Evolution of modularity

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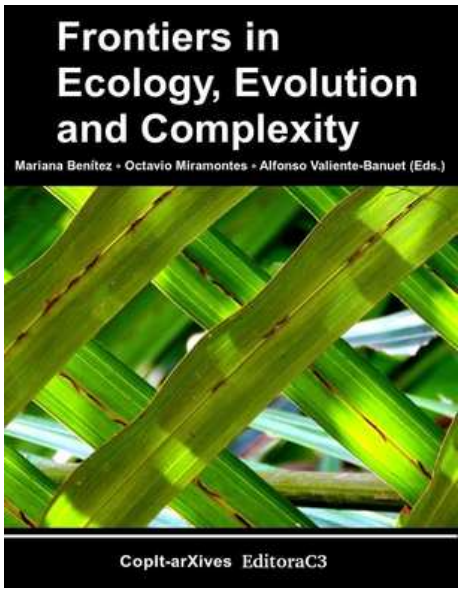

Contents

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1 Abstract

Modularity is a widespread property in biological systems. In a modular system there are sets of densely interacting components, with sparse interactions between sets. Because of this arrangement, the behavior of elements inside a module depends little on factors external to the module. Modularity is very important in adaptive evolution as it allows the adjustment of one part of the organism without affecting previously adapted traits. It is thus a major determinant of evolvability. Despite its importance, the evolutionary origins of modularity are still not clear. Because modularity, by itself, does not confer an immediate fitness advantage to an organism, explaining its evolution is not as straightforward as it is for many other phenotypic traits. However, computational studies that simulate the evolution and development of simple phenotypic traits have recently allowed the proposal of several evolutionary scenarios that increase the modularity of different kinds of biological systems. Here, I review some of these studies to show that there are many possible evolutionary paths to modularity. This observation may help to explain the prevalence of modular arrangements in living beings.

2 Resumen

La modularidad es una propiedad común en los sistemas biológicos. En un sistema modular existen conjuntos de elementos con muchas interaccioness, con pocas interacciones entre elementos de conjuntos distintos. Esta disposición causa que la conducta de los componentes de un módulo dependa poco de factores externos al módulo. La modularidad es muy importante en la evolución adaptativa, ya que permite el ajuste de una parte del organismo sin afectar otros rasgos. Por lo tanto, es un componente importante del potencial evolutivo. A pesar de su importancia, el origen evolutivo de la modularidad aun no se ha aclarado. Debido a que la modularidad no confiere una ventaja inmediata en la adecuación, explicar su evolución no es tan sencillo como lo es para otros rasgos fenotípicos. Sin embargo, distintos estudios computacionales en los que se simula la

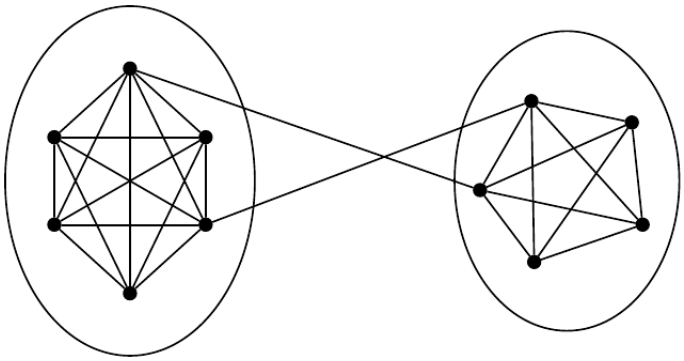

Figure 1: Modules are sets of densely interacting elements, with few interactions between elements in different sets. The figure shows a system in which elements (nodes) have interactions (straight lines) with other elements in the system. Two modules, surrounded by ellipses, are easily recognized.

evolución y el desarrollo de rasgos fenotípicos simples han permitido el planteamiento de varios escenarios evolutivos que incrementan la modularidad de distintas clases de sistemas biológicos. Aquí, yo reviso algunos de estos estudios para mostrar que existen muchos posibles caminos hacia la modularidad. Esta observación puede ser útil para explicar la alta frecuencia de estructuras modulares en los seres vivos.

3 The role of modularity in adaptive evolution

Biological systems are frequently arranged in a modular manner. This means that it is easy to recognize sets of densely interacting elements, with few interactions between elements in different sets (Figure 1). Modules exist in many different kinds of traits: from the structure of single macromolecules to complex organs and tissues. In the case of single macromolecules, a module corresponds to a structural element with a high number of bonds between monomers. In biological molecular or cellular networks, a module comprises a set of molecules, or cells, in which cross-regulatory or other kinds of interactions are significantly abundant. Such networks include metabolic networks, signaling pathways, gene regulatory circuits or neuron nets. At a higher scale, the development of a morphological structure may be modular, if morphogenetic interactions between cells and tissues occur mostly within a structure.

