Interaction

Although the response to selection is generally thought to depend only on the additive genetic variance, epistasis may have dramatic effects on the response to selection even over a few generations (Carter et al. 2005, Hansen & Wagner 2001a, Hansen et al. 2006; **Figure 3**), because epistasis makes gene effects become evolvable, and directional epistasis enables rapid changes in additive effects, additive variances, and evolvability. In contrast, Fisherian statistical definitions of gene effects implicitly assume nondirectional epistasis, which has hardly any effect on the response from standing variation (**Figure 3**). Estimates of epistatic variance components are mixtures of positive and negative epistasis, as well as different types of sign epistasis, etc. They are therefore not suitable in predicting evolvability and evolutionary dynamics.

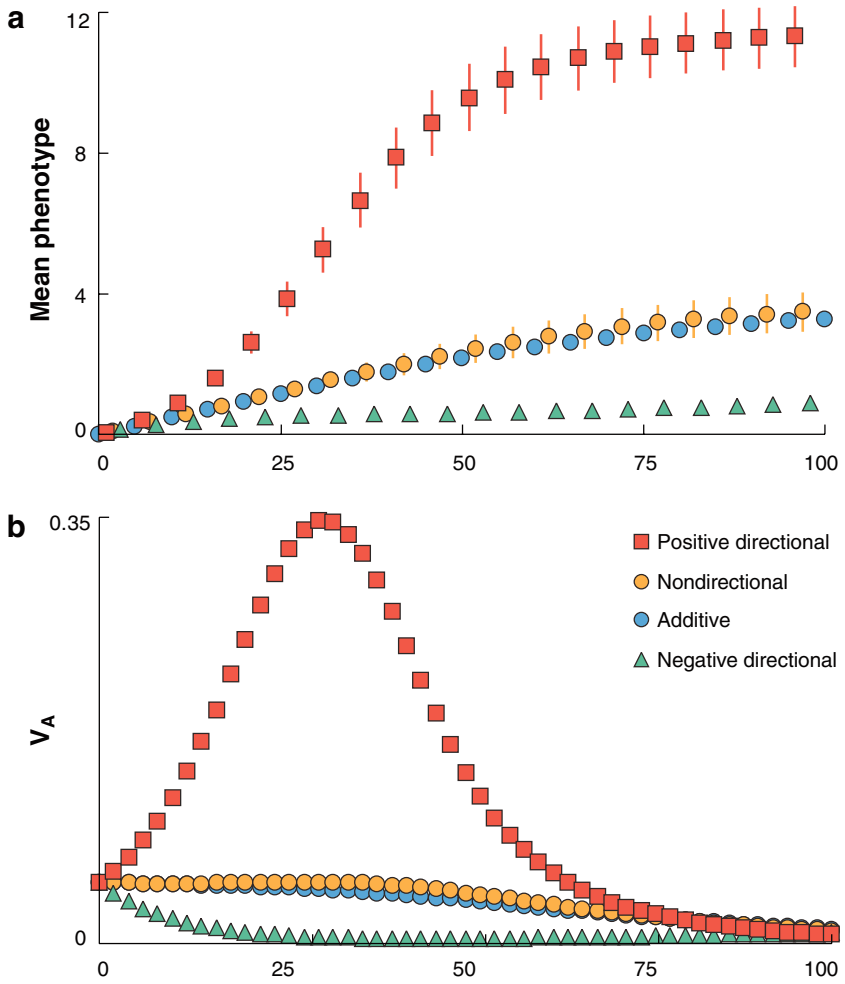

Figure 3

Individual-based simulations illustrating the effects of epistasis on the response to selection from standing genetic variation. Panel (*a*) shows the mean phenotype and (*b*) shows the additive genetic variance as averages over 100 populations subject to linear directional selection. Bars in (*a*) indicate one standard deviation over the ensemble. Four different genetic architectures are shown: pure additive, positive directional epistasis, negative directional epistasis, and nondirectional epistasis. Each simulated population consists of 1000 individuals, and there are 20 segregating loci connected with normally distributed epistasis with mean epistatic effects being 1, 0, or -1 depending on treatment. Modified from Carter et al. (2005).

An influence of patterns of gene interactions on evolvability also appears in other models. For example, analyses of Boolean gene networks indicate that evolvability is maximized at intermediate connectivity between genes (Frank 1999, Kauffman 1993).

A substantial theoretical and empirical literature has developed on how evolvability can increase during a population bottleneck by epistatic variance being converted into additive variance by genetic drift (see Barton & Turelli 2004 for an overview and general analysis). The changes in additive genetic variance due to drift are mainly the result of random evolution of additive effects of alleles caused by their epistatic interaction with a randomly changing genetic background. There is thus no direct relationship between changes in epistatic and additive variance components, and the term conversion is a misnomer. Barton & Turelli (2004) argued that these changes are unlikely to be important. Furthermore, not just drift, but any means of change in

the genetic background may cause the evolution of additive effects when epistasis is present. If the epistasis is directional, systematic changes owing to selection will have more powerful effects on the additive genetic variance. For example, Bradshaw & Holzapfel (2000) and Bradshaw et al. (2005) evoked drift to explain increased levels of additive genetic variance for photoperiodism and developmental time in recently colonized northern populations of pitcher-plant mosquitoes (*Wyeomia smithii*). Selection on a directional epistatic architecture is a more plausible alternative.

Epistasis also affects the maintenance of variation. Hermisson et al. (2003) showed that a multilinear epistatic architecture, i.e., an architecture where gene effects are linear functions of the effects of other loci, always maintains less genetic variation in mutation-selection balance than what is maintained by an additive architecture, and sometimes much less. The mutation load, however, may increase or decrease depending on the directionality of epistasis (Hansen & Wagner 2001b, Kondrashov 1988). Sign epistasis has the potential for generating protected polymorphisms and can thus sometimes maintain large amounts of genetic variation in the absence of mutation (e.g., Gavrilets 1993, Gimelfarb 1989). Overdominance for fitness (heterozygote superiority) is a similarly powerful mechanism for maintenance of variation (e.g., Turelli & Barton 2004), but appears to be rare (Charlesworth & Charlesworth 1987).

