Perspectives:

Complex Adaptations and the Evolution of Evolvability

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> One may wonder, [...] how complex organisms evolve at all. They seem to have so many genes, so many multiple or pleiotropic effects of any one gene, so many possibilities for lethal mutations in early development, and all sorts of problems due to their long development. J. T. Bonner, 1988, p173.

Abstract: The problem of complex adaptations is studied in two largely disconnected research traditions: evolutionary biology and evolutionary computer science. This paper summarizes the results from both areas and compares their implications. In evolutionary computer science it was found that the Darwinian process of mutation, recombination and selection is not universally effective in improving complex systems like computer programs or chip designs. For adaptation to occur, these systems must possess "evolvability", i.e. the ability of random variations to sometimes produce improvement. It was found that evolvability critically depends on the way genetic variation maps onto phenotypic variation, an issue known as the representation problem. The genotype-phenotype map determines the *variability* of characters, which is the propensity to vary. Variability needs to be distinguished from variation, which are the actually realized differences between individuals. The genotype-phenotype map is the common theme underlying such varied biological phenomena as genetic canalization, developmental constraints, biological versatility, developmental dissociability, morphological integration, and many more. For evolutionary biology the representation problem has important implications: how is it that extant species acquired a genotype-phenotype map which allows improvement by mutation and selection? Is the genotype-phenotype map able to change in evolution? What are the selective forces, if any, that shape the genotype-phenotype map? We propose that the genotype-phenotype map can evolve by two main routes: epistatic mutations, or the creation of new genes. A common result for organismic design is modularity. By modularity we mean a genotype-phenotype map in which there are few pleiotropic effects among characters serving different functions, with pleiotropic effects falling mainly among characters that are part of a single functional complex. Such a design is expected to improve evolvability by limiting the interference between the adaptation of different functions. Several population genetic models are reviewed that are intended to explain the evolutionary origin of a modular design. While our current knowledge is insufficient to assess the plausibility of these models, they form the beginning of a framework for understanding the evolution of the genotype-phenotype map.

1 Introduction

In a remarkable and widely reported study, Halder et al. (1995) succeeded in getting extra eyes to sprout on the wings, legs, and antennae of *Drosophila* by targeted misexpression of *Drosophila "eyeless"* gene cDNA. The out-of-place eyes contain the entire eye structures, including cornea, bristles, pigment and photoreceptors, and are electrically responsive to light, prompting Halder et al. to suggest that eyeless is a "master control" for the complex formation of the insect eye.

Why is *eyeless* so remarkable? Because it is a single signal that induces the whole complex process of eye construction, and because this process is carried out almost flawlessly despite it occurring in the wrong tissues of the fly's body. All of the functionally relevant structures stay together in their novel locations. The eye, which is a module of organismal function, is found also to have a modular genetic representation. By "modular representation" we mean that changing the expression of "eyeless" preserves all the relationships between the functionally interdependent parts of the eye, while changing only the eye's relationship to the rest of the fly's body.

What does evolutionary theory have to say about the existence of genes such as *eyeless? Eyeless* brings us to a level of phenomenon that is distinct from adaptation itself. It concerns the variational properties of the genome — the nature of phenotypic variation produced by genetic variation. Modularity is one example of a variational property.

The variational properties of the phenotype are fundamental to its evolution by natural selection. Adaptation requires that genetic change be able to produce adaptive phenotypic changes. Whether or not adaptive changes can be produced depends critically on the genotype-phenotype map. This is the underlying phenomenon being studied under many different guises in evolutionary biology, including such areas as dissociability in development, morphological integration, developmental constraints, biological versatility, fluctuating asymmetry, the Baldwin effect, epistasis, canalization, heterochrony, genetic variance/covariance matrices, identification of quantitative trait loci, and the adaptive landscape. These studies have concerned themselves with either defining or characterizing variational properties of the phenotype, considering their effects on evolution, or considering the evolution of the properties themselves. Yet despite its ubiquity in evolutionary phenomena, the genotype-phenotype map has not been seen as a unifying conceptual framework for these studies.

Levinton (1988) provides a possible reason for this state of the field when he writes,

> Evolutionary biologists have been mainly concerned with the fate of variability in populations, not the generation of variability. ... Whatever the reason, the time has come to reemphasize the study of the origin of variation.

We agree with Levinton (and Fontana and Buss, 1994) that, despite its inherent difficulties, the study of the origin of variation is fundamental and should be pursued.

In this essay, we will argue that: 1) Variational properties of the phenotype are a level of phenomenon distinct from phenotypic adaptation; 2) they are subject to distinct evolutionary dynamics; 3) they have been the subject of a wide variety of studies in evolutionary biology, and now, evolutionary computer science; 4) these disparate studies can become seen as parts of a common research project, once a conceptual framework is developed that more clearly shows the relationship between them.

2 Evolutionary Computation

The study of the genotype-phenotype map has recently been spurred by a new development: the advent of evolutionary computation. Evolutionary computation is a recently burgeoning field in which the principles of selective breeding are applied to optimization and engineering problems. It includes genetic algorithms (Holland, 1992), evolutionary strategies (Rechenberg, 1973, 1994), evolutionary programming (Fogel, Owens, and Walsh, 1966), and genetic programming (Koza, 1992).

