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Organized mayhem in Bilateria *Baupläne*: symmetry and animal complexity

Organización caótica en los Baupläne *de Bilateria: simetría y complejidad animal*

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Abstract: The body plan of bilateral animals is characterized by the early specification of three embryonic axes. One of these axes defines the plane of bilateral symmetry of the future adult, ideally dividing these organisms in two mirror-image halves, left and right. Most species of this group exhibit significant and robust departures from this ideal bilateral plan, showing a suite of asymmetric characters. This paper characterizes different patterns and processes of asymmetry, highlighting both phylogenetic and ontogenetic aspects of such a basic feature of Bilateria. In addition, the role of symmetry and asymmetry as a way to increase the amount of complexity in animal organization is explored.
Keywords: Morphology, Symmetry, Asymmetry, Organization, Complexity

Resumen: El *Bauplan* de los animales bilaterales se caracteriza por la demarcación en estadíos tempranos de tres ejes embrionarios. Uno de estos ejes define el plano de simetría bilateral del futuro adulto, el cual divide a estos organismos, en teoría, en dos mitades especulares: izquierda y derecha. Las especies de este grupo se distancian de un modo significativo y robusto de ese *Bauplan* bilateral ideal, exhibiendo un conjunto de caracteres asimétricos. Este artículo caracteriza los diferentes patrones y procesos en donde se presenta la asimetría, destacando aspectos tanto filogenéticos como ontogenéticos de esta característica básica de los Bilateria. Se apunta, también, el posible papel de la simetría y la asimetría como vehículos para incrementar la cantidad de complejidad en la organización animal.
Palabras clave: Morfología, Simetría, Asimetría, Organización, Complejidad

INTRODUCTION

The morphological organization of organisms is the main theme of evolutionary biology. Trying to understand how form organizes (how embryos become) and how form diverges (how species evolve), provides much fuel to the whole science of biology, be it from a molecular or from an organismal perspective. Historically, morphological organization can be easily recognized as the research focus of the founders of modern biology. LINNEO, BUFFON, GOETHE, CUVIER, GEOFFROY SAINT-HILAIRE, OWEN, DARWIN, to name just a few, found in morphological organization clues and hints for the formulation of concepts that have remained practically unchanged until today, such as taxonomy, homology, *Bauplan*, the principle of connection, the principle of correlation among parts, the archetype, the principle of natural selection acting on natural variation, etc. (RASSKIN-GUTMAN**,** 1995). The idea of a *Bauplan*, or

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specific body plan shared by a group of organisms, is due to the German idealist morphologists, who saw in this concept a way to unify the diversity of the natural world. Later, WOODGER (1945) systematized this concept and gave it a more formal content in terms of group theory. Today, the *Bauplan* of a clade can be characterized at different scales of observation by a suite of specific characters. A particularly important scale is the establishment of the body axes early during embryonic development. Three main *Baupläne* have arisen throughout the evolution of multicellularity; one without symmetry axes (Porifera), one with radial axes (Cnidaria) and one with a medial plane that defines bilateral symmetry (Bilateria). Whatever the scale of observation, the *Bauplan* of organisms is characterized by an intrinsic organization that also hosts a high degree of complexity in number of elements and relations: living matter is organized mayhem.

As pointed out by PALMER (1994), two main issues are at stake when examining the conceptual domain of symmetry in biology: symmetry as a pattern and symmetry as a process. The former includes the morphological realization of symmetrical traits in organisms, which is manifested as an emerging property of multicellular life, while the latter generates the conditions that, symmetrically or not, shape the form of embryos and adults. I will examine these two themes from a phylogenetic and ontogenetic perspective. Phylogeny provides patterns of symmetry and asymmetry in a broad perspective and ontogeny hints at the possible developmental processes that produces and breaks those symmetric patterns. I will briefly explore the significance of symmetry analyses for understanding sources of complexity of the organization of bilateral animals, suggesting that bilateral symmetry is an innovation that contributed to the increase in complexity in metazoan body plans.