Hidden and Cryptic Variation

One reason why epistatic genetic architectures tend to maintain less genetic variation under stabilizing selection is because epistatic interactions allow the evolution of reduced gene effects (canalization). Although this leads to less variation expressed at the phenotypic level it also allows for the accumulation of cryptic molecular variation hidden from selection. If cryptic variation can be revealed, it may fuel rapid adaptation. A genetic system can hide genetic variation through negative linkage disequilibrium, where alleles with opposite effects on a trait occur together to produce a gamete with a small total effect, or through canalization, where the effects of alleles are reduced by the genetic background through epistasis.

In a sexually recombining population it is difficult to build up much variation in linkage disequilibrium unless the loci are very strongly linked (Bürger 2000, Hastings 1989). Linkage disequilibrium may, however, be very important if recombination is infrequent, such as in cyclical parthenogens where the life history alternates between parthenogenetic and sexual phases (Lynch & Gabriel 1983). Lynch and coworkers (Deng & Lynch 1996, Pfrender & Lynch 2000) studied the accumulation and release of genetic variance in a cyclically parthenogenic population of *Daphnia pulex*. During the parthenogenetic phase hidden genetic variance accumulates as clones with successful genotypes increase in frequency. During the sexual phase this hidden variation is released leading to increased population evolvability. They also observed genetic slippage, as sexual reproduction reduced fitness components by breaking up coadapted gene complexes. Although the genetic slippage is a fitness drawback to sexual reproduction, one can easily imagine that the increased evolvability could be beneficial if the resting eggs produced from sex are dispersed to hatch in a new environment, or if parasites or predators are adapting to the more successful clones. The

maintenance of sexual reproduction in such life histories is a candidate example for adaptive evolvability.

The idea that genetic variation may get canalized under stabilizing selection and released under directional selection or under stress originated with Waddington (1953, 1957). I discuss canalization in a later section and here focus on the release of variation. Hermisson & Wagner (2004) provided a general theoretical analysis of how cryptic variation can be released during a genetic or environmental shift. They showed that a release of genetic variation is expected to happen even without canalization of the wild type. This counterintuitive result can be understood through their metaphor of the moving rug. Cryptic variation can be likened to potentially deleterious mutations accumulating like dirt under a rug. During a genetic or environmental perturbation, the rug is changed to expose the mutations. This can happen either by shrinking the rug (classical decanalization, directional epistasis) or simply by moving the rug at random (nondirectional epistasis), which also exposes cryptic variation. Note that this result undermines some of the classical evidence for adaptive canalization of the wild type, which is based on observing more genetic variation after a perturbation.

Evolutionary capacitors are mechanisms that reveal cryptic variation in a reversible fashion. The discovery that they may be common is one of the most exciting recent developments in evolutionary genetics. It started with Rutherford & Lindquist's (1998) study of the heat-shock protein Hsp90. If *Drosophila* Hsp90 protein is rendered ineffective by mutation or chemical inhibition, large amounts of cryptic genetic variation are revealed in a variety of traits. Based on the idea that Hsp90 acts as a specialized chaperone for signal-transducing proteins, Rutherford & Lindquist proposed that Hsp90 normally acts to buffer variation in signal-transduction pathways, but during times of stress Hsp90, as a heat-shock protein, may be titrated from its normal functions by binding to denatured protein, so that cryptic variation in the signal-transduction pathways is revealed. They proposed that this is an adaptation to specifically increase evolvability during periods of stress. It was later shown that Hsp90 acts the same way in *Arabidopsis* (Queitsch et al. 2002), and similar mechanisms were discovered involving heat-shock proteins in bacteria (Fares et al. 2002) and prions in yeast (Masel & Bergman 2003, True & Lindquist 2000). It is also plausible that general stress can act as a capacitor to reveal variation (Badyaev 2005, Rutherford 2000). Theoretical work has revealed many possible mechanisms for capacitance (Bergman & Siegal 2003, Eshel & Matessi 1998, Hansen et al. 2000, Masel 2005, Masel & Bergman 2003). In particular, Bergman & Siegal (2003) found that knocking out any gene in a gene network would tend to reveal variation [as expected from Hermisson & Wagner's (2004) general analysis]. The crucial and still open question is whether there exist systems that are specifically adapted for revealing variation in times of need.

Robustness may be a general feature of genetic systems that generates cryptic variation (Wagner 2005). It has been argued that the genotype-phenotype map is usually overdetermined in the sense that there are more genes than traits, and that this implies the existence of large neutral networks or neutral spaces of equivalent genotypes (Gavrilets 2004, Kauffman 1993, Schuster et al. 1994, Wagner 2005, Weiss & Fullerton 2000). Cryptic variation may accumulate in neutral spaces, and neutral drift leads to possibilities for population divergence and the evolution of novelty.

Genome Dynamics

The dynamic genome of eukaryotes is a great source of evolvability extending far beyond classical recombination. The fact that genes generally function independently of their position in the genome allows a number of genomic changes such as gene or genome duplication, gene transposition, gene conversion, and inversion, which may all generate novel possibilities. Gene duplication in particular is an important mechanism for generating new genes that may be free to evolve novel functions (Ohno 1970, Raff 1996) or to increase specialization of gene function (Force et al. 1999).

Of course, recombination of genetic material both within and between genomes is an important mechanism of evolvability allowing the decoupling of good from bad genetic material, as well as the rapid generation of good gene combination. On the other hand, recombination also acts against evolvability by precluding the maintenance of coadapted gene complexes.