In an evolutionary algorithm, for a particular problem (such as producing a neural network that recognizes a face) the space of possible solutions is represented as a data structure upon which certain "genetic" operations can act (such as mutation or recombination of the data), to produce variant "offspring". The offspring are then selected according to how well they carry out the desired behavior as parents for subsequent "breeding". An algorithm iterates this procedure, and the population of candidate solutions evolves.

In many problems, evolutionary algorithms have been found to produce solutions better than any that have been produced by rational design, or better than other search and optimization algorithms. In other cases, however, evolutionary algorithms fail miserably. The engineer is faced with the practical problem of understanding why. In so doing, researchers are gaining experience in a new domain of evolutionary phenomena. Their experience parallels in many ways the experience of animal and plant breeders, with one great exception: the programmer controls the genetic system.

What turns out to be crucial to the success of the evolutionary algorithm is how the candidate solutions are represented as data structures. This is known as the *representation problem,* and its appearance in evolutionary computation parallels its appearance in other areas of artificial intelligence (e.g. Lehmann, 1988; Rich and Knight, 1991; Winston, 1992; Jones, 1995). The process of adaptation can proceed only to the extent that favorable mutations occur, and this depends on how genetic variation maps onto phenotypic variation.

Biologists are not confronted by this problem because they study the end-products of evolution, which are *prima facie* evidence that the favorable mutations have occurred at a sufficient rate. Furthermore, a biologist wanting to study this question faces great methodological hurdles; comparative and experimental approaches to the problem are blocked because one cannot simply pick alternate genetic systems that produce the same phenotype and compare their capabilities to produce adaptive variation. In evolutionary computation, however, this is possible.

Among the earliest experiments in evolutionary computation, Friedberg (1959) attempted to evolve functioning computer programs by mutating and selecting the code, but found that mutations effectively randomized the behavior of the programs, and adaptive evolution was impossible; there is no way to improve the performance of a conventional computer program by randomly altering letters in the source code. It became understood that the mutation/selection process is not universally effective in producing adaptation if favorable mutations cannot be produced (see for instance Bossert (1967), Bremermann et al. (1966), Eden (1967), or Simon (1965)). In contrast to Friedberg's results, Koza (1992) succeeded in evolving computer programs that perform well on complex tasks (such as prediction of protein structure or random number generation) by recombining branches of parse trees for the programs. Thomas Ray (1992) succeeded in designing computer programs that exhibit evolution as an emergent property by careful design of the data structures. The difference between Friedberg and Koza's systems was in the representation of the computer programs and the way genetic operators act on them.

Hence, the Darwinian solution of optimization problems is possible if and only if the problem is "coded" in a way that makes the mutation-recombination-selection procedure an effective one. The "representation problem" is how to code a problem such that random variation and selection can lead to a solution. The representation problem underlies the issue of whether selection, mutation, and/or recombination can produce adaptation.

For biology the "representation problem" has some unsettling implications. If, as evolutionary biology asserts, all adaptations are the result of mutation and selection, organisms have to be evolvable. But once one calls into question the inevitability of organisms being evolvable, one can ask, how and why did an evolvable genome originate in the first place? Is it a fortuitous consequence of physics, or of biochemistry, or a "frozen accident" from life's origin? Are the genetic representations of the phenotype a product of evolution? What, if any, are the evolutionary forces that shape the genotype-phenotype map?

The thesis of this essay is that the genotype-phenotype map is under genetic control and therefore evolvable. Further we suggest that its evolution explains seemingly unrelated problems of evolutionary biology: the role of epistasis in adaptation, genetic canalization, developmental constraints, developmental and morphological integration, biological versatility, the evolution of complex adaptations, the biological basis of homology and perhaps the origin of body plans. Evolutionary computation may provide a fertile new source of experience from which these different problems in evolutionary biology can be integrated.

3 Variation and Variability

To accommodate a discussion of genetic representations and variational properties of the phenotype in the language of evolutionary biology, it is essential to clearly distinguish between "variation" and "variability", even though these words are often used synonymously in the literature. The term variation refers to the actually present differences among the individuals in a population or a sample, or between the species in a clade. Variation can be directly observed as a property of a collection of items. In contrast, variability is a term that describes the potential or the propensity to vary. Variability thus belongs to the group of "dispositional" concepts, like solubility (Goodman, 1955). Solubility does not describe an actual state of a substance, say sodium chloride, but its expected behavior if brought into contact with a sufficient amount of solvent, for instance water. Similarly, variability of a phenotypic trait describes the way it changes in response to environmental and genetic influences. In the field of evolutionary computation it became clear that the way mutation and/or recombination changes the behavior of a model is determined by the way the model is coded or represented in the program. The genetic representation of a character thus determines the variability of the phenotype and not directly the genetic variation within populations. In this context the concept of developmental constraints (sensu Maynard-Smith et al. 1985; Schwenk, 1995) can be understood as the limits of variability of traits caused by their representation or coding in the genome.

As a directly observable property, variation is comparatively easy to measure. Genetic variation in a population is measured by the heterozygosity or the degree of polymorphism. Quantitative phenotypic variation is measured by the phenotypic, genetic and environmental variance or any other statistical measure of dispersion (Falconer, 1981; Barton and Turelli, 1989). In contrast, variability is much harder to measure. Genetic variability at the molecular level is measured as mutation rate. Genetic variability of quantitative phenotypic traits is measured by the mutational variance Vm, the average additive genetic variance produced per generation by mutations, (Clayton and Robertson, 1955; MacKay et al., 1992), or in the case of more than one trait, by the mutational covariance matrix, $\mathbf{M}$ (Lande, 1975). Each of these quantities requires elaborate experimental designs to be estimated. An indirect method to assess the variability inherent is a body design is to determine the number and range of independently varying morphogenetic parameters, also called biological versatility (Vermeij, 1971).

