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A THEORETICAL CHARACTERIZATION OF MORPHOFUNCTIONAL AND DEVELOPMENTAL MODULES: AN APPROACH TO THE STUDY OF THE CRANIOFACIAL COMPLEX

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Contents: 1. Introduction. 2. Delimiting the Concept of the *Module*. 3. The Morphology of the Craniofacial Complex as a Complex Modular System. 4. Conclusions.

Keywords: Functional Modules, Developmental Modules, Conceptual Delimitation, Craneofacial Complex.

Abstract: *Modularity in biological systems is a central theme in current research. However, there are some problems related to the vague definitions of the concept of a module that impede both its empirical application and the comparison of data from different studies. In this article, we propose to characterize this concept which is consistent with the diverse ways in which it is conceptualized in the specialist literature. We test our characterization by analyzing the case study of the craniofacial complex. We conclude that the proposed delimitation allows a better understanding of modules since it differentiates between the concept of the module as a state (morphofunctional modules) and as a process (a product of ontogenetic or phylogenetic history).*

Introduction

The complexity of biological systems means that there is a need for theories and analytical methodologies that will enable more appropriate resolutions of the different problems connected to them. In this sense, complexity theory is an appropriate theoretical and epistemological corpus for embracing several difficulties that could not be adequately resolved through other methodologies. For example, studies of adaptation were traditionally undertaken from a one-dimensional approach, as if the feature being studied only depended on a limited set of variables (see Gould and Lewontin [1] and Gould [2]). However, with the development of complexity theory and the diverse theories associated with it (systems theory, modularity, etc.), adaptive systems studies began to make a major shift towards an explanation that made greater biological sense. In this context, it is useful to consider García's [3] proposal for understanding complex systems as a representation of a particular aspect of reality understood as an organized whole in which the elements are not separable and, therefore, cannot be studied in isolation. This definition is consistent with the characterization of modules that will be provided later in this article.

Furthermore, the notion of modularity has gained acceptance in the field of biological systems. As such, this concept is frequently used in the field of biological systems, including neurobiology, developmental biology, and molecular genetics. For instance, neurobiologists are studying cerebral organization by approaching cortical columns, areas, and systems in a modular fashion. This has led the suggestion that the overall architecture of the brain is laid out in a «mosaic» of interacting components with specialized structures and functions (Calabretta *et alii* [4]). On the other hand, hierarchical modular organization has been identified at a metabolic level in 43 different organisms, with modular networks organized into tiny, highly connected topological modules that are clustered in a hierarchical fashion into larger and less cohesive units (Ravasz *et alii* [5]).

Extensive and detailed reviews of this topic can be found in Schlosser and Wagner [6] and Callebaut and Rasskin-Gutman [7]. In recent years, the modular view of biological systems has increased exponentially, although it is still not applied on a large scale, perhaps due to certain theoretical difficulties in its application. Indeed, there are many definitions for *module*, most of which are vague and therefore difficult to apply in the empirical field.

However, the modular approach has proved useful in biology for addressing complex problems such as aspects linked to growth and development. In this sense, the development of an organism reveals highly complex coordination, however, an embryo can change during early ontogeny without altering its overall equilibrium. During this process it is worth asking how is it possible that some parts of the body are destroyed by programmed cell death (apoptosis) while neighboring structures remain unchanged? How can the study of these complex processes be approached heuristically?

Possible theoretical approaches to answering these questions were put forward by Breuker *et alii* [8], who insisted on the usefulness of modularity in the developmental process as a flexible system which would provide an integrated perspective that includes structural and functional aspects. However, it is worth considering whether *modularity* and *integration* are merely different concepts, or whether they are antagonistic, in that one way of understanding modularity implies that the organism is fragmented, rather than integrated. The answer to this question depends on how integration and modularity are defined and quantified (Eble [9]; Goswami [10]; Goswami and Polly [11]; Goswami *et alii* [12]; Klingenberg [13]).