The Major Transitions

Changes in genetic architecture and evolvability come from changes in the development or structure of the organism. The most fundamental changes involve major reorganizations of the organism. Maynard Smith & Szathmáry (1995) discussed the major transitions in evolution, which they described as major changes in how the organism transmits genetic information. Examples include the evolution of multicellularity, which vastly increased the potential for specialization and reduced the need for genetic specification by building the organism of repeated units, and the evolution of sex and recombination, which allows genes to adapt more easily without inferring with each other, and allowed large increases in genome complexity. Dennett (1995) makes much the same point when he eloquently describes the emergence of evolutionary cranes, which are biological devices that ease the building of adaptations in "design space." Increases in evolvability happen when new cranes, such as sex, multicellularity, a nervous system, a new sensory modality, or communication system, emerge to generate qualitatively new variational possibilities.

Major transitions or novelties may originate as historical contingencies, and are thus not easily accessible to population-genetic analysis. Their maintenance, however, is a question of population genetics, as evidenced by the huge literature on the maintenance of sexual reproduction, but I will not develop this important topic here.

EVOLUTION OF GENETIC ARCHITECTURE: GENERAL PRINCIPLES

Modes of Change

Beyond changes in genotype frequencies, we can identify three genetic mechanisms for the evolution of genetic architecture. The first is through epistatic interactions with an evolving genetic background. Epistasis means that gene or genotype effects depend on the genetic background, and when the background changes because of

selection, drift, mutation, or any other mechanism, gene effects will change. The character of these changes depends on the type of epistasis involved. For there to be a systematic relationship between changes in the phenotype and changes in gene effects and evolvability, the epistasis must be directional. Directional epistasis is the basis of canalization and the evolution of evolvability. Directional dominance may have similar effects.

Genetic architecture can also evolve through heritable allelic effects. If there is a correlation between the effects of alleles and the mutations they can generate, then the fixation of an allele will alter the mutational-effects distribution, and thus the variability of the trait. This can include changes in pleiotropy and epistasis. If, for example, an allele that has gained or lost a regulatory element is fixed, then most subsequent mutations to this locus will inherit this particular gain or loss. There is thus a correlation between the effects of the allele and its mutations. The generality of this scenario is supported by a high degree of modularity in the regulatory region of most genes (Stern 2000). This modularity means that many mutations will affect only a part of the spatiotemporal expression patterns of the gene, so as to set up a strong correlation between the effects of alleles and their mutations. For example, if the allele gains a regulatory element that expresses the gene in a novel context, the gene may gain novel pleiotropic effects, and these pleiotropic effects will be inherited by all further mutations of this allele that do not interfere with the new regulatory element. A possible example is discussed below.

Just like genotype effects can evolve through epistatic interactions with a changing genetic background, they can evolve through genotype-by-environment interactions with a changing environment. This may be particularly important when there are systematic biotic changes in the environment or when there are feedback mechanisms between genetic and environmental changes, as when the environment consists of other individuals (Lynch 1987, Wolf 2003).

Modes of Selection

Because genetic architecture is a function of general organismal development and structure, it can be affected by basically any evolutionary change in the organism. It is thus naive to expect any single force of selection to dominate or to think that genetic architecture evolves as a unit. Instead we must look for the effects of selection on the individual elements of architecture and be open to different answers in different cases.

We may recognize three main classes of hypotheses for the evolution of variational properties (de Visser et al. 2003). The first class is the adaptation hypotheses, which posits that variational properties are directly influenced by selection on variation or variability. The two main possibilities are that the genotype-phenotype map could be adapted to increase evolvability, or that it could be adapted to increase robustness toward genetic disturbances (mutation, recombination, hybridization, etc.). These could well be group-level adaptations.

The second class is the intrinsic hypotheses, which posit that variational properties are intrinsic features of the organism not under direct selection. As the genotype-phenotype map is fundamentally linked to organismal design, it is likely to be strongly

affected by indirect selection stemming from a variety of sources. Thus, we face the likely prospect that many or most features of genetic architecture are not primary adaptations related to variability, but instead indirect effects of selection on characters themselves, as opposed to selection on the variational properties of characters.

The third class is the congruence hypotheses, which are intermediate between the adaptation and the intrinsic hypotheses. Here we start with the premise that genetic and environmental sources of variability are often affected by the same functional pathways in the organism, such that selection to structure (usually to reduce) environmental variation will lead to correlated changes in the structure of the genetic architecture. Thus organismal architecture is not adapted to structure genetic variation, but it is adapted to structure environmental variation. The generic example of a congruence hypothesis is Haldane's view that dominance evolved owing to selection on the wild-type allele to produce excess enzyme to cover for unusual environmental circumstances. The consequence is that the wild-type allele also evolved the capacity to cover for alleles with reduced activity; dominance evolves, dominance is selected, but dominance is not an adaptation for genetic robustness.

The shape of the fitness function, the mapping from phenotype to fitness, is instrumental in understanding the evolution of variational properties. A fundamental result to bear in mind is that variation is favored when the fitness function is convex (positive second derivative), and that variation is selected against when the fitness function is concave (negative second derivative) (Layzer 1980). Hence, stabilizing selection reduces variation and disruptive selection increases variation, whereas directional selection may favor or disfavor variation depending on the exact curvature of the fitness function. The direct selection pressure on genetic correlations is determined by the second cross derivatives of the fitness function so that if selection on trait 1 leads to an increased sensitivity of fitness to trait 2, then there is selection for positive correlation between the two traits (Layzer 1980).

Note that the evolutionary quantitative genetics concept of stabilizing selection as a concave peak in the adaptive landscape (e.g., Lande & Arnold 1983) that I use here is different from the stabilizing-selection concept of Waddington (1957) and Schmalhausen (1949), who used the term narrowly to refer to intrinsic selection for developmental stability. Similarly, the term canalizing selection is sometimes used explicitly to refer to selection to reduce allelic effects, as opposed to selection on gene frequencies (Wagner et al. 1997). A more formal way of understanding the effects of selection on the genotype-phenotype map, and making notions such as canalizing selection precise, is to decompose selection into different gradients with interpretable effects. Rice (1998, 2002) has developed a very general system of this sort. He used Taylor expansions to write the mapping from genotype (or any set of underlying variables) to phenotype to fitness as a set of terms, each consisting of factors being fitness gradients and derivatives of the genotype-phenotype map. One of these terms can be taken to represent canalizing selection in the sense that, if the fitness function is quadratic, it describes a force that moves the population toward a point of minimum curvature of the genotype-phenotype map, and thus toward maximum robustness. Hermisson et al. (2003) obtained a similar result from a different decomposition.