The relationship between variation and variability is conditional. Clearly, if there is variation in a character it has to be variable, but the reverse is not true. Therefore the study of natural variation can give hints on the pattern of variability as for instance the study of osteological variation suggests the existence of constraints (Alberch, 1983; Rienesl and Wagner, 1992), but it is at best a surrogate of variability.

The genetic variance of a trait, i.e. the raw material of evolution, is a fairly ephemeral property. It depends on the complement of genes currently segregating in the population, the effect of the alleles present and their frequencies. Whenever an allele changes its frequency or gets fixed the genetic variance of the character may change (Bürger and Lande, 1994; Bürger, Wagner, Stettinger, 1989; Turelli, 1988). The same is true for genetic correlations, which not only depend on the alleles segregating but also on the linkage dis-equilibrium among them (Bulmer, 1980; Turelli, 1988). On the other hand the genetic variability of a character is a property of the genome. It remains the same as long as the complement of loci and the mutation rate is the same and as long as no epistatic mutations have been substituted (see below). However, variability is under genetic control and may thus evolve.

4 Genetic Control of Variability

Schmalhausen and Waddington were perhaps the first to clearly see that epistatic interactions between genes can produce genetic control over genetic variability, and to apprehend the theoretical implications of this (Schmalhausen, 1949; Waddington, 1942). Per definition, epistasis is the influence of the gene at one locus on the effects of alleles at other loci (for a way to measure epistatic effects see Cheverud and Routman, 1995). It thus reflects the fact that the expression of genetic variation is under the influence of other genes. Evidence that variability of phenotypic traits is under genetic control comes from research on the phenomenon of "canalization." The term was first introduced by Waddington (1942) to describe the tendency of development to produce clearly distinguished tissue and organ types. However, the concept had only limited impact on developmental biology, but became important in quantitative genetics. It describes the fact that mutant phenotypes often show much more variation than the wild type phenotype. Some of this variation is genetic variation which was "suppressed" in the wild type genetic background (for a recent review, see Scharloo, 1991). Selection experiments suggested that the sensitivity of a trait to genetic variation can be decreased by artificial stabilizing selection (Rendel, 1967; Scharloo, 1988) or increased by artificial directional selection (Lazebnyi et al., 1991). Recently it has been shown that the average effect of P-element induced mutations on life history traits in *Drosophila* is negatively correlated with the influence on fitness of the trait. The stronger the impact on fitness the smaller the average effect of a new mutation (Stearns and Kawecki, 1994).

Evidence for genetic control over phenotypic variability is of capital interest to evolutionary theory (Scharloo, 1991). This literature shows that evolution not only produces the fixation of spontaneously generated variation, but it can can also change the "rules" under which heritable phenotypic variation is produced, i.e. the variability of the traits itself can evolve. The genome has control over the "allocation" of genetic variance to phenotypic characters. Some characters that were variable can become fixed (Riedl, 1975, Stebbins, 1974), while others may become integrated into a tightly coupled complex of characters (Stearns, 1993) or others may gain variability after a developmental constraint was broken (Vermeij, 1970, 1973, 1974).

Population genetics has been developed to understand the dynamics of genetic variation. However, the issue here is the evolution of the variability of characters. So the question is how to describe the variability of a trait and its evolution in population genetic terms in order to link the theory of evolvability to the existing apparatus of evolutionary theory. Genetic variability of a character is determined by two factors: the rate of mutation of genes influencing the character and the effect of the mutations on the state of the character. Mutation rate is a standard parameter in population genetic model and there is also theory on the selection forces acting on mutation rate (Eshel, 1973; Altenberg and Feldman, 1987). The effects of mutations can either be arbitrarily assigned to individual alleles, or described as the distribution of mutational effects (Kimura, 1965). Mathematically, the relationship between the genotype and the phenotype is a function f, which assigns to each genotype G the average phenotype P (averaged over so-called 'environmental' variation) $G \xrightarrow{f} P$ (or if there is genotype-environment interaction $G \times E \xrightarrow{f} P$). The idea of a genotype-phenotype mapping function has been used in quantitative genetics, for instance in the study of genetic canalization (Rendel, 1967, Scharloo, 1987), multivariate mutation selection balance (Wagner, 1989a), the evolution of pleiotropy (Altenberg, 1995a), the study of epistatic effects (Gimelfarb, 1989, Wagner et al., 1994), and in evolutionary algorithms (for instance: Altenberg, 1994; Banzhaff, 1994; Schwefel, 1981). The genotype-phenotype mapping function describes how genetic variation is translated into phenotypic variation and is thus a way of describing how the phenotype is represented in the genotype. The evolution of genetic representations can thus be modeled as the influence of selection on the genotype-phenotype mapping function.

5 Complex Adaptations: When Are They Possible?

The digression on variability and its genetic control sets the stage to consider the issue of evolvability in a biological context. If the expression of genetic variation is itself under genetic control, is it conceivable that species evolve "strategies" of how to structure the phenotypic effects of mutations? Or, to be more precise, is it possible that evolvability is systematically produced by the evolutionary dynamics of genetic variation for variability? And does evolution produce trends in the variational properties of the genotype-phenotype map? What exactly is evolvability and what influences its degree?