According to Bolker [14], modularity is difficult to define precisely, but it can be easily recognized intuitively. In this way, the author asserts that modularity should be analyzed on multiple levels of the biological hierarchy. But this undoubtedly constitutes a major difficulty to implementing a definition for module that can be adequately applied at any level of organization. In this regard, it should be noted that the term *module* can be applied to a variety of phenomena, ranging from simple structures such as a codon to populations or ecosystems. Moreover, Schwenk [15] (p. 166) also recognizes this complexity by stating that «organisms manifest complexly nested webs of character interaction and integration, such that a phenotypic change in one character will almost certainly have an impact on others». It is this complexity that makes it difficult to propose a formal definition for the module.

Bearing in mind the above problems, the objectives of this article are: a) to put forward a clearer delimitation of the term *module*; and b) to determine whether it is possible to apply this delimitation to a particular case of morphological modules at the craniofacial level.

Delimiting the Concept of the *Module*

Numerous definitions of *modules* have been put forward from different perspectives. In this way, Raff [16] (p. 325) asserts that modules «are distinct in genetic specification, autonomous features, hierarchical organization, interactions with other modules, location, time of occurrence, and dynamic properties». And subsequently Raff and Sly [17] (p. 102) characterized the developmental modules with the following properties:

> they have an autonomous, discrete organization defined by expression of specific genes; they contain standard part units and may in turn be organized into larger hierarchical units; they occupy specific physical sites within the embryo; they exhibit varying degrees of connectivity to other modules within the embryo; they are dynamically transformed through time; and last, developmental modules are not only dynamic within the embryo, they also undergo evolutionary change, and consequently can be identified as modified homologous elements in comparable ontogenies.

As we shall see later, this characterization is compatible with our proposal. Moreover, Moss [18] recognizes that there is ambiguity in the biological use of this term and defines it as a unit that is part of a larger system and has its own structural and functional identity. All these proposals represent a broad conceptualization of the term *module* that can be applied to a vast universe of cases.

Moreover, Winther [19] asserts that the modules are entities that exist as different parts that are repeated and standardized at different levels of organization, such as molecular, cellular, morphological, and so on. He recognizes the existence of structural, physiological, and developmental modules, each of which carries out multiple functions. As such, we consider that the parts that make up an organism – such as the bones of vertebrates – would constitute structural modules. An example of physiological modules would be the cascade reactions generated by transduction systems and second messengers that facilitate the liberation of calcium as inositol 1,4,5-triphosphate to be used in bone formation. Finally, developmental modules could be represented by signaling systems that determine the organization and regulation of limb buds, such as the family of Hox genes (HOXB8, D9, D13, etc.). In synthesis, Winther proposed that modules be classified based on their functional roles, in contrast to other authors.

On the other hand, Wagner *et alii* [20] introduced a new concept known as *variational modules* which are made up of a set of covariate traits that are relatively independent of other sets of traits. According to the authors, these modules are distinguished by the high average of correlations between features. This can be understood as a statistical approach in which the level of analysis would be determined by the phenotypic traits.

One feature of modules is their link to their functional role. The problem arises with genes with pleiotropic effects, i.e. genes that may fulfill different functional roles. How can we delimit a *module* in these cases? One possible solution to this problem would be to consider modules as units that are partially independent of other modules that can perform different functions. In this sense, each module can be conceptualized as a kind of dynamic pattern of connections between the parts of a given process (Schlosser [21]). This would help solve the problem of pleiotropy at the modular functional level by showing that the structural unit could be compatible with several functional roles. However, the author takes the concept even further and asserts that modules are easily separable from other modules and could therefore serve as evolutionary building blocks.

