Neural Systems and Artificial Life Group,
Institute of Psychology,
National Research Council, Rome

Natural Selection and the Origin of Modules

Günter P. Wagner, Jason Mezey, Raffaele Calabretta

March 13, 2001

To appear in: *Modularity. Understanding the development and evolution of complex natural systems*. The MIT Press, Cambridge, MA. (In press)

Reparto Sistemi Neurali e Vita Artificiale,
Istituto di Psicologia, C.N.R., Viale Marx 15 - 00137 - Rome, Italy
voice: +39 6 86090231 fax: +39 6 824737
e-mail: gral@ip.rm.cnr.it
http://gral.ip.rm.cnr.it

Natural Selection and the Origin of Modules

Günter P. Wagner1), Jason Mezey2) and
Raffaele Calabretta3)

1) Department of Ecology and Evolutionary Biology,
Yale University, New Haven, CT 06520-8106
2) Department of Biological Sciences, University of Florida, Tallahassee, FL
3) Institute of Psychology, Italian National Research Council, Rome

Introduction

There is an emerging consensus about the existence of developmental and evolutionary modules and their importance for understanding the evolution of morphological phenotypes (Bolker, 2000; Raff, 1996; Wagner & Altenberg, 1996). Modules are considered important for the evolvability of complex organisms (Bonner, 1988; Wagner & Altenberg, 1996), the identification of independent characters (Houle, 2001; Kim & Kim, 2001; Wagner, 1995) and necessary for heterochrony (Gould, 1977). Methods to recognize and test for modularity are developed (Cheverud *et al*., 1997; Mezey *et al*., 2000) and comparative developmental data are reinterpreted in the context of the modularity concept (Schlosser, this volume) (Nagy & Williams, 2001; Raff & Sly, 2000; Stock, 2001). In contrast to the progress made in these areas, there is very little research on the origin of modules and the few results published about models for the origin of modules point in widely different directions (Altenberg, 1994; Ancel & Fontana, 2000; Calabretta *et al*., 2000; Rice, 2000). Currently there is no unitary explanation emerging for the evolution of modularity. This is surprising since modularity seems to be so common among higher organisms that one might expect a robust and unitary mechanism behind its origin.

In this paper we want to review the current models and ideas for the evolutionary origin of modules. The majority of the models discussed below have been published in the years 2000 or 2001, and we thus feel that an overview might be useful. Another goal of this paper is to identify the range of open problems we face in explaining the ultimate causes of modularity.

Kinds of Modules

While the intuitive idea of modularity is pretty simple, the distinction between different types of modularity and their operational definition stimulates ongoing conceptual development (McShea this volume; Schlosser, this volume; Winther, this volume) (Brandon, 1999; Dassow & Munro, 1999; Nagy & Williams, 2001; Sterelny, 2000). In this paper, however, we do not want to enter the discussion about the more subtle aspects of the modularity concept but rather use a few fairly simple and perhaps

robust distinctions and definitions sufficient to communicate about models for the origin of modularity.

The biological modularity concept has several largely independent roots. In developmental biology the modularity concept is based on the discovery of semi-autonomous units of embryonic development (Raff, 1996). The empirical basis for *developmental modules* is the observation that certain parts of the embryo can develop largely independent of the context in which they occur. Examples are limb buds or tooth germs (Raff, 1996), developmental fields (Gilbert *et al*., 1996), or clusters of interacting molecular reactions (Abouheif, 1999; Gilbert & Bolker, 2001; Wray, 1999). On the other hand, *evolutionary modules* are defined by their variational independence from each other and the integration among their parts, either in interspecific variation or in mutational variation (Wagner & Altenberg, 1996). The preliminary definition of an evolutionary module used in this paper is a set of phenotypic features that are highly integrated by pleiotropic effects of the underlying genes and are relatively isolated from other such sets by a paucity of pleiotropic effects (see Figure 1). This preliminary definition is also the basis for attempts to measure and test for modularity in genetic data (Cheverud et al., 1997; Mezey et al., 2000). *Functional modules*, on the other hand are parts of organisms that are independent units of physiological regulation (Mittenthal *et al*., 1992), like bio-mechanical units (Schwenk, 2001) or an isolated part of the metabolic network (Rohwer *et al*., 1996). The precise definition of all these concepts is somewhat difficult and still controversial. The real challenge, however, is to determine how these different kinds of modules relate to each other. Are, for instance, evolutionary and developmental modules the same? If not, why and in what respects are they different?

Intuitively developmental and evolutionary modules should be closely related. The developmental process determines how a gene influences the phenotype, and hence the existence of developmental modules should influence the structure of the genotype-phenotype map. This is a largely correct argument, but fails to show that developmental modules map one to one to evolutionary modules. One of the reasons why there is no simple one to one relationship between developmental and evolutionary modules is that developmental modules can be deployed repeatedly like in the case of the left and right forelimb bud. Each of the two forelimb buds are independent developmental modules since each is a self-contained developmental unit with its own capacity for self-differentiation. From a variational point of view, however, the left and right forelimbs are not independent since they express the same genetic information. Mutations are thus expected to affect both forelimbs simultaneously and the genetic variation of the two limbs is correlated. Hence the two forelimbs indeed are two *different developmental modules* of the organism, and are also parts of the *same evolutionary module*.

In this paper we review models aimed at explaining the evolutionary mechanisms for the origin of evolutionary modules, i.e. of variationally individualized parts of the organism. The models thus do no address the question why and how developmental modules arise in evolution. The existence of developmental modules, however, may play a role in the origin of evolutionary modules. One of the most common modes for the origin of evolutionary modules, i.e. phenotypic units of variation, is the differentiation of repeated developmental modules (Raff, 1996; Riedl, 1978; Weiss, 1990). Examples are the evolutionary differentiation of teeth. Each individual tooth germ is a developmental module, but each differentiated tooth class is an evolutionary module (Stock, 2001).