Evolvability is the genome's ability to produce adaptive variants when acted upon by the genetic system. This is not to say that the variants need to be "directed" (a la Foster and Cairns, 1992) for there to be evolvability, but rather, that they cannot be entirely "misdirected", that there must be some small chance of a variant being adaptive. The situation is analogous to obtaining a verse of Shakespeare from monkeys banging away on typewriters. Typewriters make this far more likely than if the monkeys had pencil and paper. The typewriters at least constrain them to produce strings of letters. Similarly, the genotype-phenotype map constrains the directions of phenotypic change resulting from genetic variation.

Evolvability has its counterparts in various fields of computer science such as heuristic search, genetic algorithms, and genetic programming. In each of these fields the same problem occurs: one is searching a large set of objects (such as genotypes, programs, or combinations of parameters) for the objects that best fulfill some measure of quality (such as fitness, performance, efficiency, etc.), and one wishes to use the samples taken so far as a guide to what samples to take next, so that one is not merely doing random or exhaustive search. Usually the set of possibilities is too large to be searched exhaustively. As a consequence success depends on some kind of heuristic hint, an Ariadne thread, which guides the researcher, the algorithm, or the population through the maze of possibilities.

The Darwinian heuristic is to choose sample points by perturbing the more fit ones among those sampled thus far. Implicit in the Darwinian heuristic is the notion of perturbation, and the assumption that the fitness function is not completely randomized by a perturbation (thus the genome is not a "House of Cards" (Kingman 1978) in which any genetic alteration brings it tumbling down).

The paradigmatic image for successful Darwinian search is Wright's image of the population walking up the side of a "fitness peak" (Wright, 1964). If one wants to find the highest point in a landscape and one can not see far into the distance, the best guess is to walk uphill. This will lead to at least one of the high points in the landscape, but of course not necessarily to the highest point. A population is slowly accumulating better and better mutations in a stepwise fashion. However, whether this approach is successful depends on whether the shape of the fitness function with respect to the genetic perturbations actually provides the information necessary to find the best genotype or the best solution to a technical problem.

Within computer science a growing body of theory has been developed which tries to pin down exactly why certain search problems are difficult and others are easy for the Darwinian heuristic. The concepts include the ideas of deceptiveness (Goldberg, 1987) and ruggedness (Kaufmann, 1989) of fitness landscapes, epistasis variance (Davidor, 1991), and the idea of strong causality (Rechenberg, 1994) to name a few. Here we want to mention but three of these concepts which all point to the same direction.

The idea of strong causality comes from physics but is used extensively in evolutionary strategy (ES) research to explain ES performance (Rechenberg, 1994). "Strong causality" simply means that small changes in the system parameters shall, on the average, correspond to small changes in system performance (fitness). If this is the case it is easy to find a path towards the best or at least a good solution of a problem.

Similar ideas have been developed in genetic algorithms theory. The classical idea of heritability appears in correlation statistics used to characterize the ruggedness of adaptive landscapes and how far adaptation may proceed before it gets caught in a local peak (Weinberg, 1991; Stadler, 1992; Mhlenbein and Schlierkamp-Voosen, 1995). Another approach (Jones and Forrest, 1995) measures the correlation between fitness or performance and the distance from the optimum in the search space as a predictor of how well adaptation proceeds. Evolvability is dealt with directly by generalizing Price's (1970) covariance theorem of natural selection to predict the rate at which new, fitter adaptations will be produced (Altenberg, 1995a). This rate depends on the rate of production of genetic variation by what ever means, and the correlation between the fitness of genotypes and their likelihood of producing still fitter offspring.

All these approaches are different formal ways of capturing the same intuitive notion of a (statistically) "smooth" fitness landscape: it is easy to evolve by natural selection if better genotypes are found in the mutational "neighborhood" of the good genotypes. Another way of expressing this result is that adaptations are possible if improvement can be achieved in a cumulative or stepwise fashion.

But what are the structural features that make stepwise improvement possible? The key feature is that, on average, further improvements in one part of the system must not compromise past achievements. This is the essence of the so-called "building block hypothesis" to explain the performance of genetic algorithms (Holland, 1992; Forrest and Mitchell, 1993). Independent functions shall be coded independently so that the improvement of each function can be realized with minimal interference with other already optimized functions. Pleiotropy cannot be wholly "universal" (Wright, 1968), but must be limited for many mutations. A primary problem for complex adaptation is how to avoid unbounded pleiotropy in the face of the combinatorial explosion in the number of possible interactions between parts. This is accomplished by modularity, which underlies many of the explanations of complex adaptations offered by biologists.

6 Modularity of Development

Independent genetic representation of functionally distinct character complexes can be described as modularity of the genotype-phenotype mapping functions. A modular representation of two character complexes C1 and C2 is given if pleiotropic effects of the genes fall mainly among members of the same character complex, and are less frequent between members of different complexes (see Fig. 1). This depiction should be understood as mainly illustrative, because a full and quantitative characterization of modularity would have to allow for hierarchies, gradations, and overlapping of modules. The development of a quantitative characterization of modularity is a part of the research program advocated here.