Elements inside a module behave semi-independently from elements outside the module because there are few interactions between them. For example, a structural element in a modular macromolecule can fold or unfold with little influence from other parts of the molecule. Thus, a stem-loop in the secondary structure of a modular RNA molecule may be preserved after other stem-loops in the molecule fold or unfold. Accordingly, the dy-

namic behavior of nodes inside a module of a biological network are only weakly affected by nodes in other modules. As for the development of a module-like body structure, it would occur semi-independently from adjacent tissues and organs.

Modularity has important effects on evolution. The reason is that genetic changes that affect one module are frequently constrained to that module. In a hypothetical modular RNA molecule, a mutation that changes the sequence that produces one stem-loop would only rarely affect a different stem-loop in the same molecule. Thus, distinct traits, such as stem-loops in the secondary structures of an RNA molecule, can be tuned independently by mutation and selection, without affecting those traits that are already adapted. For example, the catalytic function of one such stem-loop may be modified without altering interactions to other cell components mediated by other parts of the RNA molecule. Modularity affects the evolution of biological networks and macroscopic organismal traits in a similar manner. Consider, for instance, Darwin's finches. In these birds, the beak depth depends on a module of interacting genes and proteins that includes the protein BMP4. At the same time, the beak length depends on a different module including the protein calmodulin. Because of the modular structure of these interaction networks, there are mutations that change beak depth but leave length untouched, and mutations that alter beak length without changing depth [1]. Beak depth and length can be adjusted independently, thus allowing mutational access to a wide diversity of beak shapes. The increased access to many different combinations of trait variants makes modularity an essential component of evolvability, the potential to produce novel beneficial variation through random mutations [2, 3]. In fact, that modularity facilitates adaptive evolution is also supported by a study that links modularity of developmental stages to rates of diversification and adaptive radiations in insects [4]. In the case of Darwin's finches, modularity of beak development has apparently been paramount in adaptation to a wide diversity of foods, and hence to the finches' adaptive radiation [5].

That modularity increases evolvability is well established. However, how modularity itself evolves is not so easily explained. Since modularity only refers to the organization of interactions among a system's components, it does not increase fitness by itself [6]. Hence, the evolution of modularity cannot be explained in the same manner as the evolution of body structures, metabolic abilities, or of many other traits that, if altered, have immediate effects on organismal fitness. To study the origins of modules we must understand how modularity interacts with other properties of biological systems [6]. An additional complication in the understanding of the origins of modularity is that, among random structures, non-modular configurations far outnumber modular ones. Because of the importance of modularity for adaptive evolution, how modularity evolves in different kinds of biological systems, from single molecules to molecular and cellular networks to body parts, is a central question in evolutionary biology. Answering it would be a major advance in the understanding of the mechanisms that make organisms evolvable.

Despite the difficulties, there have been many recent advances in the study of the evolution of modularity. These advances are largely due to studies where the evolution and

development of phenotypic traits are simulated *in silico*. Although limited by the necessary simplifications, such computational studies have many important advantages. First, a model of a developmental mechanism permits the analysis of how random genotypic change affects the production of the phenotypic properties that we study. Thus, we can study variational properties of a genotype, like its robustness to mutations [7] or its potential to access new phenotypes [8]. Implementing random genetic changes and selection we can also study the effects of different evolutionary scenarios on an evolving population of 'simulated organisms'. Because we can "re-run the tape of life" by repeating these simulations as many times as wanted, we can distinguish real evolutionary trends from historical accidents. Moreover, we can trace all ancestors of an 'evolved' population to study the genetic changes that occurred across such a lineage. In the following section I review some of the recent studies that have importantly enhanced our understanding of the evolution of modularity by following a modeling approach.

4 Evolutionary scenarios for the origin of modularity

Understanding how RNA molecules fold to attain their final structures, and how different structures evolve is an interesting topic in biology. One reason why the study of RNA structures is pertinent is because the catalytic activities that an RNA molecule performs depend on the shape that the molecule adopts. Many of the reactions that RNA molecules catalyze, like protein synthesis, are crucial to the cell. Indeed, RNA molecules may have been critical players in the earliest stages of the evolution of life. The reason is that, unlike DNA or proteins, RNA molecules can both carry genetic information and catalyze the chemical reactions that a primordial metabolism would require. In addition, we can use biophysically grounded algorithms to determine the secondary structure that an RNA sequence adopts. Thus, the relationship between genotype (RNA sequence) and phenotype (structure) can be assessed.