Another example are arthropod segments, which are potential developmental modules and tagmata like thorax and abdomen are evolutionary modules derived from the differentiation of a set of segments (Nagy & Williams, 2001). The main problem is to explain how repeated developmental modules that ancestrally expressed the same genetic information become genetically individualized. This can be either accomplished by differential suppression of genes that originally were expressed in all repeated modules, or by differential recruitment of genes into some modules but not in others (Williams, pers. communication). From a population genetic point of view the first mode of differentiation is equivalent to the suppression of pleiotropic effects of genes among modules. There are some models that simulate this scenario (see below). To our knowledge the second mode, i.e. differential recruitment of genes into the development of modules has not been modeled.

Evolutionary Mechanisms for the Origin of Modules

In this section we review models for the evolutionary origin of modules. The objective is to understand how natural selection may have acted on the phenotype as to produce evolutionary modules. As defined above, evolutionary modularity is a statement about the statistical structure of the genotype-phenotype map (Mezey et al., 2000). It implies that certain sets of phenotypic features are affected by the same set of genes, and thus are highly integrated, but these genes have few pleiotropic effects affecting other parts of the body. An evolutionary model for the origin of modules has to explain how natural selection could produce this distribution of genetic effects. Hence the origin of modules is a special case of the evolution of genetic architecture. So far we recognize two classes of models. In one class of models there is a more or less direct selective advantage associated with evolutionary modularity. Different models in this class differ with respect to the kind of connection assumed between modularity and fitness. In the second class of models no direct selective advantage is associated with modularity, but modularity arises as a dynamical side effect of evolution (Calabretta et al., 2000; Force *et al*., 1999).

Direct Selection for Modularity

For natural selection to cause modularity there has to be a connection between a selective advantage and modularity. One of the most frequently noted effects of modularity is its potential to increase evolvability (Altenberg, 1995; Bonner, 1988; Galis, 1999; Galis, 2001; Gerhart & Kirschner, 1997; Holland, 1992; Liem, 1973; Riedl, 1978; Vermeij, 1970; Wagner & Altenberg, 1996). Modularity is expected to increase evolvability if functionally independent characters are also variational modules. The idea is that variational independence of distinct functional units avoids deleterious side effects if a functional unit undergoes adaptive evolution. Hence it is tempting to suggest that modularity evolves as a result of selection *for* evolvability (Gerhart & Kirschner, 1997; Riedl, 1978). We will explore this possibility first.

1) Selection for Evolvability: the question whether modularity can be explained as an adaptation for evolvability has to be discussed in the broader context of whether selection

for evolvability can be a factor in the evolution of genetic architecture. This question is unresolved. In principle selection for evolvability is possible, in particular in asexual species. The mechanism is a simple Darwinian selection process based on a differential in mean fitness between clones caused by differences in the rate of adaptation among clones (Wagner, 1981). Experimentally it has been shown that alleles that increase mutation rate get selected in bacterial populations if the population faces a new environment, which is consistent with models for the selection for evolvability (Cox & Gibson, 1974). However, the mechanism only works well if there is either no recombination or otherwise strong linkage disequilibrium between say the mutator locus and the genes which mutate to advantageous alleles. With recombination, the mutator gene can no longer ride to fixation on the coat tails of the other genes, a process that has been called "hitch hiking" (Maynard-Smith & Haigh, 1974). The reason is that recombination will separate the mutator from the advantageous mutations. The same argument holds for any other mechanism that may influence the rate of adaptation, like differential epistasis that may suppress deleterious pleiotropic effects (see below). Consequently, with recombination, selection for evolvability is predicted to be a very weak force.

At this point, we want to report the results of a study that was aimed at modeling the evolution of pleiotropic effects (Wagner and Mezey, in prep.). Let us consider two characters, one under directional selection and the other under stabilizing selection. This model represents a fairly generic scenario for a complex organism. Whenever natural selection acts to change a character many other characters of the same organism will remain under stabilizing selection (Wagner, 1984). It has been shown that pleiotropic effects among these two characters decrease the rate of evolution of the character under directional selection (Baatz & Wagner, 1997). Hence pleiotropic effects among characters experiencing different selection regimes (directional versus stabilizing) decrease evolvability. The question then is whether natural selection could fix a modifier allele that suppresses the pleiotropic effects and thus increases evolvability (Fig. 2). We used an individual based model to investigate this question and estimated the selection coefficients of the modifier allele by measuring the time to fixation. The result was that there was quite strong selection for the modifier (a sample of the results is given in Table 1). However, the selection coefficient alone does not tell us whether we are dealing with selection for evolvability. The mean fitness of genotypes with different modifier alleles is influenced by at least two factors: 1) the amount of variation in the character under stabilizing selection, and 2) the relative location of the genotypes along the direction of directional selection (Fig. 3). Only the second factor can be called selection for evolvability since it derives from differential rates of adaptation. We determined the relative contributions of these to factors to the selection coefficient of the modifier and found that in all cases the fraction of the selection advantage due to selection for evolvability was less than 10%. In other words, more than 90% of the selective advantage of suppressing pleiotropic effects is due to a direct selective advantage rather than related to evolvability *per se*. Hence, we conclude that even if natural selection can be effective in removing pleiotropic effects, the resulting increase in evolvability is not explained by selection for evolvability, i.e. is not due to differences in evolvability among genotypes.

Another study about the evolution of evolvability had a similar result (Turney, 2000). The model considered mutations which increased the dimensionality of the phenotype and thus the number of degrees of freedom for adaptive variation. It was

shown that evolvability increases during the simulation runs. The evolutionary mechanism was a direct selective advantage to the mutations that increased evolutionary versatility. Mutations that increased versatility directly led to higher fitness phenotypes that were inaccessible before.

Hence evolvability can evolve and even improve, but evolvability per se is perhaps not the target of selection. We conclude that evolution of modularity is unlikely to result from direct selection for evolvability. One caveat in this argument, however, is that we are not aware of any work on selection for evolvability in populations with spatial structure. Spatial structure may make selection for evolvability more likely than selection in panmictic populations (J. Mitteldorf, personal communication).