The classical approach to studying selection on genetic architecture is through modifier models. A modifier is a hypothetical gene that does not have a direct effect on the trait in question, but can alter the effect of other genes on the trait, or affect other aspects of architecture such as mutation or recombination rates. A general result from this type of model is that selection on the modifier is on the second order of, and thus much weaker than, selection on the direct effects (e.g., Proulx & Phillips 2005). The use of very few loci may, however, give a misleading picture of the opportunity for selection on variability. The more loci that are affected by the modifier, the larger the opportunity is for selection (Proulx & Phillips 2005), and the more modifiers there are, the larger the evolvability. The concept of a modifier of gene effects is also problematic in that the symmetry of epistasis (Hansen & Wagner 2001a) implies that a modifier must have direct effects on the phenotype for some state of the modified locus. The evolution of modifiers will usually be determined by their direct effects. For these reasons, it may be more instructive to focus on sets of mutually interacting loci.

EVOLUTION OF THE GENOTYPE-PHENOTYPE MAP

Canalization and Genetic Assimilation

The general hypothesis that emerged from the classical work on canalization (Rendel 1967, Scharloo 1991, Waddington 1957) was that wild types, i.e., the common genotypes found in natural populations, were typically canalized in the sense that they had evolved robustness toward genetic and environmental perturbances. The evidence is based on the common observation that perturbed individuals, such as hybrids, carriers of large-effect mutations, or stressed individuals, are often more variable than the wild type (Flatt 2005, Scharloo 1991; but see Hermisson & Wagner 2004). As illustrated in **Figure 1**, this can be explained with a genotype-phenotype map that is flat in the region of the wild type and steeper away from the wild type (Moreno 1994, Rendel 1967). Perturbances could then shift the genotype away from the flat, canalized region into the steeper region where variation can be expressed. If we think of the genotype in **Figure 1** as an underlying physiological variable (e.g., Rice 1998), this model can also explain genetic assimilation, because environmental perturbations may push the physiological variable into the steeper regions where phenotypic differences between genotypes will be amplified and can thus be selected upon.

Does Stabilizing Selection Favor Canalization?

The question remains, why should we expect to see the wild type in the robust regions of the genotype-phenotype map? Waddington (1957) proposed that this was caused by selection against variation. Because stabilizing selection is generally expected to be the most common mode of selection, it has the potential to explain the general phenomenon. There is a body of recent theory addressing this question (Azevedo et al. 2006; Eshel & Matessi 1998; Gavrilets & Hastings 1994; Hermisson & Wagner 2004; Hermisson et al. 2003; Kawecki 2000; Proulx & Phillips 2005; Rice 1998, 2002; Siegal & Bergman 2002; van Nimwegen et al. 1999; A. Wagner 1996; Wagner et al.

1997). Although all studies find that genetic canalization is possible under stabilizing selection, they differ on its universality, power, and exact mechanisms.

In general, stabilizing selection for an optimum phenotype controlled by a polygenic system allows evolution to choose among many equivalent genotypes. A number of researchers have found that selection in such a situation tends to favor the more robust genotypes in the flatter regions of the genotype-phenotype map or into the interior of the neutral space (e.g., Rice 1998, 2002; van Nimwegen et al. 1999; A. Wagner 1996). Hermisson et al. (2003), however, found that complex epistatic interactions often introduce constraints that limit optimal robustness. In an analysis of the multilinear epistatic model under stabilizing selection, they found a general tendency to evolve to reduce additive genetic variation, but mutational variability is not generally minimized. The problem is that, in a complex epistatic system, the canalization of different loci may conflict with each other and with selection to keep the mean at optimum. Some loci, typically those with high mutation rates, may become canalized, but at the price of decanalizing other loci. This predicts a negative correlation between mutation rates and mutation effects if adaptive canalization has taken place.

Wagner et al. (1997) found that, near mutation-selection equilibrium, genetic canalization was relatively independent of the strengths of stabilizing selection, as stronger selection removed variation thereby reducing the opportunity for selection on genetic canalization. In general, the opportunity for selection on genetic canalization is strongly dependent on the mutational target size. Studies of two-locus models have typically found that genetic canalization is implausible, as selection becomes too weak (e.g., Nowak et al. 1997, Proulx & Phillips 2005, Wagner 1999). It has been argued that there is much less opportunity for direct selection for genetic canalization than there is for environmental canalization because there is much less mutational than environmental variation (e.g., Wagner 2005). If true, this would make the congruence scenario much more likely than the adaptive scenario. This neglects, however, to take into account that selection acts on segregating alleles and not only on new mutations, and the variation generated by segregating alleles is usually comparable in magnitude to the environmental components of variation (e.g., Houle 1992). Thus, the opportunities for genetic and environmental canalization may be comparable. The likelihood of the adaptive scenario may depend more on the commonality of mechanisms that can canalize many loci at once. Selection for canalization of individual loci is weak, but selection for the canalization of large systems of loci is stronger. Similarly, the opportunity for environmental canalization may depend on the commonality of mechanisms that simultaneously provide robustness toward many sources of environmental disturbance.

These results leave us with a complex picture of the effects of stabilizing selection on genetic canalization. A direct effect of selection is theoretically possible, but depends on the details of genetic and organismal architecture. One general insight is that canalization may be less dependent on strength of stabilizing selection than it is on mutation rates and target sizes (Hermisson et al. 2003, Houle 1998, Proulx & Phillips 2005, Wagner et al. 1997). The models also suggest some plausible alternatives involving indirect selection based on environmental robustness or developmental

stability. Genetic canalization may also be effective on deleterious variation generated by segregation or migration load (Proulx & Phillips 2005).