SYMMETRY AND ASYMMETRY IN BILATERIA

Bilateral animals share a common *Bauplan* characterized by the early establishment of two main body axes. Different onset times and dynamics mark the appearance of the three spatial axes for different taxonomic groups. Typically, they are all specified in the early stages of embryo development by gene differential expression before any morphological manifestation is apparent. The axis that defines left and right appears as a secondary effect of the interaction between the dorso-ventral (D-V) and the antero-posterior (A-P) axes, configuring the medial or left-right axis (L-R), which is sometimes viewed as a proximo-distal axis that extends away from the mid plane and therefore exists on both sides (GILBERT, 2000). While the D-V and the A-P axes are markedly asymmetrical in their morphological, functional, and biochemical realizations, the L-R axis hides subtle asymmetries under a seemingly symmetrical external appearance. Symmetry hides the true nature of life as a physico-chemical process: the inherent asymmetry of its most intimate components, from the chirality and high asymmetry of organic molecules, to the heterogeneity of cells and tissues, up to the complex shape of internal organs. Asymmetry is a ubiquitous pattern and symmetry-breaking is a common process during metazoan development (GARCÍA-BELLIDO, 1996).

For example, in vertebrates, asymmetry is generally found in most internal organs, while symmetry is conspicuous in their skeleton and their external appearance, with some notable exceptions. This explains, in part, why it is not common for vertebrate paleontologists to ponder the existence of asymmetries. After all, the premium finding on a very successful field trip is a perfectly symmetrical skull or, even better, a beautifully preserved whole skeleton, showing an amazing left and right symmetry. On occasions, more often than not, only one half (or even a mix of left and right pieces) is preserved, and the researcher does not hesitate for a moment in using one side as a mirror-image of the other. Moreover, when left and counterpart right pieces are found, any deviation from perfect mirror images between left and right halves is automatically "explained" by external forces that might have acted during various taphonomic processes. To be fair to this bone-obsessed vertebrate paleontologist, to find almost perfect left/right symmetry in a skeleton is a reasonable expectation: other things being equal, any departure from this "perfection" would put too much of a burden on the locomotion demands endured by the vertebrate internal skeleton. However, external characters show asymmetry in a variety of ways. Among vertebrates there are well documented departures from bilateral symmetry (reviewed in PALMER, 1996; MØLLER & SWADDLE, 1997). Some examples include flat fishes (Pleuronectiformes), which have both eyes on the same side of the body; or the males in the fam-

ily Phallostethidae that show the priapum (a clasping device derived from the pelvis used during copulation) preferentially on one side; and the cichlid *Perissodus*, which shows a side preference for its mouth opening. In birds, there are many examples, such as in several owl species showing a larger ear opening in one side, or *Anarhyncus* (Charadriidiformes) that has a preferential direction of bill twist. In mammals, Cetaceans show a deviation of the dorsal midline of their skulls; the male toothed whales (Monodontidae) show also a preferential side for its tusk; and some bats (*Myonycteris*) lack a lower internal incisor only in one side.

A great number of internal organs (those that usually escape the scrutiny of paleontologists) in vertebrate body plans (some are also present in other metazoans) are highly asymmetrical, such as the heart, the lungs, the stomach, the liver, the pancreas, the spleen or the intestines. The coordinated handedness among many of these organs form what is known as *situs solitus*. Many departures from normal *situs* have been documented, such as *situs inversus*, where the whole asymmetrical condition, organ by organ, is totally reversed (IZPISÚA-BELMONTE, 1999).

Asymmetry may be either random (i.e., the trait appears unpredictably on either side) or fixed, where