An alternative to the idea that modularity evolves because of its effect on evolvability is that the genotype-phenotype map may have a direct impact on mean fitness, in particular if the population is far from equilibrium (see also (Rice, 1990)). Hence it is conceivable that modularity results from the fact that pleiotropic effects can decrease the mean fitness of a population if the population experiences directional selection. An other possibility is that mutations that produce modularity break genetic constraints on adaptation and thus would be selected because they make advantageous phenotypes accessible (Leroi, 2000).

2) Direct selection against pleiotropic effects: above we reported the result that a combination of directional selection on one character and stabilizing selection on another character can lead to selection against pleiotropic effects. Based on this insight we attempted to evolve modularity by alternating directional selection among two characters. The rational was that directional selection on a single character selects against pleiotropic effects on other characters. If two characters never experience directional selection simultaneously a modular genetic architecture for the two characters may arise, i.e. one set of genes with most of their effects focused on one character and another set of genes with most of its effects on the other character. The results, however, showed that alternating selection alone does not lead to a separation of genes into two character specific sets. The distribution of gene effects did not settle into a modular patter, but rather any episode of directional selection tends to recruit genes into the selected character (Mezey, 2000). From this we concluded that alternating selection alone cannot account for the origin of evolutionary modularity.

3) Modularity as an escape from adaptive constraints: the second alternative to selection for evolvability mentioned above is that modularity may result from mutations which overcome constraints among adaptive traits. This idea is related to the fact that structural and functional decoupling of characters can facilitate adaptation (Galis, 2001; Liem, 1973). This idea was proposed as a mechanisms for the origin of modularity by Leroi (2000), but to our knowledge it has not been explicitly modeled and is thus hard to evaluate at that time. Perhaps the most relevant, but still limited, model is that of Turney (2000) on the evolution of evolutionary versatility discussed above.

4) Constructional selection: the oldest model for the origin of modularity that in fact works, at least in simulations, is constructional selection proposed by Altenberg

((Altenberg, 1994); and this volume). It is based on the assumption that genes with fewer pleiotropic effects have a higher probability to establish duplicated copies of themselves in the genome. This model is thus based on intra-genomic competition among genes with different degrees of pleiotropy. It predicts the evolution of lower and lower average degrees of pleiotropy. The problematic aspect of this model, however, is the assumptions that the degree of pleiotropy is heritable among copies of genes, in particular if the genes acquire new functions. In fact there is evidence for lower pleiotropy among duplicated gene copies, but this fact may be better explained by subspecialization of duplicated genes due to degeneration of and complementation among modular enhancer elements (Force et al., 1999).

5) Phenotypic stability: in an important computational study on the evolution of RNA secondary structure Ancel and Fontana (2000) described that selection for phenotypic stability also leads to modularity (see also Ancel, this volume). Ancel and Fontana found that in RNA there is a three way correlation between phenotypic stability in the sense of robustness against thermal noise, mutational robustness and modularity of the RNA secondary structure, a phenomenon that has been called "plasto-genetic congruence." Of these three properties phenotypic stability is most effectively selected, i.e. best "seen" by natural selection (Wagner *et al*., 1997). The evolution of mutational robustness and modularity is a correlated response to selection on phenotypic robustness. Similar principles have been found to hold for protein structure (Bornberg-Bauer & Chan, 1999).

A structurally similar situation was found by Calabretta and collaborators in a model simulating the evolution of an artificial neural network. The network is selected to perform two independent functional tasks, the so-called “where and what” task (DiFerdinando *et al*., 2001) and (Calabretta and Parisi, this volume). The network is expected to produce two kinds of outputs. One indicating the location of an object and another its identity (shape). The model has two components. The neural architecture, i.e. the question which neurons are connected with each other, is genetically determined and evolves by mutation and selection. On the other hand the strength of the neural connections is determined by a learning algorithm based on back propagation, i.e. was acquired by each individual during its ontogeny. This model lead to the evolution of modularity. The reason is that the effectiveness of the learning algorithm depends on the neuronal architecture. Only a modular architecture provides the basis for successful learning. Hence modularity, which was genetically determined, had a direct fitness advantage mediated through its influence on the effectiveness of individual learning. In addition, the modular neural architectures are also genetically modular with respect to certain mutations. However, the genetic modularity, quite evidently, did not evolve in this model because of its variational (genetic) consequences. All attempts to evolve modularity without learning (i.e. only with genetic mutations) failed.

This scenario is similar to the one described by Ancel and Fontana (Ancel & Fontana, 2000) in that there is an interaction between genetic modularity and plasticity or learning. Without modular architecture the fitness of the phenotype is highly variable because the learning algorithm could not reliably find the most effective connection weights (DiFerdinando et al., 2001). This is analogous to the RNA example where the highest fitness phenotype attainable but at a lower frequency because the folding process did not reliably find the lowest energy secondary structure.

These results suggest the intriguing possibility that modularity and other properties of the genetic architecture may evolve as a side effect of the evolution of phenotypic robustness against environmental perturbations. It is thus of greatest importance to investigate whether similar congruence principles may hold for organismal characters as well.

In the older literature about genetic and environmental canalization the question had been addressed whether there might be a correlation between these two forms of robustness (reviewed in (Scharloo, 1991)). In general the conclusion, however, was negative. There seems to be no simple relationship between genetic and environmental canalization of a character. The methods available at the time, however, were quite limited and the question requires new studies with better experimental techniques. One set of papers which supports the notion of a correlation between genetic and environmental robustness for organismal characters are the studies on the canalization of life history characters of Drosophila melanogaster (Stearns *et al*., 1995; Stearns & Kawecki, 1994). Stearns and his collaborators found that characters that have a strong impact on fitness also tend to have higher mutational and environmental robustness than characters with smaller impact on fitness. The results, however, do not address the question whether genetic and environmental robustness evolved as independent characters or whether they are genetically correlated, i.e. whether there is plasto genetic congruence.