Modularity in RNA structures may allow tuning different parts of the molecule involved in different sub-functions. Indeed, RNA stem-loops that are conserved across lineages tend to tolerate changes in adjacent sequences [9]. In other words, such stem-loops may be considered modules, since they are little affected by neighboring monomers.

Ancel and Fontana simulated the evolution of populations of RNA molecules by implementing random mutations on RNA sequences. They used computational tools to determine the secondary structure adopted by each RNA molecule in an evolving population [10]. The authors designed their simulations so that selection favored structural similarity to a predetermined RNA secondary structure but also robustness of the minimum free energy secondary structure to thermal fluctuations. These conditions result in RNA molecules for which an increased fraction of mutations do not change the minimum free energy secondary structure. Importantly, this selection regime also leads to modularity: In a typical molecule from the evolved population, individual stem-loops

fold an unfold independently from other structures in the same molecule [10]. Thus, scenarios that increase robustness to thermal fluctuations and mutations produce modular secondary structures in RNA molecules.

At a higher level of organization we find molecular and cellular networks. These networks include signal-transduction pathways that coordinate cellular functions and communicate cells, gene regulatory circuits, that direct changes in gene activity across development, or neuron nets that link nerve cells to orchestrate neural activity. Molecular and cellular networks also exhibit modularity. For example, that gene regulatory circuits are modular is sustained on several independent observations: i) Measures of clustering in large-scale maps of transcriptional regulation networks indicate highly connected sets of genes with sparse connections between sets [11]; ii) the existence of modularity in morphological traits, as in the finches' beaks, suggests an underlying modularity of the regulatory networks that produce those traits [1, 6]; and iii) many experimentally grounded computational models of gene regulatory circuits successfully reproduce specific developmental processes by considering only a handful of genes [12, 13]. This last observation also suggests modularity, as it shows that the influence of other factors in the processes under study is negligible.

One may think that the observations on the modularity of RNA structures could be extrapolated to molecular and cellular networks. However, this is not the case. While increased robustness to mutations results in modularity of RNA secondary structures [10], evolution of robustness in these networks does not produce modular configurations [14, 15]. Thus, there must be other mechanisms behind the evolution of modularity in these networks.

Kashtan and Alon used computer simulations to evolve networks while selecting them for their ability to perform a task, which is to compute a specific boolean function. Modular networks can evolve when selection oscillates so that it sometimes favors systems that perform one task A and sometimes favors those networks that perform a different task B [14]. A crucial additional requirement is that each of the alternative tasks A and B must be decomposable into sub-tasks, so that B contains the same sub-tasks as A, but combined in a different manner. Hence, this scenario demands that the goals that the environment imposes fluctuate in a modular manner. Modularity arises because, among systems that perform one task (e.g. A), those that are modular are more easily modified to produce the other task (B). Therefore, modular networks have higher chances to survive fluctuations. This scenario is currently our best explanation for modularity of traits for which the direction of selection fluctuates along time. Notwithstanding, while it is true that many environmental demands fluctuate, whether they do it in a modular manner is still an open question. Moreover, in this scenario modularity decays rapidly once fluctuations stop. Thus, this scenario cannot explain modularity where environmental demands do not fluctuate. This may be the case for gene regulatory circuits that perform the same function in the face of different kinds of perturbations in a wide range of species [12, 13].

Modularly-varying environmental demands are not essential for the evolution of mod-

ularity in molecular and cellular networks. Andreas Wagner and I studied a simple model of gene regulatory circuit dynamics that has been valuable to address different questions in evolutionary biology, like the relationship between sexual reproduction and robustness [16] or the role of plasticity in evolution [8]. Despite the necessary simplifications, this model is useful to study how cross-regulation produces the gene activity patterns that distinguish different parts of an organism. Moreover, because of its simplicity, the model allows the analysis of thousands or millions of gene regulatory circuit 'genotypes' and the gene activity phenotypes that they produce.

In our setup, a circuit 'genotype' specifies how a gene changes its activity state in response to the activity of other genes in the circuit. The genotype is summarized in a matrix W, in which non-zero entries w_{ij} indicate regulatory interactions. Specifically, gene j promotes (obstructs) the activity of gene i whenever w_{ij} is positive (negative). Given a matrix W, and an initial gene activity pattern, the model allows to follow the changes in gene activity until the system attains either a steady or an oscillatory gene activity pattern. We can consider such a final activity pattern as the output of the circuit's developmental dynamics, and thus, it defines the system's gene activity phenotype. Details of the model may be consulted in [15].