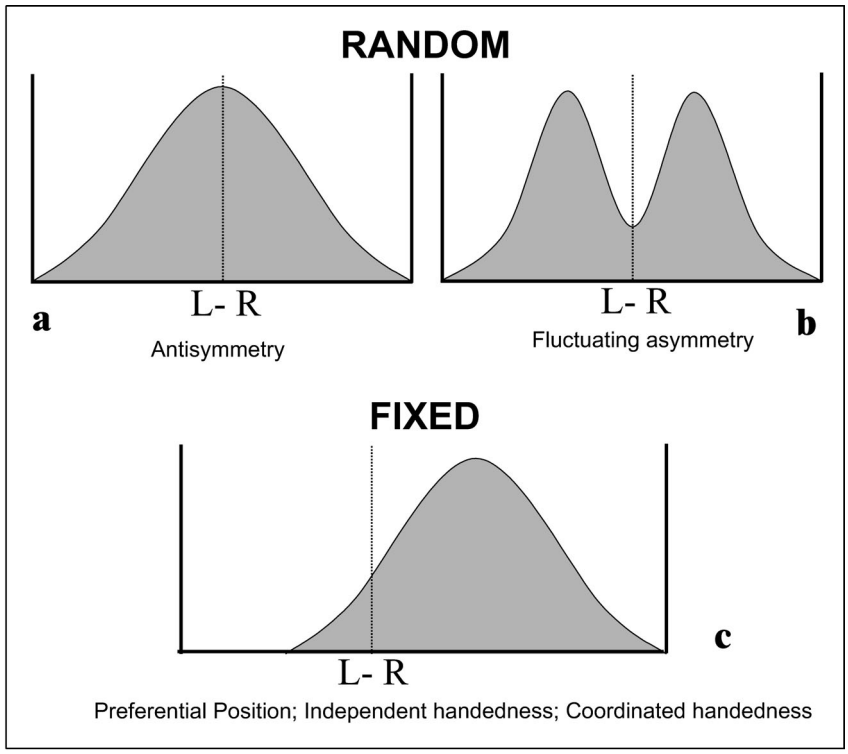

Figure 1.- Three most important types of Left-Right (L-R) distribution of variation patterns of a specific trait in a species. a) In Fluctuating asymmetry, a trait "fluctuates" randomly favoring right or left size and/or shape indistinctly, most likely as a result of developmental instability. b) Antisymmetry shows no preference between L-R difference. c) Directional asymmetry is most likely to have a genetic, non-random component; the trait consistently shows a difference in shape and/or size on one preferred axis (after PALMER, 1994; 1996).

Figura 1.- Los tres tipos más importantes de distribución en los patrones de variación izquierda-derecha para un carácter de una especie. A) En la asimetría fluctuante un carácter "fluctúa" de manera aleatoria, favoreciendo un tamaño o una forma a izquierda o derecha indistintamente. Esto ocurre, muy probablemente, como resultado de un desarrollo inestable. B) La antisimetría no muestra ninguna preferencia por la izquierda o la derecha. C) La asimetría direccional posee, muy probablemente, un componente genético, no aleatorio: el carácter muestra una diferencia en forma o tamaño siempre en el mismo lado (modificado de PALMER, 1994; 1996).

most individuals will exhibit the trait on one, preferred side (see figure 1). This division is not an arbitrary one, because the causes behind both kinds of asymmetry are totally different. Random asymmetry is due to external triggers such as an environmental cue or differential usage, while the control over fixed asymmetry has been taken over by internal causes, such as a strict developmental pathway.

Random, conspicuous asymmetry variation patterns are known as "antisymmetry". An example of antisymmetry is the specialization of the claws in lobsters (F. Nephropidae) into "crushers" and "cutters", which has been demonstrated to appear unpredictably on the right or on the left as a response to differential use (GOVIND, 1989). Fluctuating asymmetry is a special case of random asymmetry in which the trait variation is very subtle. There is a big literature on the subject of fluctuating asymmetry for a variety of reasons: it may be due to developmental instability and it may lead to speciation events (see, for example, ALIBERT *et al*., 1994; WATSON & THORNHILL, 1994; PALMER, 1994; 1996; MØLLER & SWADDLE, 1997).

Fixed asymmetry appears when the trait is consistently different in the same side. This is also known as directional asymmetry. The trait in question may be positional or may show independent or coordinated handedness. In positional asymmetry, an unpaired structure does not appear in the midline, but always on the same side, such as the heart in humans. In independent handedness, an organ shows a directional arrangement, such as heart looping or gut coiling in humans. Coordinated handedness results when more than one asymmetrical trait appears together, as is the case with the *situs* commented above (CAPDEVILA *et al*., 2000). Fixed asymmetry has a strong genetic and/or developmental component, unlike antisymmetry, which is triggered environmentally.

SYMMETRY AND ASYMMETRY IN PHYLOGENY

Looking for patterns of symmetry and asymmetry in phylogeny is a tricky business. While most of the evidence regarding asymmetries lies inside the organism, fossils show mostly hard parts. Nevertheless, the comparative biology of extant organisms shows a vast array of forms from which evolutionary patterns can be inferred.