6) Modularity from "frustration." In a study on the general mathematical theory of gene interactions Sean Rice discovered an new mechanism for the origin of modules (Rice, 2000). Rice found that positive correlations are expected to evolve if the effects of two characters on fitness are synergistic, i.e. if the increase of one character value increases directional selection on the other character. On the other hand the evolution of a negative correlation is predicted if the characters are antagonistic with respect to fitness. If we consider more than two characters with pairwise antagonistic interactions on fitness, however, something unexpected happens. It is impossible to have negative correlations among three or more characters simultaneously. The evolution of negative correlations is said to be "frustrated." The only stable solution is that the characters evolve variational independence. It is simple to find a scenario for this phenomenon. For instance assume that three characters contribute to a composite characters C=x+y+z. In addition assume that the composite character C is under stabilizing selection, then there is antagonism between all three characters, and Rice's theory predicts selection for independence between the characters. Hence, modularity, i.e. character independence, can result from antagonistic fitness interaction among three or more character.

Evolution of modularity as dynamical side effect

In all the models discussed above modularity is directly or indirectly connected to some sort of selective advantage. In a study on the evolution of functional modularity using an Artificial Life model Calabretta and collaborators (Calabretta et al., 2000) discovered a mechanism which can not be classified as direct or indirect selection for modularity *per se*. Functional modularity arises from sub-specialization of duplicated structural modules

without any intrinsic benefit in terms of performance or rate of evolution. Modularity arises entirely as a side effect of evolutionary dynamics.

Calabretta *et al.* (2000) investigated an Artificial Life model in which a genetic algorithm has the task to evolve both the architecture and the connection strength for a population of neural networks controlling the behavior of a mobile robot. Each robot lives in a walled arena and it has the task to explore the arena and pick up objects and drop them at the margins of the arena. The robot has infrared sensors that inform the robot of the presence of objects and walls. The robot has two wheels for moving and turning in the environment and a gripper for picking up an object and transport the object outside the arena. The task of the robot is to move in the arena by differentially rotating the two wheels, to find an object, to pick the object up with the gripper and to transport it near one of the walls, and finally release the gripper in such a way that the object is placed outside the arena. To do this the robot has four motor systems: the two wheels, the motor that controls the opening and rising of the gripper, and the motor controlling the lowering and opening of the gripper.

As one can easily see this is a difficult task to learn. The neural network must be able to control the correct sequence of sub-behaviors: to explore the environment, to find an object by discriminating it from the wall, to pick up the object and lowering and then rising the gripper, to find the wall while avoiding the other objects, to release correctly the object outside the arena. Hence there are a number of behavioral tasks that require different neuronal control over the motor output. Basically there are two types of behaviors: searching for a new object and removing the object from the arena. The absence of an object in the gripper shall lead to searching and pickup behavior and the presence of an object in the gripper should lead to a behavioral sequence leading to the removal of the object from the arena. The question is whether these two behavioral sequences are represented by different neuronal substrates, i.e. functional modularity.

In a study by Nolfi and collaborators (Nolfi, 1997) it has been shown that functional modularity is not necessary for solving this problem. Nolfi provided the robot with duplicated neuronal elements to control the motor output. He found that the genetic algorithm can solve the problem but that the behaviors were not represented by different neuronal elements. No functional modularity evolved. This result shows that functional modularity is not necessary for solving a complex adaptive challenge consisting of a number of different tasks.

Calabretta and colleagues have conducted slightly modified simulations. The robots start out with only one neuronal control element per output unit (i.e. motor). During the evolution of the neuronal network, however, a new form of mutation is allowed, namely the duplication of these control units (Fig. 5).

By analyzing the behavior exhibited by the robots the authors showed that duplication-based modular networks possess a high degree of specialization (Calabretta et al., 2000). Some neural modules are specialized for some sub-tasks (e.g., controlling the robot's movements when the robot is exploring the environment searching for objects) while other neural modules are specialized for other sub-tasks (e.g. picking up an object). It is important to note that the populations that evolved functional modularity reached the same level of performance as the populations that did not. Furthermore modular neural networks do not reach the solution faster than others. Hence there is no intrinsic adaptive

benefit to functional modularity. But what is then the mechanism producing functional modularity in these simulations?

Various observations point to an evolutionary scenario like the following. First the duplication of a neuronal control unit. This step is neutral in this model, since the two duplicates are identical. Second, the acquisition of a neutral change in the regulation of the duplicated modules which made one unit more likely to be deployed in one situation, for instance during searching for another object rather than during object removal. Finally follows the accumulation of mutations which adapt the neuronal control unit to the functional context in which it is deployed more frequently. This step leads to a co-adaptation between the regulatory and the functional parts of the control units that lock the system into the functionally specialized state.

From a population genetic point of view the evolution of functional specialization in this model is caused by epistatic interactions among genes that influence in what situation a control unit is active and genes which control the motor output that is produced. There is a ratchet between mutations that cause a bias in deployment of a control unit and mutations that lead to the specialization of the output to the behavioral context in which it is more frequently used. One can think of this process like a dynamical bifurcation that leads to increasing specialization between control units.

Conclusions

The above overview of models to explain the origin of evolutionary modules identified seven distinct mechanisms. The majority of them have been proposed within the last two years and none is understood well enough to be excluded as a candidate. A massive amount of research is necessary to sort out these various possibilities and perhaps even discover additional ones. We think that there are two particularly pressing research questions that need to be addressed in order to make progress in this area.

Evolution of evolvability: as summarized above the results on the possibility of direct selection for evolvability are ambivalent and possibly fatal for this idea, but we still lack important results to entirely dismiss this possibility. The most glaring gap is a lack of studies with subdivided populations. There is the possibility that in structured populations selection for evolvability is more likely than without (Mitteldorf, pers. communication).