Environmental Canalization and the Congruence Hypothesis

Stabilizing selection favors increased robustness toward environmental noise, and genetic mechanisms that reduce such noise can be favored and lead to the evolution of environmental canalization. If there is a genetic link between the mechanisms leading to environmental canalization and genetic canalization, the latter can evolve due to indirect selection. This is known as the congruence hypothesis for the evolution of genetic canalization, which has been found plausible by a number of theoreticians (Ancel & Fontana 2000, de Visser et al. 2003, Gavrilets & Hastings 1994, Nowak et al. 1997, Wagner et al. 1997).

A link between genetic and environmental robustness is plausible, because genetic and environmental disturbances may often affect the same functional pathways in the organism, and any increase in the robustness of a pathway leads to both genetic and environmental canalization. Evidence for a correlation between environmental and genetic robustness has been found in studies of RNA folding (Ancel & Fontana 2000), in the effects of heat-shock proteins (Rutherford 2000), and in effects of P-element insertions in *Drosophila* (Stearns et al. 1995). Particularly striking is the recent finding by Rifkin et al. (2005) of a strong correlation between mutational and environmental variance in gene expression in a panel of mutation accumulation lines of *Drosophila*. Dworkin (2005b), however, did not find a link between environmental and genetic canalization in *Drosophila* bristles.

A variant of the congruence hypothesis is that genetic canalization evolves as a side effect of selection for developmental stability (e.g., Gavrilets & Hastings 1994; Siegal & Bergman 2002). While theoretically plausible, a number of recent studies failed to find a link between canalization and measures of developmental stability such as fluctuating asymmetry (Debat et al. 2000, Dworkin 2005a, Milton et al. 2003, Pélabon et al. 2004, Rutherford 2000).

Does Directional Selection Favor Decanalization?

The other part of the classical theory of canalization is that directional selection away from the canalized wild type should lead to decanalization and increased evolvability. A decanalizing effect of directional selection has been suggested by a number of theoreticians (e.g., Layzer 1980, Rice 1998, Wagner 1996, Wagner et al. 1997). The results of Carter et al. (2005) and Hansen et al. (2006), however, show that this depends on the directionality of epistasis (**Figure 3**). Positive directional epistasis indeed leads to decanalization under directional selection, but negative directional epistasis causes canalization. The exact curvature of the fitness landscape is also likely to be important.

Prolonged response to directional selection may not be frequent in nature, and an important, but neglected, area of theoretical research is investigating the effects of fluctuating directional selection, or moving optima, on the evolution of genetic

architecture. To my knowledge, Kawecki's (2000) simulation study is the only contribution. Kawecki considered the evolution of a modifier of the effects of a set of other loci that additively determines a trait under different forms of fluctuating selection. He found that a canalizing allele was favored when the period of fluctuation was short, but that polymorphisms or advantages to decanalization may result when the period becomes longer. Given the results on directional selection, we expect that the details of genetic architecture, such as the directionality of epistasis would be important, and further investigations of different genetic architectures under fluctuating selection are called for. I note that fluctuating selection can favor increased mutation rates through mutation-rate modifiers hitchhiking with the beneficial alleles they create (e.g., Ishii et al. 1989). See also Bürger & Gimelfarb (2002) and Jones et al. (2004) for analysis of the effects of fluctuating optima on the maintenance of genetic variation in additive architectures.

A recent theoretical study addresses the effects of disruptive selection on the evolution of genetic architecture. Kopp & Hermisson (2006) showed with a modifier approach that disruptive selection generated by intraspecific competition favors the evolution of an asymmetric genetic architecture where most of the effects are concentrated on a few major loci.

Evolution of Pleiotropy

Pleiotropy can evolve through differential epistatic modification of different traits (Cheverud 2001; Cheverud et al. 1997, 2004; Wolf et al. 2005). Although this process still lacks dynamical analysis, its operation can be extrapolated from the results on the evolution of single trait architecture. If the epistatic modifications of the effects of a gene on different traits are the same (i.e., not differential), then pleiotropy will not change. If epistasis is differential, then changes in pleiotropy will depend on the details of how epistasis acts on the different trait effects, and in particular the directionalities of this epistasis. Thus, we need to look for differential directional epistasis. For a precise understanding of the dynamics of pleiotropy we must distinguish between trait-specific epistatic effects and cross epistasis, where changes in gene effects on one trait modify effects of other genes on another trait (Hansen & Wagner 2001a, Wagner & Mezey 2000).

Pleiotropy can also evolve through heritable allelic changes in modular regulatory sites. There are no established models or examples of this, but the possibility may be illustrated with the gene *Bab2*, which affects abdominal pigmentation and trichome patterning in *Drosophila* (Gompel & Carroll 2003). In *D. melanogaster Bab2* represses melanic pigmentation and trichomes, and explains much of the segregating variation in abdominal pigmentation, and presumably also in trichome patterns, making it likely that the two are pleiotropically correlated. In some other species, however, *Bab2* has by various mechanisms lost its effects on either one or the other of the two traits. Presumably pleiotropy is also lost and further changes in the expression pattern of *Bab2* will affect only one of the traits.