We asked what happens to the structure of gene regulatory circuits when organisms acquire the ability to produce new gene activity patterns. The evolution of such new activity patterns is very frequent across the history of life. It precedes the evolutionary appearance of new cell types, organs or body structures. We found that gene regulatory circuits that have evolved under selection to produce a single gene activity pattern I increase their modularity after selection for both the ancestral activity pattern I and, from a different initial condition, a new *additional* gene activity pattern II [15].

The vast majority of pairs of gene activity patterns I and II picked at random comprise two sets of genes: i) a first set S where selection requires that each gene has the same activity state (active or inactive) in the two gene activity patterns that the circuit produces, and ii) a second set of genes D where selection promotes different activity states in the gene activity phenotypes (Figure 2A). In this scenario, modularity evolves because interactions between genes in S and genes in D obstruct adaptation. Assume a circuit in which genes in the first set S indeed comply with selection, so that each of the genes in S has the same activity state in the two gene activity patterns that a circuit produces. In this case, genes whose activity depends mainly on genes in S are prone to also have the same activity state in the two patterns that the circuit produces. Thus, selection would not favor that genes in D were under control of genes in S. Along the same lines, if genes in D fulfill selection demands, genes regulated mainly by genes in D would likely have different activity states in the two patterns. Therefore, regulation of genes in S by genes in D is selected against. The result is the appearance of two densely connected sets of genes with only few regulatory interactions between sets. Modularity increases further when more new activity patterns evolve, and under a wide range of parameter values [15].

In contrast to gene regulatory circuits, in neuron nets there are clear connection costs:

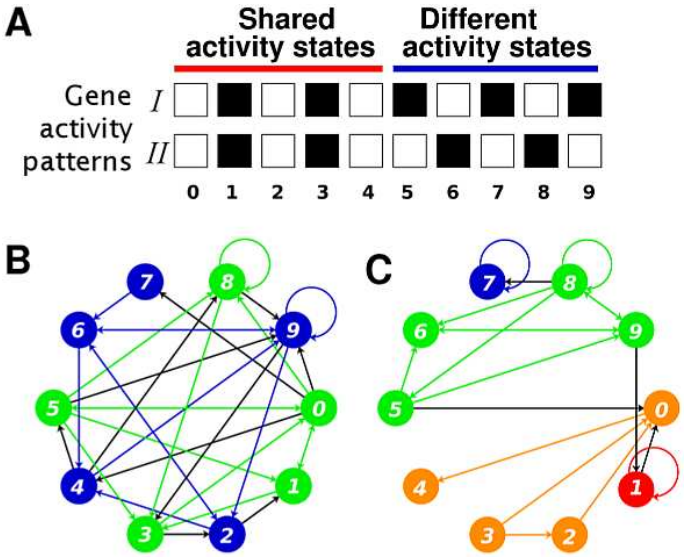

Figure 2: Evolution of modularity after selection to produce an additional gene activity pattern. A) In this evolutionary scenario, circuits that have evolved under selection for a single gene activity pattern I start being selected for an additional activity pattern II. B) A typical non-modular circuit after selection for a single gene activity pattern I. C) A typical modular circuit after selection for both gene activity patterns I and II. Panels taken from [15].

an organism must spend resources (proteins, membranes, ATP molecules) to create more connections. Clune and collaborators have recently analyzed the evolution of modularity in evolving populations of networks in a scenario where, like in neuron nets, there are connection costs. The authors found that modularity does not evolve when selection favors the efficient performance of one task. However, modularity increases if, in addition, selection promotes minimization of connection costs. This regime produces modular networks when selection disfavors the appearance of new connections and also when selection punishes an increased length of the summed length of all connections [17].

5 Conclusion

Here I have reviewed some of the evolutionary scenarios that increase modularity in different kinds of systems. The list is forcefully incomplete, as many other scenarios that lead to modularity have arisen in recent years [6, 18]. Is there a 'winner' among the several plausible explanations for the origin of modularity in living organisms? An open possibility is that several evolutionary mechanisms lead to the appearance of modularity, under different circumstances. Perhaps this is the reason why modularity is so widespread and why biological systems, across all levels of organization, are evolvable.

Advocating for a pluralistic perspective on the evolution of modularity does not mean considering that the issue is settled. The many roads to modularity may not be equally transited. It is necessary to define precisely the conditions under which each evolutionary scenario produces modularity. This will allow us to develop a consensus on the most relevant mechanisms for the appearance of modules in biological systems. It is also necessary to deepen in the consequences that modularity has in the evolution and development of phenotypic traits. Simulation studies will also have an important role in this endeavor. For example, this approach has already suggested that modularity favors the recurrent co-option of some sets of genes [15], and it has allowed deepening on how modularity facilitates adaptation [19]. New and exciting advances are expected from the study of the modular organization of biological systems and its impact on evolution.

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