Congruence principles: many of the models that have been shown to create modularity in simulations imply some sort of congruence between modularity and other, directly selectable properties. The best example is the study on modularity in RNA secondary structure by Ancel and Fontana (2000) in which a correlation was found between the degree of modularity and phenotypic stability against environmental noise. But other models can be understood along similar lines. For instance the model of Di Ferdinando and collaborators on the “where and what” task points to a congruence between physiological and genetic modularity that leads to a selective advantage of modularity (DiFerdinando et al., 2001). Constructional selection assumes a congruence between variational pleiotropy and probability of fixation of a duplicated gene (Altenberg, 1994). The simulations about the evolution of pleiotropic effects point to a congruence between evolvability and mean fitness in non-equilibrium populations.

We think that there is sufficient cause to consider congruence principles as an important component of many scenarios for the evolution of modularity that they should

be made the focus of future research. Congruence principles have been discovered in models of macro-molecular stability and neuronal networks rather than modeled themselves. We think that it is time to develop abstract models of congruence principles to incorporate them into population genetic theory. In addition, it will be important to find new examples of congruence principles in models of physiology or development and in empirical model systems.

Mechanistic plurality is a real possibility: it would be a mistake to assume that we will discover one and only one mechanism that explains the origin of modularity under all circumstances. For the origin of species, for instance, it is clear that there are many population biological and genetic mechanisms that can lead to the origin of a new species (Otte & Endler, 1989). There is no unitary “speciation mechanism.” Similarly in nature there might be a multitude of mechanisms contributing to the evolution of modular genetic architectures. Hence, it might not be productive to try to identify one mechanism among the proposed models to be "The Solution." Each model needs to be judged on its own merits and it may be that we end up with an array of mechanisms each of which may play a role some situations but not in others.

Acknowledgement: the authors want to thank Dr's Chi-hua Chiu, Joachim Hermission and Terri Williams for comments on a previous draft of this manuscript. GPW is grateful to the former and current members of the Wagner lab for many stimulating discussions on this and related topics.

Table 1: selection coefficients s of a modifier that suppresses pleiotropic effects and the percentage of the selection coefficient explained by selection for evolvability. Note that the selection coefficient is quite high with 8%, but only 2 to 5% of that (i.e. s'=0.0016 and s'=0.0036, respectively) can be attributed to selection for evolvability. Vs is the strength of stabilizing selection, the directional selection was 0.1 and the population size 100.

	s	% expl. by evolvability
Vs=2	0.08	2.0%
Vs=10	0.08	4.5%

Figure captions:

Figure 1: variational modularity of a set of phenotypic characteristics is defined as integration due to the presence of many pleiotropic effects of genes and relative independence from other phenotypic characters due to a lack of pleiotropic effects. It is also often the case that a phenotypic module also is primarily dedicated to a specific function. In this case the variational module is also an adaptive character, or an evolutionary module.

Figure 2: a modifier model in which the genotype at a modifier locus determines the relative size of pleiotropic effects between two characters. With MM the effects on the two characters of a mutation are of the same magnitude, with Mm the effects on x2 are smaller than the effects on x1 and with mm the mutations have no effect on x2. The modifier allele m suppresses the pleiotropic effects on the character that is under stabilizing selection. Selection of this allele increases evolvability (Baatz and Wagner, 1997).

Figure 3: comparison of the distribution of genotypic values of two classes of genotypes. The MM genotypes have equal mutational effects on the two characters and the distribution is thus circular in this model. The other class of genotypes Mm has smaller effects on the second character and the distribution of genotypic values is thus more extended along the axis of the first characters. If the first character is under directional selection for larger character values and the second is under directional selection the relative mean fitness of these two classes of genotypes is influenced by two factors: 1) by the relative location of the genotype distribution along the z1 axis. The more the distribution is to the right the higher is the mean fitness. 2) by the amount of variation in the second character. Since z2 is under stabilizing selection the fitness is higher the smaller the variance for the second character. In this case the Mm distribution has higher fitness, but only the component of this fitness advantage that is due to the location along the axis of the first character can be said to be selection for Mm caused by selection for evolvability. As seen in table 1, this contribution is in fact very small, less than 5% in most cases tested.

Figure 4: the effect of directional selection on one character on the genetic architecture of a two character phenotype. When ever there is directional selection on any one character all the genes increase their contribution to this character. Even directional selection strictly alternating between the two characters does not lead to a segregation of genes into a modular pattern.

Figure 5: schematic representation of the genomes of the hardwired and duplication-based modular architectures (LM = genetic encoding for the connection weights of the left motor; RM = right motor; PU= pick-up motor; RL = release motor). (Modified from Calabretta *et al.*, 2000).

References

Abouheif, E. (1999). Establishing homology criteria for regulatory gene networks: prospects and challenges. In *Homology* (Bock, G. R. & Cardew, G., eds.), pp. 207-221. Wiley, New York.

Altenberg, L. (1994). The evolution of evolvability in genetic programming. In *Advances in Genetic Programming.* (K. E. Kinnear, J., ed.), pp. 47-74. MIT Press, Cambridge.

Altenberg, L. (1995). The schema theorem and the Price's theorem. In *Foundations of Genetic Algorithms 3.* (Whitley, D. & Vose, M. D., eds.), pp. 23-49. MIT Press, Cambridge. MA.

Ancel, L. W. & Fontana, W. (2000). Plasticity, evolvability and modularity in RNA. *J exp Zool (Mol. Dev. Evol.)* **288**, 242-283.

Baatz, M. & Wagner, G. P. (1997). Adaptive inertia caused by hidden pleiotropic effects. *Theor. Pop. Biol.* **51**, 49-66.

Bolker, J. A. (2000). Modularity in development and why it matters in Evo-Devo. *Am. Zool.* **40**, 770-776.

Bonner, J. T. (1988). *The Evolution of Complexity*, Princeton University Press, Princeton, NJ.

Bornberg-Bauer, E. & Chan, H. S. (1999). Modelling evolutionary landscapes: mutational stability, topology and superfunnels in sequence space. *Proc. Natl. Acad. Sci. USA* **96**, 10689-10694.