This leads us to believe that Winther's above-mentioned classification of modules may not be entirely compatible with Schlosser's description of modules as evolutionary units. This assertion is based on ability of different modules to dissociate from one another, which would weaken the rigid categorization between structural, physiological, and developmental modules proposed by Winther. Likewise, Schlosser [21] put forward a restricted definition of the *module* as a «cascade of constituents» that are connected at the functional and developmental levels, such as in a subprocess that develops and operates completely independently of other subprocesses. This definition implies that the elements of a module are strongly connected and integrated with each other both functionally and ontogenetically.

The functional interrelationship is an important aspect in the delimitation of the concept of the *module*. In this regard, as will be discussed below, the partial independence between modules is an essential part of the delimitation. Nevertheless, this particular aspect does not rule out the possibility of there being interaction between modules belonging to the same hierarchical level of organization. As Franco [22] asserts, the interaction between developmental modules can lead to three possible outcomes: a) both modules may stop growing or changing their orientation; b) one module is inhibited while the other continues to grow; c) neither is affected by the presence of the other. An interesting consequence of case (b) is that a module may have regulatory capacities, which would enable strong relationships with other modules and the environment. In this case, Schlosser [21] asserts that these modules may follow on one of two forms ways: plasticity or canalization.

Thus, for Gerhart and Kirschner [23], plasticity involves «exploratory mechanisms» that allow the module to accommodate itself to different environments. An example of this might be the increased number of cortical neurons in a specific brain module in relation to the increased utilization of a route or particular structure such as vision. Canalization (Waddington [24]; Gibson and Wagner [25]; Wagner *et alii* [20]), however, is associated with alternative cascades of linkages that are contingent on different environmental conditions but that all lead to the same result. Therefore, canalization allows modules to retain some integrity and autonomy beyond environmental disturbances. An example of the latter would be the canalization of human development wherein nutritional disturbances in children allow the basic general features of growth to be maintained, despite also restricting growth to a certain degree, depending on their intensity.

As has been revealed above, some variety can be seen in the concept of the *module* and the interrelationships among different modules. This is reasonable as this notion may vary slightly according to the field of knowledge to which it is applied. Thus, in colonial organisms, the delimitation of a *module* is strongly related to reproduction, whereas in other organisms, the delimitation is related to other functional aspects. Moreover, the properties of a module must have in order to considered as such are not clearly established, and there are a range of different proposals in this regard. Wagner [26] defines modular phenotypic units as a complex of characters that (1) collectively serve a primary functional role; (2) are tightly integrated by strong pleiotropic effects of genetic variation; and (3) are relatively independent from other such units. Other interpretations are related to the way in which functional modules are parts of organisms that are independent units of physiological regulation (Mittenthal *et alii* [27]) but may interact within a metabolic network (Rohwer *et alii* [28]). Moreover, a module can be understood as a multidimensional structure with different levels of organization (morphological, genetic, developmental pathways, physiological, etc.) and its own informational content (Dressino [29]; Dressino and Lamas [30]).

At this point, we believe it necessary to characterize the concept of *module* in a way that includes the different notions expressed above. In this sense, a biological module can be said to have six properties:

(i) Individuality;
(ii) strong functional internal integration;
(iii) the information necessary to function;
(iv) relative independence from other modules belonging to the same hierarchical level of organization;
(v) hierarchical integration at higher levels;
(vi) ability to modify its spatiotemporal characteristics.

The first quality refers to the *individuality* necessary in every module. That is, a module must have its own characteristics that differ from those of other modules – it must show singularity. This is consistent with the proposal made by Moss [18] discussed above. These distinctive features need *strong functional internal integration* to be able to function cohesively, i.e., all the components of a given module must maintain close relationships between one another, either to carry out a certain function or because they are related in terms of their ontogenic trajectories. The third characteristic refers to the module's *informational content*, i.e., all its components must possess the necessary information to function with the rest of its components in an integrated manner. This is to do with Fodor's [31] concept of «informational encapsulation». Each module, thus, contains several specific messenger molecules (e.g., cAMP, calcium, etc.) that allow an easy flow of information that integrates the functions of the module under study (Berman *et alii* [32]).