Some adaptations may intrinsically have a modular genetic representation because they are simple, and involve direct gene action. Examples include immunoglobulin antigen binding, hair color, enzyme activity, etc.. These are functions with low polygeny and low pleiotropy. Morphogenesis presents the greatest challenge in producing a modular representation because it is a dynamical system emerging from the complex interactions of many genes and structures. Modularity in morphogenesis is facilitated by at least one intrinsic property, the branching structure of clonal lineages and spatial proximity initially shared by a clone of differentiating cells. But the ontogeny of many functional complexes involves interactions between distantly diverged clones, and again modularity becomes a property to be explained rather than a given. The challenge that morphogensis presents in achieving a modular genotype-phenotype map perhaps explains why most of the study of the genotype-phenotype map has been undertaken by evolutionary morphologists.

The concept of modularity was clearly expressed by John Bonner in his concept of gene nets (Bonner, 1988):

> "I will call [...] a 'gene net' [...] a grouping of a network of gene actions and their products into discrete units during the course of development." (p. 174) "This general principle of the grouping of gene products and their subsequent reactions into gene nets becomes increasingly prevalent as organisms become more complex. This not only was helpful and probably necessary for the success of the process of development, *but it also means that genetic change can occur in one of these gene nets without influencing the others, thereby much increasing its chance of being viable. The grouping leads to a limiting of pleiotropy and provides a way in which complex developing organisms can change in evolution."* (p. 175, emphasis by GPW&LA)

The idea that development is organized into semi-autonomous processes is actually much older, dating back to the beginnings of developmental biology and was summarized under the term "dissociability" by Needham (1933). Needham pointed out that even if development is a perfectly integrated process its component parts can be disentangled experimentally: growth can occur without differentiation and nuclear division without cell division and so on. The evolutionary importance of this fact was emphasized by Gould (1977, p 234) who suggested that dissociability is the developmental prerequisite for heterochronic change (see also Raff and Kaufman, 1983, p 150, Raff, in press).

Evolution of complex adaptations requires a match between the functional relationships of the phenotypic characters and their genetic representation. This was clearly expressed by Rupert Riedl (1975) in his thesis of the "imitatory epigenotype." If the epigenetic regulation of gene expression "imitates" the functional organization of the traits then the improvement by mutation and selection is facilitated. Riedl predicts that selection tends to favor those genotype-phenotype maps which imitate the functional organization of the characters. Imitation means that complexes of functionally related characters shall be "coded" as developmentally integrated characters but coded independently of functionally distinct character complexes (see also Frazzetta, 1975).

The existence of semi-autonomous units of the phenotype might be particularly important in connection with sexual reproduction (Stearns, 1993). Sexual reproduction rearranges genetic variation in every generation which creates the problem of maintaining functional phenotypic units intact. Stabilizing the development of functionally related character complexes allows the recombination of integrated traits rather than true "random" variation.

The fact that the morphological phenotype can to a great extend be decomposed into basic organizational units, the homologues of comparative anatomy, has also been explained in terms of modularity. It has been suggested that properly identified homologues are developmentally and genetically individualized parts of the organisms (Wagner, 1989b,c). The biological significance of these semi-autonomous units is their possible role as "building blocks" of phenotypic adaptation (Wagner, 1995a).

7 The Evolution of Modularity

Even if the fact and importance of modularity has long been recognized, there is little understanding of how modularity has originated. We have suggested that, although modularity may sometimes be intrinsic to the mechanism of an organismal function, in many cases, especially development, modularity appears to be an evolved property. Is modularity the result of integrating disconnected parts or, on the contrary, the result of parcellation of primarily integrated parts? Parcellation, a process which produces modularity from an integrated whole, consists in the differential suppression of pleiotropic effects among characters belonging to different functional complexes (Fig 2).

The first possibility, that modularity is a primitive property of all living beings, is unlikely. As much as the evolution of higher organisms consists in the acquisition of modular parts, like specialized organs the origin of modularity is most likely the result of evolutionary modification.

As to the 'direction' of evolution, integration or parcellation of modules (Fig. 2), the most prevalent direction seems to be parcellation, at least among metazoan animals. The origin of metazoans is the integration of conspecific unicellular individuals into a higher level unit (see Buss, 1987). Each of these units consists of cells which have the same genotype and only secondarily organize in specialized cell populations and anatomically separated organs. A very frequent mode of morphological innovation is the differentiation of repeated elements (Mller and Wagner, 1991; Weiss, 1990), for instance the differentiation of metameric segments at the origin of insects (see for instance Akam, 1989). The specialized organs acquire developmental autonomy in the course of phylogeny (Bonner, 1988). Vermeij has found a general trend towards higher biological versatility (Vermeij, 1973, 1974). Taxa with a higher number and range of independently varying morphogentic parameters are found at successively younger stages in the fossil record. Hence, the origin of differentiated, complex animals appears to be dominated by the process of parcellation rather than secondary integration, even if integration certainly occurs, for instance in symbiotic integration of cells of different origin (mitochondria and plastids for instance).

Provided that modularity is most likely the derived state in the phylogeny of animals and is perhaps the result of parcellation rather than integration, the question

Figure 1: Example of a modular representation of the character complexes C1={A, B, C, D} and C2={E, F, G} which serve to functions F1 and F2. Each character complex has a primary function, F1 for C1 and F2 for C2. Only weak influences exist of C1 on F2 and vice versa. The genetic representation is modular because the pleiotropic effects of the genes M1={G1, G2, G3} have primarily pleiotropic effects on the characters in C1 and M2={G4, G5, G6} on the characters in complex C2. There are more pleiotropic effects on the characters within each complex than between them.