Brandon, R. N. (1999). The units of selection revisited: the modules of selection. *Bio Phil* **14**, 167-180.

Calabretta, R., Nolfi, S., Parisi, D. & Wagner, G. P. (2000). Duplication of modules facilitates the evolution of functional specialization. *Artificial Life* **6**, 69-84.

Calabretta, R., Parisi, D., (this volume). Evolutionary connectionism and mind/brain modularity. In: Callebaut, W., Rasskin-Gutman, D. (Eds.), Modularity. Understanding the development and evolution of complex natural systems. The MIT Press, Cambridge, MA.

Cheverud, J., Routman, E. J. & Irschick, D. K. (1997). Pleiotropic effects of individual gene loci on mandibular morphology. *Evolution* **51**, 2004-2014.

Cox, E. C. & Gibson, T. C. (1974). Selection for high mutation rates in chemostats. *Genetics* **77**, 169-184.

Dassow, G. v. & Munro, E. (1999). Modularity in animal development and evolution: elements of a conceptual framework for EvoDevo. *J exp Zool (Mol Dev Evol)* **285**, 307-325.

Di Ferdinando, A., Calabretta, R. & Parisi, D. (2001). Evolving modular architectures for neuronal networks. In *Proceedings of the sixth Neural Computation and Psychology Workshop: Evolution, learning and development.* (French, R. & Sougné, J., eds.), pp. in press. Springer Verlag, London.

Force, A., Lynch, M., Pickett, F. B., Amores, A., Yan, Y. L. & Postlethwait, J. (1999). Preservation of duplicate genes by complementary, degenerative mutations. *Genetics* **151**, 1531-1545.

Galis, F. (1999). Why do almost all mammals have seven cervical vertebrae? Developmental constraints, Hox genes, and cancer. *J. exp. Zool. (Mol. Dev. Evol.)* **285**, 19-26.

Galis, F. (2001). Key innovations and radiations. In *The Character Concept in Evolutionary Biology.* (Wagner, G. P., ed.), pp. 581-605. Academic Press, San Diego, CA.

Gerhart, J. & Kirschner, M. (1997). *Cells, Embryos, and Evolution.*, Blackwell Science, Malden, MA.

Gilbert, S. F. & Bolker, J. A. (2001). Homologies of process and modular elements of embryonic construction. In *The Character Concept in Evolutionary Biology* (Wagner, G. P., ed.), pp. 435-454. Academic Press, San Diego, CA.

Gilbert, S. F., Opitz, J. & Raff, R. A. (1996). Resynthesizing evolutionary and developmental biology. *Dev. Biol.* **173**, 357-372.

Gould, S. J. (1977). *Ontogeny and Phylogeny*, Harvard University Press, Cambridge, MA.

Holland, J. H. (1992). *Adaptation in Natural and Artificial Systems.* 2nd edit, MIT Press, Cambridge, MA.

Houle, D. (2001). Characters as the units of evolutionary change. In *The Character Concept in Evolutionary Biology.* (Wagner, G. P., ed.), pp. 109-140. Academic Press, San Diego.

Kim, J. & Kim, M. (2001). The mathematical structure of characters and modularity. In *The Character Concept in Evolutionary Biology.* (Wagner, G. P., ed.), pp. 215-236. Academic Press, San Diego.

Leroi, A. M. (2000). The scale independence of evolution. *Evolution & Development* **2**, 67-77.

Liem, K. F. (1973). Evolutionary strategies and morphological innovations: cichlid pharyngeal jaws. *Syst. Zool.* **22**, 425-441.

Maynard-Smith, J. & Haigh, J. (1974). The hichhiking effect of a favourable gene. *Genet. Res.* **23**, 23-35.

Mezey, J. (2000). Pattern and evolution of pleiotropic effects: analysis of QTL data and an epistatic model. PhD Thesis, Yale University.

Mezey, J. G., Cheverud, J. M. & Wagner, G. P. (2000). Is the genotype-phenotype map modular? A statistical approach using mouse Quantitative Trait Loci data. *Genetics* **156**, 305-311.

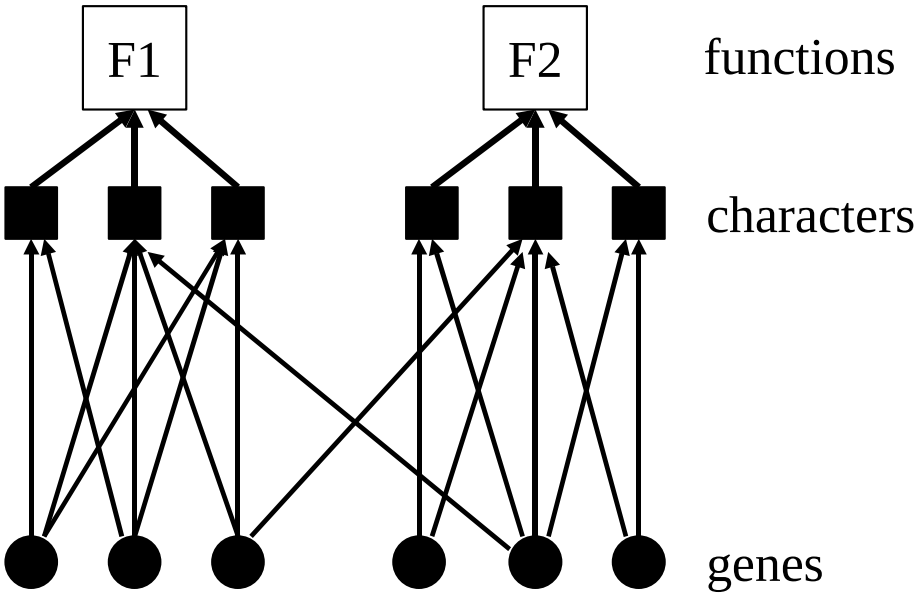
Mittenthal, J. E., Baskin, A. B. & Reinke, R. E. (1992). Patterns of structure and their evolution in the organization of organisms: modules, matching, and compaction. In *Principles of Organization in Organisms.* (Mittenthal, J. E. & Baskin, A. B., eds.), pp. 321-332. Addison-Wesley, New York.