The classic question on the evolution of pleiotropy is whether selection for a particular functional relationship between traits can lead to a corresponding functional

organization of the pleiotropic effects (e.g., Cheverud 1996, Riedl 1977, G.P. Wagner 1996)? For example, can selection strengthen pleiotropy between two traits that are functionally interdependent, and can it decouple two traits that are functionally unrelated? Cheverud (1982) argued that the G-matrix would evolve to match the shape of the fitness landscape. G.P. Wagner (1996), however, argued that stabilizing selection is not a very powerful mechanism for the evolution of pleiotropic integration and/or decoupling, as it would favor canalization in all directions. This is underscored by the observation that canalization is relatively unaffected by the strength of stabilizing selection (Wagner et al. 1997). Instead, G.P. Wagner (1996) suggested that fluctuating directional selection on one character combined with stabilizing selection on another character could be a powerful mechanism for the evolution of pleiotropic decoupling. These suggestions need be investigated with formal models. The sensitivity of the evolution of gene effects to directional epistasis suggests that these hypotheses may depend on genetic detail. It seems plausible, however, that a combination of directional and stabilizing selection may favor alleles with heritable loss of pleiotropic effects, and thus support Wagner's hypothesis. At the population level, joint directional selection on two characters can increase their genetic correlation when there are alleles with different pleiotropic effects in the population (Slatkin & Frank 1990).

In general, pleiotropy is determined by organismal architecture and may evolve by intrinsic mechanisms (Houle 2001, Klingenberg 2005). An understanding of the evolution of pleiotropy by intrinsic mechanisms requires an understanding of the development of the specific phenotypes in question. The continued progress of research in developmental biology will prove illuminating.

Evolution of Gene Interactions

Epistatic gene interactions are not just a cause of the evolution of individual gene effects, they are also themselves evolvable according to similar principles. A particular epistatic interaction can be modified by higher-order epistasis (Hansen & Wagner 2001a, Hansen et al. 2006, Wagner et al. 1998), and epistatic interactions can evolve through inherited allelic interaction effects, as when an allele loses or gains the ability to physiologically modify another locus.

Hansen et al. (2006) studied the evolution of epistatic interactions under long-term directional selection. The evolution of pairwise interactions is influenced by the directionality of third-order interactions and, in general, the evolution of m-order interactions is influenced by the directionality of m+1-order interactions. In addition to this there was a strong inherent tendency for positive epistatic interactions to weaken and for negative epistatic interactions to strengthen when epistasis is measured with reference to the mean genotype of the evolving population. A tendency toward the evolution of negative epistasis has also been found in simulations based on several specific models (Azevedo et al. 2006; Wilke & Adami 2001). Hansen et al. (2006) identified three types of nonadditive quasi-equilibrium architectures that, although not strictly stable, could be maintained for an extended time: (*a*) nondirectional epistatic architectures, (*b*) canalized architectures with strong erratic epistasis, and (*c*) near-additive architectures where epistasis gets weaker.

Hermisson et al. (2003) studied the evolution of pairwise epistatic interactions under a balance between mutation and stabilizing selection and found that directional epistasis measured with reference to the mean genotype tends to disappear. If some directional epistasis remains at equilibrium, it will act as a constraint and keep the population mean away from the optimum. Liberman & Feldman (2005) found that stronger epistasis could evolve in a two-locus system with a modifier locus under conditions of polymorphic equilibrium for the two loci. The key to this result appears to be that mean fitness was an increasing function of the epistasis parameter. In general, however, we have shown that epistasis does not necessarily evolve to maximize fitness or evolvability (Carter et al. 2005, Hansen et al. 2006, Hermisson et al. 2003).

Dating back to Wright's shifting-balance theory there has been a lot of interest in the evolution of coadapted gene complexes, combinations of alleles from different loci that work well together. A supergene can only be effectively maintained segregating in a population under strong linkage, and few examples are known. There is, however, good evidence for coadapted genomes from crosses between isolated populations (e.g., Fenster & Galloway 2000). In fact, postzygotic isolation is generally thought to result from genetic incompatibilities between isolated genomes. Such coadaptation may result from the fixation of new mutations that work well with, or at least are compatible with, the genetic background. Randomness in the order of appearance and fixation of new mutations will typically make the genetic architectures of isolated populations diverge (Mani & Clarke 1990). In this sense, we expect coadapted, integrated genomes to evolve.

Evolution of Dominance

Mutations with deleterious effects on fitness generally have a degree of recessivity, and various hypotheses to explain this phenomenon have been with us almost since the beginning of population genetics. Fisher, Haldane, and Wright took different positions that may be described as adaptive, congruent, and intrinsic (de Visser et al. 2003). Fisher's view that dominance is an adaptation to minimize the deleterious effects of mutations is now viewed as problematic on both theoretical and empirical grounds. Theoretically, it has long been argued that the strength of selection on dominance modifiers is very weak (e.g., Proulx & Phillips 2005), and Fisher's model has not been able to explain why mutations with small effects should be close to additive, whereas those with large effects should be recessive (e.g., Phadnis & Fry 2005). Orr (1991) made the telling observation that dominance also occurs in species of *Chlamydomonas* that spend almost all of their life cycle in a haploid state.

Haldane, and to some extent Wright, held a congruence view where dominance was seen as a safety factor against disturbances. However, a model of dominance as an intrinsic consequence of enzyme biochemistry became the favored explanation when Kacser & Burns (1981) showed that dominance is inherent in models of metabolic flux, and that these models can also explain why dominance is correlated with the homozygous effect of the mutation (for review see

Keightley 1996). The Kacser-Burns theory is, however, limited in that it applies only to flux in linear pathways under Michelis-Menten kinetics, and cannot explain the general phenomenon (e.g., Bagheri-Chaichian & Wagner 2004, Omholt et al. 2000, Phadnis & Fry 2005). Furthermore, Bagheri-Chaichian et al. (2003) point out that epistasis makes dominance evolvable in the same sense as it makes gene effects evolvable, and thus they challenge the notion that any particular pattern of dominance is inevitable.

Genetic Architecture: Intrinsic or Adapted?

Most theory on the evolution of genetic architecture focuses on adaptive or congruent scenaria, as the selection pressures are well defined. The intrinsic scenario is harder to represent in a population-genetics framework, as almost any complex relationship between genotype and phenotype would lead to changes in genetic architecture under selection on the phenotype and the character of the changes would depend on the details of the system. We may recognize two classes of models of intrinsic phenomena. One type are general, but very abstract, models that look for intrinsic properties such as order or robustness (e.g., Kauffman 1993). These may provide some general insight, but do not yield much in terms of testable hypotheses or measurable parameters in empirical systems. The other class of models are highly specific representations of particular physiological or developmental genotype-phenotype maps, as for instance in models of metabolic or gene-regulatory networks. The problem with these models is that their results are highly system specific.