The evidence from the body fossil record shows that the simplest, diploblastic non-bilaterian metazoans were present at least 610 million years ago. With the appearance of triploblastic bilaterians, some 40 million years later, metazoans began to explore morphological organizations based on bilateral symmetry (reviewed in ERWIN, 1999). In addition, the major period of innovations regarding the bilateral body plan occurred in the subsequent 45 million years, up to 525 ma (see figure 2). This implies that, by then, all major metazoan groups had originated.

An important question to ask is what relationship this evolutionary tempo bears to the possible scenarios that witnessed the evolution of symmetry. Thus, from a developmental program that generated radial organisms (with no preferred axis) to the first bilaterians, an evolutionary innovation occurred, in which one of the radial axes was fixed and remained as the D/V axes configuring a plane along with the A/P axis that divided the body into two mirror-halves, i.e., the L/R axis in Bilateria. Once the L/R axis was fixed, new ways to break the novel symmetry took place. This all happened in about 100 million years. However, WILLMER (1990) argues against this scenario, supporting instead the idea that bilaterality (biradiality) is an ancestral condition in the evolution of pluricellularity, while (full) radiality is a very specialized feature of cnidarians. Furthermore, WILLMER strongly disagrees with the very notion of a bilateral/radial dichotomy in the metazoan lineage, challenging the radiality of some groups (see also BUSCALIONI, 1999).

CAPDEVILA *et al*. (2000) have proposed an evolutionary scenario with three possible steps in the acquisition of asymmetric features, based on recent molecular evidence. These steps are: 1) the origin of individual organ asymmetries; 2) the origin of globally coordinated asymmetry; and 3) the origin of global, handed asymmetry. In this evolutionary scenario, an initial stage in which metazoans acquired bilateral symmetry is implied as a primitive stage in the evolution of this group. However, the fact that bilateral metazoans evolved from non-bilateral groups suggests that we also need to explain how symmetry was originally generated (but, see above the ideas of WILLMER, 1990).

A rather trivial remark, but worth considering, is that a symmetry state must exist in the first place before non-random patterns of asymmetry can arise. This implies that robust developmental mechanisms