Nagy, L. M. & Williams, T. A. (2001). Comparative limb development as a tool for understanding the evolutionary diversification of limbs in arthropods: challenging the modularity paradigm. In *The Character Concept in Evolutionary Biology.* (Wagner, G. P., ed.), pp. 455-488. Academic Press, San Diego, CA.

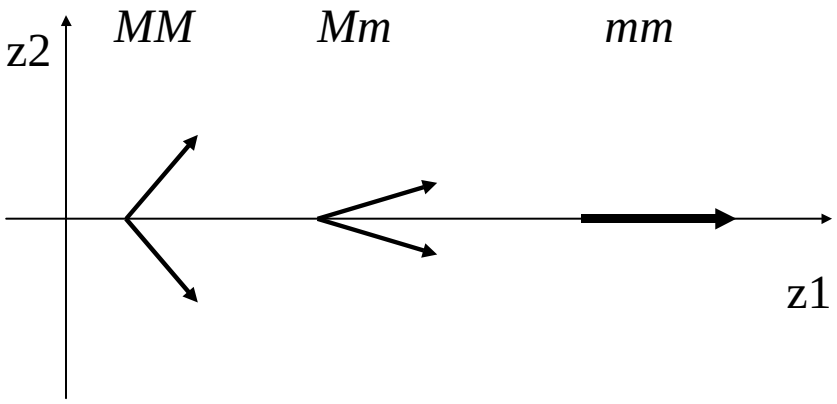
Nolfi, S. (1997). Using emergent modularity to develop control system for mobile robots. *Adaptive behavior* **5**, 343-364.

Otte, D. & Endler, J. A. (1989). *Speciation and its Consequences.*, Sinauer, Sunderland, MA.

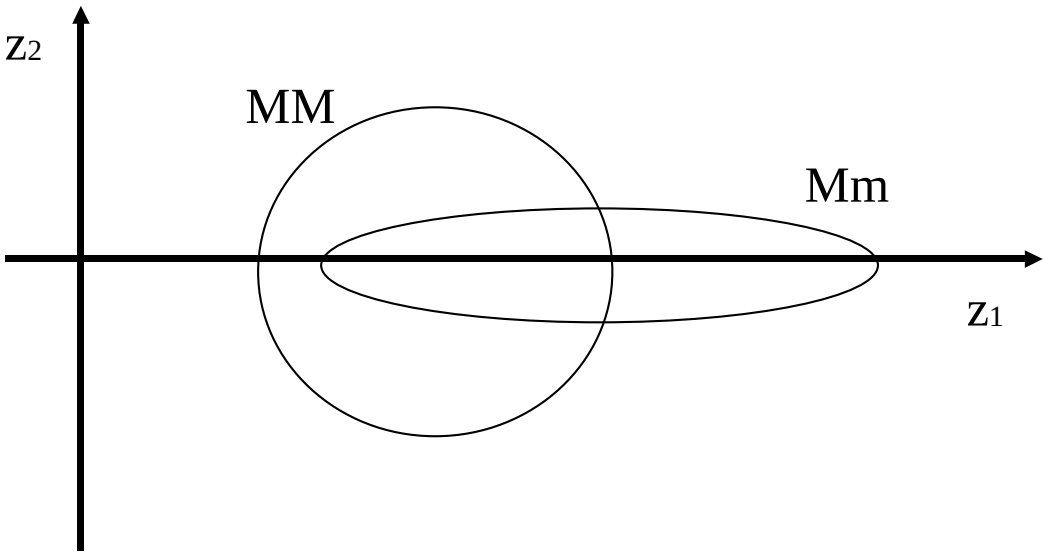
Raff, R.-A. (1996). *The Shape of Life.*, University of Chicago Press, Chicago, Ill.
Raff, R. A. & Sly, B. J. (2000). Modularity and dissociation in the evolution of gene expression territories in development. *Evolution & Development* **2**, 102-113.
Rice, S. H. (1990). A geometric model for the evolution of development. *J. theor. Biol.* **143**, 319-342.
Rice, S. H. (2000). The evolution of developmental interactions. In *Epistasis and the Evolutionary Process.* (Wolf, J. B., III, E. D. B. & Wade, M. J., eds.), pp. 82-98. Oxford University Press, Oxford.
Riedl, R. (1978). *Order in living organisms: A systems analysis of evolution*. Trans. R. P. S. Jeffries, Wiley, New York.
Rohwer, J. M., Schuster, S. & Westerhoff, H. V. (1996). How to recognize monofunctional units in a metabolic system. *J. thor. Biol.* **179**, 213-228.
Scharloo, W. (1991). Canalization: Genetic and developmental aspects. *Ann. Rev. Ecol. Syst.* **22**, 65-93.
Schwenk, K. (2001). Functional units and their evolution. In *The Character Concept in Evolutionary Biology*. (Wagner, G. P., ed.), pp. 165-198. Academic Press, San Diego, CA.
Stearns, S. C., Kaiser, M. & Kawecki, T. J. (1995). The differential canalization of fitness components against environmental perturbations in Drosophila melanogaster. *J. Evol. Biol.* **8**, 539-557.
Stearns, S. C. & Kawecki, T. J. (1994). Fitness sensitivity and the canalization of life history traits. *Evolution* **48**, 1438-1450.
Sterelny, K. (2000). Development, evolution and adaptation. *Phil. Science* **67**, S369-S387.
Stock, D. W. (2001). The genetic basis of modularity in the development and evolution of the vertebrate dentition. *Proc. Roy Soc., B* **in press**.
Turney, P. D. (2000). A simple model of unbounded evolutionary versatility as a large-scale trend in organismal evolution. *Artificial Life* **6**, 109-128.
Vermeij, G. J. (1970). Adaptive versatility and skeleton construction. *Amer. Nat.* **104**, 253-260.
Wagner, G. P. (1981). Feedback selection and the evolution of modifiers. *Acta Biotheoretica* **30**, 79-102.
Wagner, G. P. (1984). Coevolution of functionally constrained characters: Prerequisites for adaptive versatility. *BioSystems* **17**, 51-55.
Wagner, G. P. (1995). The biological role of homologues: A building block hypothesis. *N. Jb. Geol. Paläont. Abh.* **19**, 279-288.
Wagner, G. P. & Altenberg, L. (1996). Complex adaptations and the evolution of evolvability. *Evolution* **50**, 967-976.
Wagner, G. P., Booth, G. & Bagheri-Chaichian, H. (1997). A population genetic theory of canalization. *Evolution* **51**(2), 329-347.
Weiss, K. M. (1990). Duplication with variation: Metameric logic in evolution from genes to morphology. *Yearbook of Physical Anthropology* **33**, 1-23.
Wray, G. A. (1999). Evolutionary dissociations between homologous genes and homologous structures. In *Homology* (Bock, G. R. & Cardew, G., eds.), pp. 189-203. Wiley, New York.