Models of metabolic networks have been used to predict patterns of dominance (see above) and epistasis (Bagheri-Chaichian & Wagner 2004, Bagheri-Chaichian et al. 2003, Keightley 1989, Szathmáry 1993, Wagner et al. 1998). One general insight from these models is that both dominance and epistasis are likely to be ubiquitous. Similar results emerge from models of gene-regulatory networks (Omholt et al. 2000). It is, however, doubtful how far any particular patterns should be extrapolated. For example, Szathmáry (1993) showed that mutations acting on different enzymes in a linear unsaturated pathway would act antagonistically on flux, but were likely to act synergistically on the pool size of metabolites, as long as these were not downstream from both mutated enzymes. He then argued that we should expect antagonistic epistasis in prokaryotes, because their fitness is determined by flux, but synergistic epistasis in eukaryotes, because fitness here would be determined by pool sizes. This argument ignores the complexity of physiology where metabolic pathways normally involve feedback loops and forks and the fact that the mapping from genotype to phenotype would usually consist of many physiological or developmental steps. A metabolic reaction is but one step in the process. It therefore appears difficult to predict specific epistatic properties of most genotype-phenotype maps from metabolic first principles.

Certain generic properties, such as robustness, may, however, exist. Wagner (2005) argued that there are many equivalent solutions to any given biological problem and that evolution tends to find solutions supported by many possible genotypes just by chance. These solutions also tend to be robust toward mutations, because many mutations are other genotypes coding for the same solution, particularly because

equivalent solutions tend to form connected networks in genotype space (e.g., Schuster et al. 1994). Thus, robustness may be intrinsic to many biological systems. Many researchers have also found robustness in specific systems (e.g., Alon et al. 1999; Ancel & Fontana 2000; Barkai & Leibler 1997; A. Wagner 1996, 2000, 2005; Wagner & Stadler 1999; von Dassow et al. 2000).

Evolution of Genome Architecture

The number and type of genes affecting a character is the basis of its genetic architecture, as it will determine its mutational target size, the number of possible gene interactions, and the potential for specialization and refinement of the character's variational properties. New genes affecting a character appear by recruitment (cooption) or by gene duplication. These two events have different consequences for genetic architecture; recruitment tends to increase the integration of the genotype-phenotype map, while duplication tends to favor parcellation.

A recruited gene may normally come with heritable pleiotropic effects on other characters (its original function) and may act to increase the complexity and pleiotropy of the genotype-phenotype map. In contrast, a gene duplication may produce a new gene that is similar to an old gene, and have the same pleiotropic and epistatic effects. Importantly, gene duplication can also generate genes that are more specialized through subfunctionalization, where each duplicate loses different parts of the original functions (e.g., by losing different regulatory regions). Force et al. (1999) showed that subfunctionalization is a likely outcome of a gene duplication event. A subfunctionalized gene may conduct only a subset of the functions of the old gene and may thus be less burdened by pleiotropic and epistatic constraints. Subfuctionalization may lead to the evolution of modularity (Force et al. 2005) and may indeed be a way to evolve new autonomous evolutionary characters through parcellation in the sense of Wagner & Altenberg (1996).

Wagner (1994) showed that gene duplication is most likely to be nondeleterious if either a single gene or the entire genetic system is duplicated. Whole-genome duplications may qualify as major transitions in evolution producing material for increase in genome complexity through specialization and novelty.

Lynch & Conery (2003) argued that the retention of gene duplications, as well as mobile genetic elements and introns, were more likely in small- or moderately sized populations, because selection against weak deleterious effects, which may be the most common immediate effect of a duplication, is less efficient in a small population. Based on this they suggested that that the increase in genome complexity among eukaryotes could be explained as a result of lower effective population sizes. As larger organisms generally have smaller population sizes, large size may be the origin of complexity, rather than the other way around.

There are many other evolvable aspects of genome architecture, including mutation rates (Drake et al. 1998) and recombination rates (Barton 1995), that I will not address owing to space constraints. I note that directional epistasis is also instrumental in understanding the evolution of recombination rates (Barton 1995; Otto & Feldman 1997).

EMPIRICAL CHALLENGES

Theory and Experiment

Although there is a huge empirical literature describing genetic architectures in many systems on many different levels, most of this is poorly connected to theory. This situation has a number of causes. The first is that the statistical models of classical quantitative genetics were set up in a way that did not facilitate either the empirical or the theoretical study of gene interactions. A second problem is that most of the dynamic theory is based on models that lack parameters that are experimentally measurable even in principle. The situation resembles that described by Gavrilets (2003) for models of speciation, where there are a number of highly specific, arbitrary, and often confusing, simulation studies, but a lack of simple general analytical results that can guide empirical work. Thus, a major challenge for the field is achieving a better connection between theory and experiment.

One fundamental problem with many models and representations of gene interaction is that they lack an adequate representation of the phenotype. Genetic architecture is about the mapping from genotype to phenotype, and some arbitrary assignment of fitness to genotypes does not help us understand how this mapping evolves. A haphazard treatment of the phenotype combined with detailed modeling of the genetic system may also introduce conceptual biases. For example, could it be that the notions of overdetermined phenotypes and neutral spaces of equivalent genotypes are artifacts of models with simple one-dimensional phenotypes and complex genotypes? One avenue to connect genotype and phenotype goes through a better understanding of gene-regulatory networks underlying specific phenotypes. The rapid accumulation of data on gene networks will make it possible to assemble realistic dynamic models of the variational properties of phenotypes. These can then be studied from the vantage point of interesting theoretical entities such as the directionality of epistasis or the extent of variation in pleiotropy. Another interesting possibility might be to use artificial selection on phenotypes with well-understood underlying gene networks to understand what parts are changing and whether those parts would be the same in replicate experiments. Beldade et al. (2002) provide a nice example.