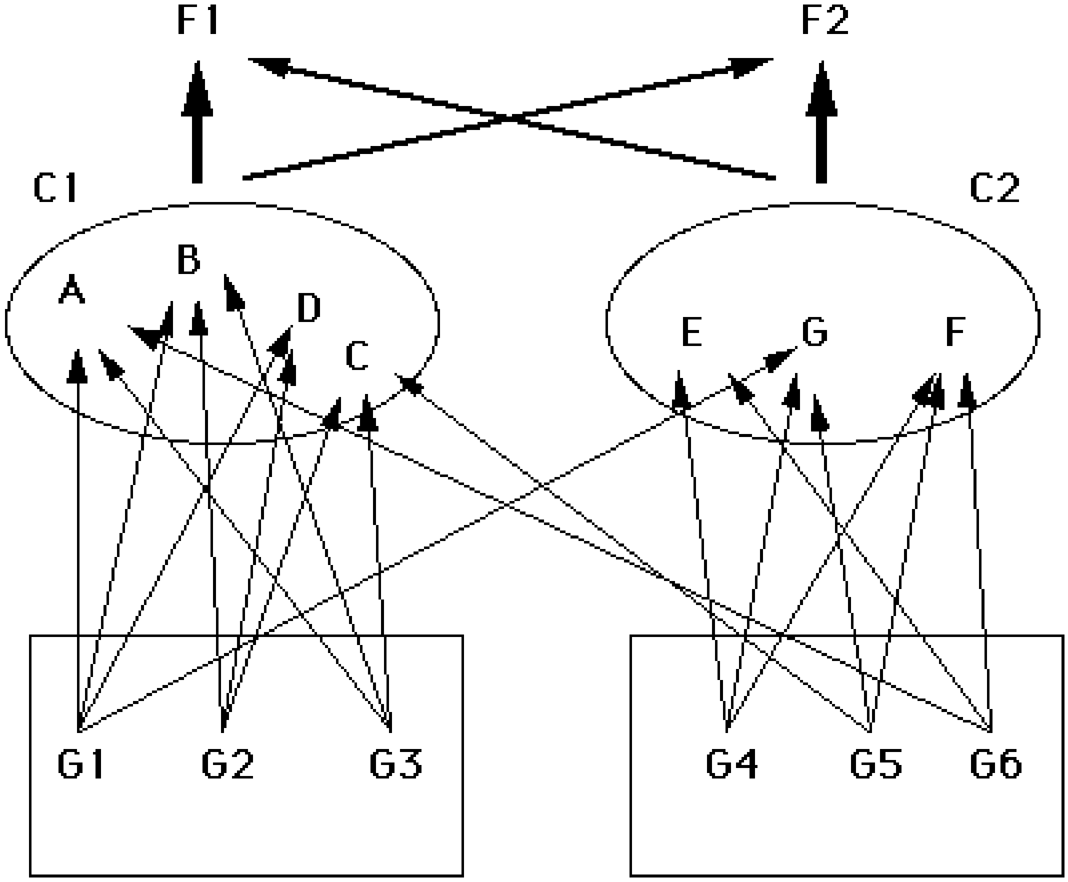
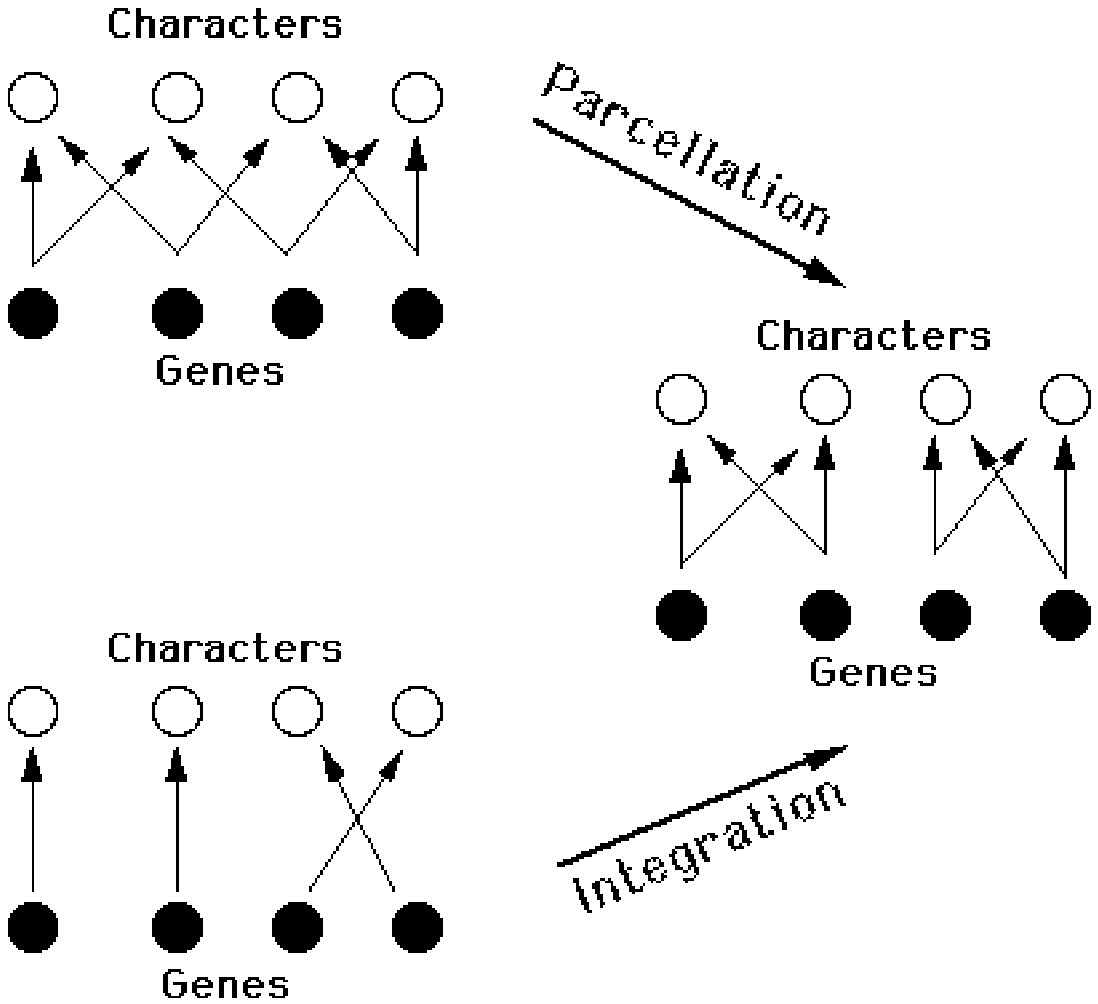