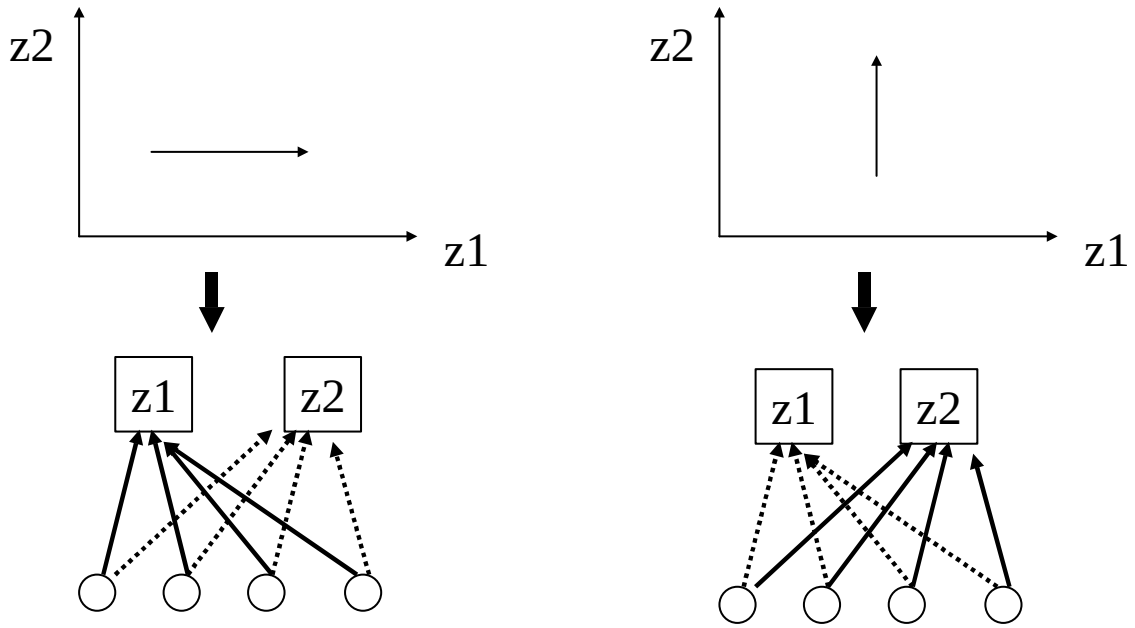
Wagner et al., Fig.1



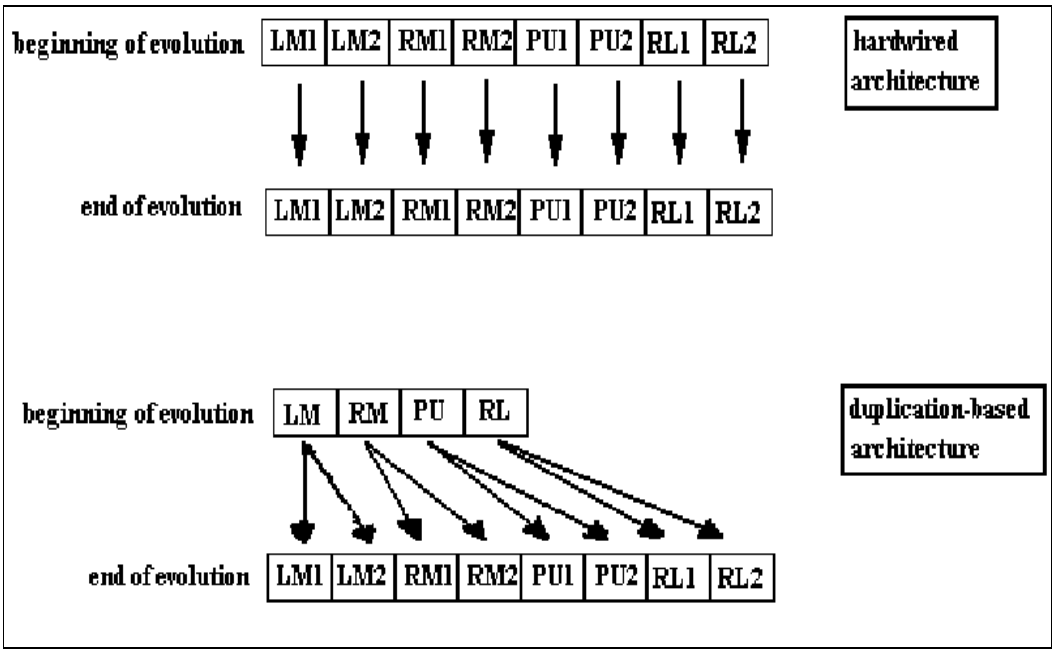
Wagner et al., Fig. 2



Wagner et al., Fig. 3



Wagner et al., Fig. 4



Wagner et al., Fig. 5