Independence between modules is a matter of debate between some authors (for a more detailed discussion see Schlosser and Wagner [6]; Callebaut and Rasskin-

Gutman [7]. Modules that share a certain level of organization need some relative independence from one another to be examined. For example, on the genetic level, we can delimit modules that are functionally independent of other genetic modules. However, these modules work in an integrated way if a higher level of hierarchical organization is taken into account. Thus, genetic modules work together when they are analyzed from an organic development approach. In this sense, the second requirement, *strong functional integration*, occurs between modules that belong to the same level of hierarchical organization; however, this feature is less marked when modules belonging to higher levels are analyzed.

In relation to the fifth characteristic, *hierarchical integration at higher levels*, higher-level modules must be interrelated in such a way that the entire system is able to function.

The last feature – related to the possibility of a module being able to *change its spatial and temporal features* – is particularly important because it will allow us to understand the module in a dynamic manner, i.e., to understand its changes both in space and in time. These dynamics will also allow modules to participate flexibly in the adaptive processes of organisms, contributing to evolvability, in particular. It is worth pointing out that this last feature, which relates to the spatial and temporal dynamics of modules, is applicable to the module understood as a *process* but not to the module understood as a *state*.

These two types of analysis, *state* and *process*, entail two different ways of approaching the study of a module, depending on the researcher's objectives. Thus, for example, if the craniofacial complex is studied as a *state*, the components and functional relationships of this module are analyzed at a given time t. In contrast, if it is studied as a *process*, there are two possibilities: a) to examine how its components (for example, mandibular, ocular, etc.) have developed along the organism's ontogenetic trajectory and what mechanisms have been involved, and b) to examine its evolution throughout its phylogenetic history. In short, the approach that considers the module as a *process* compares its dynamics of change over a period of time $t_1 \ldots t_n$. This is why we have stated that the sixth feature proposed in our characterization of the module only applies to modules as *processes*. In sum, modules understood as *states* must meet the first five items of our characterization, whereas modules understood as *processes* must meet all six requirements.

The Morphology of the Craniofacial Complex as a Complex Modular System

The craniofacial complex is a particularly interesting case of modular organization. This structure has different modular components, each of which has its own characteristics. However, the modularity of the skull represents two basic concepts: (a) modularity as the result of a common embryological origin; and (b) functional modularity, in response to environmental demands (for example, muscular insertions). In the first case, although the skull as a whole derived from multipotent cells of the neural tube, difference is established through cellular differentiation during embryonic development. In contrast, morphological and integrational differences in functional modularity emerge as responses to functional demands as a result of environmental pressures. This involves differential activity of the muscles, dental development, and so on. In this sense, the production of an integrated morphological structure as the skull can be understood as *developmental choreographies* in which the ontogeny of these separate morphogenetical components are spatially and temporally coordinated (Atchley *et alii* [33, 34]).

In the case of the mammalian jaw, structures derive from three basic cellular groups: chondroblasts, osteoblasts, and odontoblasts. These cells give rise to diverse structures such as alveolar bone, dentary, Meckel's cartilage, the mandibular branch, and the coronoid, condylar, and angular processes. In this case, the modules correspond to processes of differentiation from cellular groups derived from neural tube and functional modules, i.e. modules characterized by the particular functions of the morphological structure (Cheverud [35]; Wagner *et alii* [20]).

For example, the jaw is a unique structure but has different functional responses according to the functional specialization of the teeth. Thus the pressure due to the activity of the molars is different from that related to the activity of the incisors. In the first case, the strong pressure the molars put on the dentary generates responses from the latter which strengthen its structure through increased osteoblast activity. Thus, heterochronic processes associated with differential growth and development also come into play, together with mechanisms of mechanotransduction that stimulate osteoblasts to deposit bone. In synthesis, the history of the embryological development of the jaw strongly suggests a modular embryological and functional layout (Cheverud [35]; Wagner *et alii* [20]). Moreover, the above-mentioned variational modularity as a representation of the correlational matrix of quantitative traits (Wagner *et alii* [20]) is consistent with the structural component of complex systems (García [3]). Indeed, the principle of the stratification of complex systems allows elements to be laid out in levels of organization with dynamics of their own but that interact with one another (García [3]).