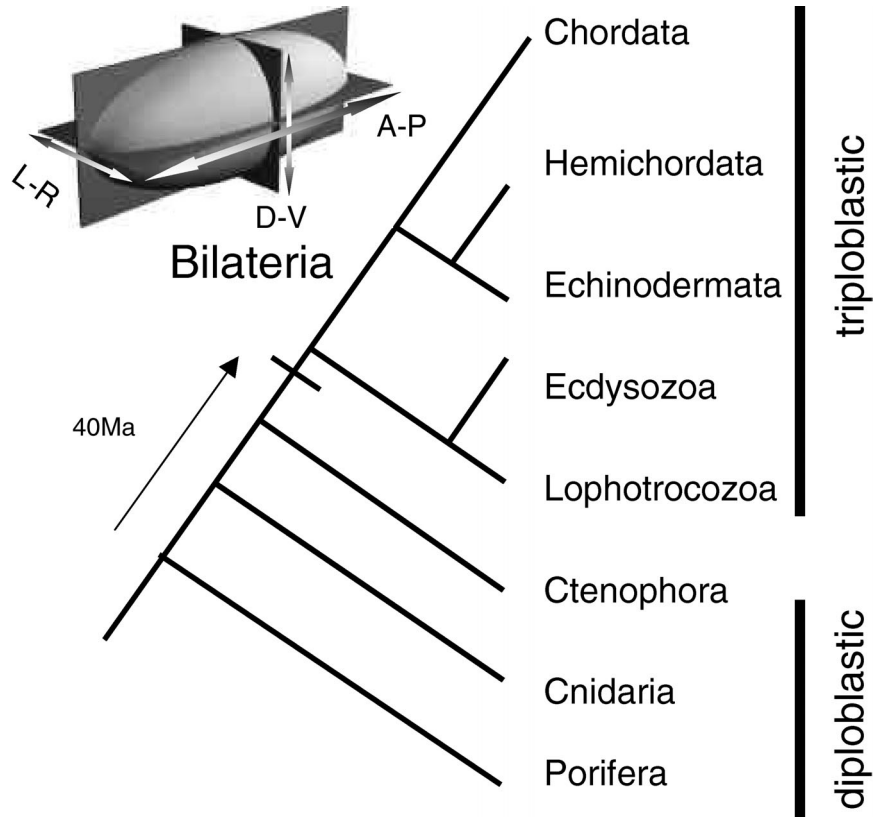

Figure 2.- A simplified phylogenetic relationship among the main extant metazoan groups. From radial symmetry (diploblastics) arose bilateral symmetry (triplolastics). Later on different stages of newly acquired asymmetry arose in bilateral groups (see WILLMER, 1990 for a different view). The appearance of the third embryonic layer, the mesoderm, seems to have been necessary (but not sufficient) to generate asymmetries, with one exception in hydrozoans. The main symmetry planes that appeared in Bilateria are shown in the diagram.

Figura 2.- Relación de parentesco simplificada entre los principales grupos actuales de metazoos. De la simetría radial (diploblásticos) se originó la simetría bilateral (triploblásticos). Más tarde, en animales bilaterales, aparecieron diferentes estadios donde se fueron adquiriendo nuevas asimetrías (WILLMER, 1990, difiere de esta interpretación). La aparición de una tercera capa embrionaria, el mesodermo, parece haber sido un paso necesario (pero no suficiente) para generar asimetrías (con una excepción en hidrozoos). El diagrama muestra los principales planos de simetría que aparecieron en Bilateria.

must have evolved in order to generate bilateral symmetry since this is an unlikely design for multicellular organisms that grow by successive mitotic divisions. Instead of a bilateral design, in the absence of differential forces, the end product of such a growth dynamic should be a quasi-sphere. Thus, spherical symmetry and, later, radial symmetry, seems to be the natural design or "default" body plan of multicellular organisms. The question arises, then, how is bilateral symmetry accomplished? And later, how is bilateral symmetry broken so that the three steps in the evolution of asymmetry may take place?

Morphological innovations, such as symmetry, are the necessary first step in the evolutionary process. After the innovation has occurred, the feature must be fixed at a genetic level in the population in order to have success over other features. This is accomplished following the dynamics of populations genetics. External pressure will favor or not the fixation of the feature in a given environment, playing with its functionality. Thus, external bilateral symmetry has been favored by evolution as a suitable design for locomotion in organisms that must show certain ability to progress in fluids, such as water and air (see

WILLMER, 1990). However, as jelly fishes remind us, bilateral symmetry is not a unique solution to cope with this ecological necessity. In any case, at some extent, bilateral symmetry is positively correlated with horizontal locomotion, and thus natural selection should have favored the acquisition and maintenance of bilateral features. Furthermore, environments both in the ocean and land niches have a markedly up and down polarity due to light and food resources. In contrast, the left/right surroundings of an organism show essentially a total homogeneity, again favoring the external symmetry of the L/R axis.

PALMER (1996) has attempted to identify, using external characters, broad phylogenetic patterns where transitions occurred among the three types of asymmetries. The most common evolutionary transition pattern is a sequence that goes from symmetry to antisymmetry to fixed asymmetry. In other words, first there is an environmental cue that determines, randomly, a side preference, followed by genetic assimilation of this preference. Other transitions are less common, such as directly going from symmetry to fixed asymmetry, or a total reversion from fixed asymmetry to symmetry.

SYMMETRY AND ASYMMETRY IN ONTOGENY

During the development of an organism there is an interplay between the molecular interactions that occur inside the cells and what cells really do (morphogenetic processes) in order to generate symmetries and asymmetries, as well as any other embryonic patterns. What we ideally would like to know is how, during development, the embryo forms a bilateral axis and later on breaks it consistently, generating asymmetries.

In the past 25 years, the advent of molecular techniques has promoted a widespread interest in the issue of asymmetry. A quest for signaling pathways involved in the differential expression on the left and right sides of bilateral developing embryos has led to important discoveries, such as the involvement of *Nodal* and the effects of mutations on the *iv* and *inv* genes. Several mutants (*iv*, *inv*) exhibit, at different rates, wrong handedness for certain organs, such as the coiling of the gut (LEVIN 1996; IZPISÚA-BELMONTE, 1999; CAPDEVILA *et al*., 2000).