Epistasis

Both the theoretical and the empirical study of epistasis have suffered badly from the statistical definitions of epistasis as variance components. Empirically, epistatic variance components are difficult to estimate, and when they are estimated they tend to be small (e.g., Whitlock et al. 1995). Small epistatic variance components are, however, compatible with strong epistasis in the underlying genotype-phenotype map (Cheverud & Routman 1995, Keightley 1989, Moreno 1994, Templeton 2000). A more serious problem is that epistatic variance components cannot be used to distinguish between different types of epistasis (Hansen & Wagner 2001a). Different types of epistasis can have profoundly different evolutionary effects, and we need methods that can identify and measure the relevant aspects of epistasis, directional epistasis and sign epistasis in particular.

On the surface, QTL analysis is a promising avenue to estimate directional epistasis, sign epistasis, and pleiotropic effects (Carlborg & Haley 2004, Mackay 2001, Zeng 2005). Epistasis is often found in QTL studies. A telling example is Dilda & Mackay's (2002) finding of many epistatic QTLs for *Drosophila* bristle number, the classic textbook example of an additive character. There are, however, serious shortcomings with current methodology for estimating QTL effects. The use of significance thresholds for QTL detection biases the results toward the detection of too few loci with too large effects (Beavis 1998). When it comes to epistasis this bias is extreme, as there is less power for the detection of interaction effects. In other words, only the extreme tail of the epistasis distribution is studied, and we have little guarantee that this is representative of the general pattern of epistasis, which may be dominated by numerous weak effects. Developing methods for accurately estimating the number, mean, and variance of epistatic (and additive) effects from QTL data is a major statistical challenge.

With these caveats in mind there is at present little evidence pointing to strong directional epistasis. Most QTL data display nondirectional epistasis (e.g., Weber et al. 2001). Due to the importance of directional epistasis for the mutation load and the maintenance of sexual reproduction (Hansen & Wagner 2001b, Kondrashov 1988), many studies have looked for evidence of synergistic epistasis among deleterious fitness mutations (de Visser et al. 1997a, b; Elena & Lenski 1997, 2001; Lynch et al. 1999; Mukai 1969; Remold & Lenski 2004; Whitlock & Bourguet 2000), but the results are equivocal. In any case, this literature illustrates how good experimental work can be motivated by theoretical questions, but we need to study directional epistasis in more traits than fitness.

The study of canalization also has methodological problems (Dworkin 2005a). It is now clear that a simple increase in genetic variation after a perturbation is not necessarily evidence for canalization of the wild type (Hermisson & Wagner 2004). Better evidence, looking directly at changes in genotype effects, is necessary. Stearns & Kawecki (1994; Stearns et al. 1995), studied canalization by looking at the effects of inserted P-elements on the variation of different traits in *Drosophila*. Across life-history traits they found a negative correlation between the genetic variation induced by the insertions and the fitness sensitivity of the traits, and interpreted this as evidence of increased canalization under stronger selection. Apart from the difficulty that theory predicts canalization to be relatively insensitive to the strength of selection, this is also problematic in that the traits differ in the mutational target size. Houle (1998) argued that differences in mutational target size are more likely to explain the pattern. Future studies must distinguish differences in gene effects from differences in mutational target sizes.

Pleiotropy

Evolutionary developmental biology has provided an enormous amount of data on character variability. The theoretical framework used to interpret this data has, however, been largely verbal and focused on the issue of modularity. The effects of pleiotropy are, however, more refined than its mere absence or presence. It is necessary to describe the pleiotropic effects in more detail. One important issue is studying

the signs and degree of variation in pleiotropic effects. Tentative evidence for variation in pleiotropic effects come from Phillips et al. (2001), who found differences in estimated G-matrices for *Drosophila* wing characters across lines inbred from the same base population. It is, however, unclear how much of the differences were due to sampling error. Several researchers have studied patterns of pleiotropy and the degree of modularity between characters with QTL data (Cheverud 1996; Cheverud et al. 1997, 2004; Hall et al. 2006; Juenger et al. 2005 Mezey et al. 2000; Weber et al. 2001; Wolf et al. 2005).

An important challenge is estimating the underlying dimensionality of characters, so as to better understand what absolute pleiotropic constraints exist. This may in principle be approached by estimating the dimensionality of G- or M-matrices, but there are formidable statistical difficulties that must be overcome (Houle et al. 2002, Mezey & Houle 2003).

A final question of theoretical interest concerns the degree of pleiotropic constraint on new mutations. There is a need for focus on the quality rather than just the quantity of new mutations (Hansen 2003, Hansen & Houle 2004).

CONCLUSIONS

Fisher's focus on additive effects was a very successful research strategy that clarified the first principles of character evolution. His treatment of gene interactions, however, was designed to minimize and hide their effects. The result was that the modern synthesis was left without tools to study the evolution of genetic architecture and consequently without tools to study the evolution of evolvability. This situation is now improving owing to several conceptual advances. These include the notion that gene effects, and not just gene frequencies, are evolutionary variables, as well as the distinctions between variation and variability and between statistical and biological effects. Particularly important is the emerging understanding that the statistical notion of gene interaction is not equivalent to the way genes interact in the genotype-phenotype map and that different types of interaction have very different evolutionary consequences. To a first approximation, the evolution of evolvability depends on the directionality of epistasis.

We still need much more theoretical work on the dynamic evolution of genetic architecture under different selection regimes. Another theoretical challenge is providing a better connection to experiment through the identification of measurable parameters and general analytical results. On the empirical side, the general challenge is connecting the masses of genetic data to interesting phenotypes. I thus support Houle's (2001) call for a science of phenomics.

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Volume 37, 2006

Contents

Indexes