The modular structure of the development of the jaw is similar to that of the modular development of the craniofacial complex although the two have different ontogenetic histories (Pucciarelli and Niveiro [36]; Dressino and Pucciarelli [37, 38]). However, according to Anderson [39], it is not known whether the modules are included in the morphology of the skull or if there are «extra-modular» areas inside the skull or jaw. This suggestion is the result of a very general definition of modularity. For instance, patterns of cranial integration and modularity arise from developmental features and factors that have a variety of pleiotropic effects. These global factors can affect craniofacial development (Mitteroecker and Bookstein [40]).

If we consider the mandibular module as a *state,* we can see that it satisfactorily meets the first five requisites of our characterization. As it is a structure that is clearly differentiated from other related modules, such as the rest of the splanchnocranium and neurocranium, it complies with the *individuality* requirement. It also meets the second characteristic, since all the cellular components of the module act in a cohesive manner in order to maintain *functional internal integration*. Moreover, it complies with the third item of our proposal, because its constituent cells (osteoblasts, osteoclasts, osteocytes, etc.) possess all the necessary information for this module to function properly.

To meet the fourth requirement, it should be *relatively independent of other modules belonging to the same hierarchical level of organization*. In this sense, the jaw is relatively independent of the maxillary module (which is on an equivalent hierarchical level of organization), and both modules present ontogenetic and functional independence. Finally, the fifth item proposes *the need for hierarchical integration at higher levels*, and in this case, the mandibular module is integrated with a higher-level module, namely, the splanchnocranium and the skull as a whole.

The integration of the cranial bones may manifest itself in the dynamic of bones as they develop, from the interactions between separate ossification centers to the heterochronic sequence of ossification time. In other words, there may be topographic closeness between ossification centers, and heterochrony (differential growth over time) between these centers, as was shown by Goswami [41] when he examined the modularity of ossification sequences in embryos and neonates from 12 therian mammals with clearing and staining techniques. The study indicated that the bones which are highly integrated in adult morphology were not necessarily integrated during the developmental stage.

The studies mentioned seem to indicate that the modularity of the diverse components of the skull modifies its characteristics throughout ontogeny and that the intermodular relationships in the adult skull do not necessarily correspond to those existing during the early stages of ontogeny. Indeed, the variation in the integration of the various osseous elements of the skull in the specimens studied by Goswami [11, 41] corresponds with the modification in the spatio-temporal behavior of modules in item (iv) of our description.

Conclusions

This study arose in response to the polysemous use of the term *module* present in the bibliography, because, as we have seen above, the concept of *module* is vague and difficult to define precisely, although several classifications that respond to different research strategies and interests have been proposed (Winther [19]).

Thus, our efforts have been aimed at developing and justifying a delimitation of the module that coincides with the various meanings given to the term by different researchers. For this reason, the starting point was a more general theoretical framework, the theory of complex systems, through which to approach the various definitions, since there are modular proposals for specific states as well as for biological processes. The proposed delimitation was applied to the analysis of the craniofacial complex, but it is also applicable to other structures and processes of the organism, provided that the ontogenetic and phylogenetic processes or functionality are taken into account so as to be consistent with the assumptions of the abovementioned theory of complex systems.

Finally, the proposed delimitation of module needs to be put to the test under different conditions in order to be able to determine its strengths or weaknesses. Furthermore, applying the proposed delimitation would make it possible to compare the results of different research works, because they would share the same basic postulates.

In conclusion, we believe that our proposed characterization of the term *module* as applied to craniofacial components coincides with the modular heterochronic approaches of Goswani [41] and Bastir and Rosas [42], allowing an evolutionary analysis of the modularity of cranial complex.

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