The implication of this genetic underpinning is that several proteins seem to be involved, at a molecular level, in the establishment of handedness by showing differential expression during the early stages of the development of the embryo. For example, nodal is consistently expressed on the left side of the chick embryo, undoubtedly providing signals for handedness. At a morphological level, presumably as a response to these molecular cues, a preference for positioning at one or another side of the L/R axis is also manifested promptly during embryogenesis. One of the first morphogenetic organ events in the development of vertebrates involves the looping of the heart tube, which shows a consistent handedness (OLSON & SRIVASTAVA, 1996). Furthermore, organs break the symmetry constantly, generating intricate structures that are a consequence of "local" embryonic processes. The identification of several genes that display side-specific patterns of expression within developing organs has provided an entry point for understanding the molecular and cellular mechanisms underlying asymmetric morphogenesis. Other studies have implicated several genes that encode proteins such as Pitx2, SnR and Nkx3.2 in implementing side specific developmental programs within the various organ systems. Researchers have also begun to propose cellular mechanisms that break the initial symmetry in mice, based on the extracellular flow in one direction by monociliated nodal cells (NONAKA *et al*., 1998; OKADA *et al*., 1999)

Multicellularity provides at the same time a vast number of possible combinations to generate an animal and a serious constraint to its morphological architecture. Thus, the body plans of bilateral animals have to be necessarily based on the proliferation and specialization of cells during embryogenesis. Two embryonic tissues in diploblastic metazoans (poriferans and cnidarians) and three in triploblastic ones (bilaterians) form the developing organism (GILBERT, 2000). Different mechanical forces are exerted on these tissues and their constituent cells, gradually shaping the various anatomical parts that emerge in a timely fashion (see review in FUJINAGA, 1997).

The appearance of the mesoderm coincides phylogenetically with the appearance of bilateral animals. Thus, radial metazoans are diploblastic (only exhibit endoderm and ectoderm embryonic layers), while bilateral metazoans are triploblastic (they added the mesoderm, as an intermediate layer between the other two). This suggests that the mesoderm induces asymmetries during the growth of the endoderm, although there are asymmetrical hydrozoan colonies,

such as the by-the-wind sailor, *Velella velella*, which occurs in both "right" and "left" forms.

Finally, symmetry breaking pre-patterns have been identified in multiple occasions as biochemical processes that break the homogeneity of cells, eliciting differential gene expression and facilitating cell differentiation. Reaction-diffusion mechanisms provide a rich literature of this math-computational approach to the molecular dynamics of pre-patterns (see, for example, HARRISON, 1993). GRAHAM *et al.* (1993) specifically address the issue of feedback mechanisms and the usage of reaction-diffusion mechanisms as models to account for the generation of symmetries and asymmetries during embryo development. Their models incorporate chaotic dynamics as part of development, that is, they predict high sensitivity for initial conditions and multiple threshold effects in the generation of asymmetries. Their simulations relate fluctuating asymmetry with antisymmetry by changing from phase-locked periodicity to chaos in the hypothetical production of a morphogen at both sides of the embryo, whereas, in order to generate directional asymmetry, an extra bias has to be introduced on the model.

SYMMETRY AND COMPLEXITY IN *BAUPLAN*

A common view portrays biological organisms as both organized and complex entities. However, organization and complexity are two elusive features that escape an operative definition that might be used efficiently in a comparative framework. Yet, we recognize the strict hierarchical organization of biological matter: molecules, organelles, cells, tissues, and organs, along with their multiple functional relationships. At the same time, we grant biological design with a complexity never seen in any other forms of organized matter. The usual example employed as the epitome of biological complexity (and organization) is the mammal brain, with its intricate organization composed of billions of neuronal connections with multiple functional relationships.

MCSHEA (1996) has analyzed and systematized different ways to look at complexity based on three dichotomies: 1) differentiation/configuration; 2) objects/processes; and 3) hierarchy/non-hierarchy. Despite these sound efforts to create operative notions, complexity remains as a very elusive concept, because it is dependent on different scales of observation. For the purpose of this paper, it is enough to highlight this interrelationship between organization and complexity so that we can introduce the notion of symmetry and asymmetry as features that are precisely situated at their borderline.