Figure 2: Two ways of obtaining modularity. Parcellation consists of a differential suppression of pleiotropic effects between groups of characters. Modularity through integration consists in the selective acquisition of pleiotropy among characters from the same group.



arises of how parcellation has been caused by natural selection. The mechanisms by which modularity can evolve are distinct from organismal adaptation itself, because modularity is a variational property, not the property of any given individual. Modularity can evolve only through systematic association with features directly under selection.

Perhaps the most common and long lasting form of selection experienced by any species is stabilizing selection (Endler, 1986). However, stabilizing selection alone is the least likely candidate for causing parcellation. Stabilizing selection on all characters simultaneously favors suppression of all mutational effects (Wagner, in preparation). It is thus unlikely to lead to modularity.

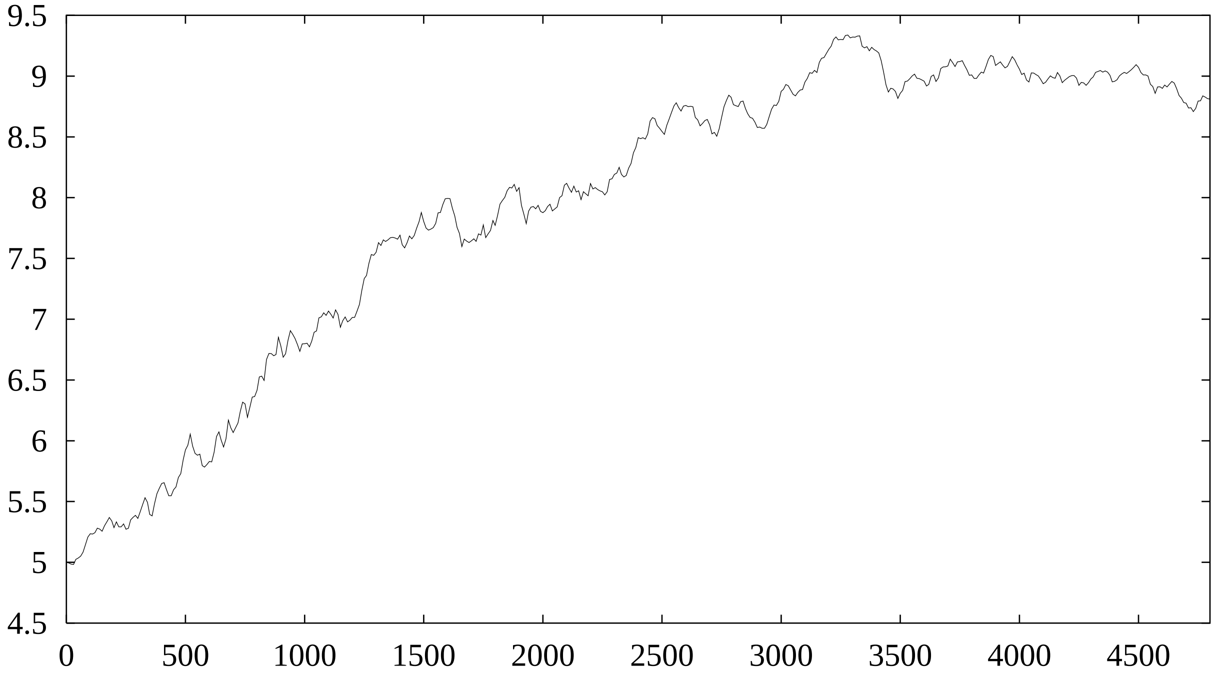
One possibility of sufficient generality is that the combination of directional and stabilizing selection leads to the differential suppression of pleiotropic effects (Wagner, 1995b). This proposal assumes that adaptation to environmental perturbations includes directional selection on one or a few functions or character complexes (mosaic evolution). It implies that directional selection on adaptively challenged character complexes occurs simultaneously with stabilizing selection on all the other characters. This combination of selection forces creates strong selection for suppressing exactly those pleiotropic effects which connect the characters under different selection regimes (directional and stabilizing). However, the process of selecting epistatic effects to modifying the genetic representation of quantitative characters is slow (Fig. 3). The reason mainly is that this process required the interaction of pairs of loci, one providing the direct effect to be modified and the other the epistatic effect. It is not yet clear what the necessary conditions are under which this process is a likely explanation of modularity, and whether these conditions are realized in nature.