In the classic *Materials for the Study of Variation*, William Bateson brought together several morphological patterns that shared a common denominator, namely, repetition of parts (BATESON, 1894). He called these characters "Meristic," and made the important observation that symmetry is a fundamental meristic character, as is segmentation and metamerism. The fundamental idea of Bateson is that symmetry is caused by repetition. Repetition, in turn, would be in his view a universal, necessary effect caused by cellular division. Moreover, Bateson found evidence that the geometrical arrangement and disposition of repeated parts generates a geometrical constraint with respect to the possible variations that may occur in a given structure. CARROLL (2001) reviewed recently some of the attempts to quantify complexity in morphology and diversity. He concluded, with Bateson, that the repetition of parts, the modular architecture of body plans, is responsible for the many trends in increase in complexity, suggesting a mechanistic explanation in the developmental independence of embryo parts.

The organization of the bilateral body with a fixed axis of L/R symmetry with subsequent processes that break the mirror images at both sides of this axis, giving rise to different kinds of asymmetries provides an unprecedented source of complexity in biological design. Symmetry, as repetition of parts *sensu* Bateson, can be seen as a secondary effect of modular design in the construction of forms. Modularity, in turn, involves the existence of parts that are highly integrated as well as semi-independent from other parts. They are subject to genetic and developmental control, and, as pointed out by SIMON (1962), they provide biological evolution with a rapid and efficient way to change and explore new morphological designs (see also, RAFF, 1996; WAGNER, 1996; VON DASSOW & MUNRO, 1999; KLINGENBERG *et al*., 2001; and CALLEBAUT & RASSKIN-GUTMAN, in press).

Symmetry appears when parts (modules) are repeated consistently, following one or more axes of repetition. As a meristic character, symmetry is both a source of organization and a trigger for complexity in biological design. Furthermore, fixed asymmetry

introduces new ways to increase complexity by breaking the developmental mechanisms that generate symmetry in the first place. The fact that modules can be independently coordinated and controlled by genetic and developmental mechanisms make of symmetrical repeated parts an ideal raw material to increase complexity in a variety of ways in bilateral *Baupläne*. Among them, breaking the L-R symmetry allows the exploration of new portions of morphospace that were previously empty.

As it has been pointed out above, both symmetry and fixed asymmetry patterns need very tight genetic and developmental controls in order to appear consistently in a lineage. Thus, the appearance of symmetry was only possible by generating a way to coordinate in space and time specific developmental processes that researchers are just now starting to understand. The causes of asymmetry can be reduced to: 1) differential gene expression; 2) an orchestrated and robust developmental mechanism; 3) an environmental cue; and 4) a preferential functional use. The first two are essentially non-random processes that originate always the same asymmetry. Undoubtedly, signaling and communication, especially among neighboring cells, were paramount for the origination of symmetry out of cell division events. In order to coordinate these events, the embryo must harmoniously orchestrate cell behaviors, i.e. cell divisions, migrations, and deaths. The source for this spatiotemporal coordination might be found, at the cellular level, on synchrony (GRAHAM *et al*., 1993), a pattern generation process that controls both in time and space biochemical reactions and physical interactions among neighboring cells. By using the concept of synchrony it is easy to explain how the initial homogeneity of the early embryo is broken in local areas of organization that form the primordia of developing structures. Synchrony (and asynchrony) may well prove to be a universal pattern generation process, not only in embryo development, but also in adult structures, as it occurs in neural communication.

CONCLUSION

The morphological organization of bilateral animals offers a rich field of inquiry, in which developmental and evolutionary issues find a common framework. There is an organized and complex mayhem in their design, including a vast array of asymmetric variation patterns that break the initial bilateral symmetry of the embryo. It has been suggested, following the early ideas of William Bateson, that symmetry and asymmetry are both patterns and processes that are manifestations of meristic, repeated characters or modules. Understanding the nature of these modules, how they are controlled and how they can change during development will provide a sound venue towards an understanding of the evolution of complexity in organismal design. Processes of synchrony at a cellular level may be responsible for the establishment of patterns during embryo development, including symmetries, whereas asynchronies may be responsible for asymmetries. As such, synchrony and asynchrony might be at the root of heterochronies, providing the biological mechanisms that underlie evolutionary processes.

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To Remmert, we are still in Washington D.C. looking up *mayhem* in the dictionary.

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