Another general condition which may give rise to selection on the genotype-phenotype map is when the genetic representation "frustrates" the action of selection in some way, preventing the maximal adaptation from being achieved. This is the common feature in several processes by which modularity has been proposed to evolve — canalization, the breaking of developmental constraints, and morphological integration.

For instance developmental constraints frustrate selection by restricting the phenotypic variation selection has to act upon. Adaptations would be able to evolve only to optima within the constrained space of variability. At such constrained optima, stabilizing selection would appear to act, but there would remain a "latent" directional selection that would be manifest once the constraints were broken and new fitter phenotypes introduced (Altenberg, 1995b). A mutation that helped break these constraints could thus gain a fitness advantage. This suggests that there should be a trend toward breaking developmental constraints and increasing the degrees of freedom of the phenotype. Such a trend has in fact been documented in various cases (Vermeij, 1971, 1973, 1974).

Another way the genotype-phenotype map can frustrate selection is by making the generation of adaptive variants exceedingly rare. This occurs, for example, when multiple mutations are needed to improve a function. Selection for adaptation

Figure 3: Evolution of the genetic variability of a quantitative character under directional selection. The second character is always under stabilizing selection. Genetic variability of the first character is measured by the mutational variance $V_m(z_1)$. Note that the mutational variance is increasing of the character under directional selection, z_1. Selection on the epistatic effects leads to a modification of the genetic variability of the characters, in this case more variability of the first character, which is under directional selection and less for the second character which is under stabilizing selection (not shown). The gradual increase in the mutational variance goes on for about 4000 generations. Under these conditions the modification of the genetic variability is much slower than the evolution of the characters, which evolved about 14 environmental standard deviations in the same time. The model has 100 genes, which have both direct additive effects on the characters as well as mutually epistatic effects with a per locus mutation rates of 10^{-3}. Recombination is free. The population size is 200. The fitness function for the two characters is $w(z_1, z_2) = \exp\left\{sz_1 - \frac{z_2^2}{2\omega^2}\right\}$.



rate has been proposed as response to this frustration (Rechenberg, 1973; Riedl, 1975). Selection for adaptation rate assumes that modular or otherwise favorable representations of the phenotype will get selected because they enable the genome to respond more quickly to directional selection.

This is indeed the case and can happen without group selection (Wagner, 1981). In this case, alleles that change the genotype-phenotype map and increase the frequency of adaptive mutations at other loci can hitchhike along with those mutations. However, the problem is that selection for adaptation rate requires high degrees of linkage disequilibrium (Wagner and Bürger, 1985) and is only effective in the absence of recombination. The reason is that recombination during sexual reproduction leads to a mixing of genotypes and thereby eradicates the adaptive advantages achieved by genotypes with a better genetic representation (Wagner, unpublished).

Riedl (1975) proposes another mechanism for selection of adaptation rates, namely, the evolution of new genes. A model of how gene duplication in general affects the evolution of the genotype-phenotype map has been proposed (called "constructional selection", Altenberg, 1985, 1994, 1995b). The genes functioning in the genome can be seen as a highly selected group. Many new genes are randomly generated by the genome, and they exhibit a diversity of effects on the phenotype. But only a subset of these genes are stably incorporated in the genome. The genes most likely to be eventually preserved by selection as functioning genes are those which least perturb functions under stabilizing selection, while supplying variation under directional selection. The trend among the genes that the genome keeps is thus towards a modular genetic representation of the phenotype. Simulations of selective genome growth have shown that such a process would lead to modular organizations (Altenberg, 1995b).

More research into the population genetic theory of genotype-phenotype mapping functions is necessary to assess the plausibility of these and the other scenarios to explain the evolution of modularity. More knowledge of the developmental and evolutionary processes underlying the origin of modular parts of organisms is required to understand the significance and extent of modularity.

8 Conclusions

To understand the conditions under which mutation, recombination and selection can lead to complex adaptations is of importance for evolutionary biology as well as its applications in computer science (evolutionary algorithms). The central idea uniting these two fields is the insight that the genotype-phenotype map determines the evolvability of the phenotype (the so-called representation problem). A recurrent theme in the biological literature is the concept of modularity, the fact that higher organisms are composed of semi-autonomous units (gene nets, Bonner (1988); dissociability, Needham (1933) and Gould (1977); independent morphogenetic parameters, Vermeij (1973, 1974); individuality, Wagner (1989b,c); self-maintaining organizations, Fontana and Buss (1994); developmental modules, Raff (in press)).

However, even if the fact and the importance of modularity seems to be widely appreciated, there is little understanding of what selective forces have generated genetic and developmental modularity. This convergence of interests of biologists and computer scientists harbors a unique opportunity for evolutionary biology to acquire new conceptual and computational approaches to fundamental problems of biology.

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