A new paradigm for animal symmetry

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My aim in this article is to soften certain rigid concepts concerning the radial and bilateral symmetry of the animal body plan, and to offer a more flexible framework of thinking for them, based on recent understandings of how morphogenesis is regulated by the mosaically acting gene regulatory networks. Based on general principles of the genetic regulation of morphogenesis, it can be seen that the difference between the symmetry of the whole body and that of minor anatomical structures is only a question of a diverse timing during development. I propose that the animal genome, as such, is capable of expressing both radial and bilateral symmetries, and deploys them according to the functional requirements which must be satisfied by both the anatomical structure and body as a whole. Although it may seem paradoxical, this flexible view of symmetry, together with the idea that symmetry is strongly determined by function, bolsters the concept that the presence of the two main symmetries in the animal world is not due to chance: they are necessary biological patterns emerging in evolution.

1. Animal symmetries

The symmetry of an animal body is one of its most salient features: it inherently characterizes the body plan. Sponges and placozoans are two groups that comprise animals with asymmetrical bodies, even if some smaller poriferan groups like calcareous sponges build symmetrical bodies. All other animals are characterized by some kind of overall body symmetry, and these are of only a few types: radial, biradial and bilateral symmetry (for an overview on body plans, see [1]).

It also has to be said that the symmetry types which are practically possible in animals living in macroscopic three-dimensional space are also few in number [2], constituting a subset of all theoretically possible geometrical symmetries [3]. When an endless—or a great but finite—number of symmetry axes can be drawn through a body, then it is said to be spherically symmetrical (figure 1). True spherical symmetry is absent from animal body plans. The axis of symmetry is the axis around which the body preserves its shape when rotated. Similarly, the symmetry plane is an imaginary plane which theoretically divides the body into two equal parts. When the body has one symmetry axis through which several symmetry planes may pass, it is said to have radial symmetry (figure 1). Of course, the number of these planes determines diverse subtypes of radial symmetry, but they all are still radial symmetries—also including, in this view, cylindrical symmetry. Finally, when the body is organized with one symmetry plane and no symmetry axes, it is bilaterally symmetrical (figure 1). In biradial symmetry (figure 1), the body has a symmetry axis, through which two symmetry planes may be drawn, and the four sections of the body are identical to the opposite, but not to the adjacent, parts. It is a type of radial symmetry with two symmetry planes [3]. Biradial symmetry is typical of ctenophores, in which the two symmetry planes are constituted by the plane of the tentacles and that of the pharynx (figure 1). For a slightly different framing of the symmetry of ctenophores, see [4].

In the radial and biradial animal body, the diverse anatomical structures—still retaining their rotational symmetry around the symmetry axis—are arranged following a certain order along the axis of symmetry. In this sense, the symmetry axis also constitutes another, abstract, axis: the polarity axis. The two ends of the
body may thus be regarded as two different poles, called the oral and aboral or the posterior and anterior. Hence, the polarity axis is referred to as the oral–aboral (OA), or the anteroposterior (AP) axis. A similar ordering of polarity can be observed in a bilateral body. The imaginary axis of polarity that runs from the head to the tail is the AP axis, while the one that is perpendicular to it is the dorsoventral (DV) axis. A more detailed description of the diverse animal symmetries can be found in [3].

Bilateral symmetry dominates the animal world with more than 99% of species showing this symmetry type. Radial symmetry, besides appearing in smaller sponge groups like, for example, the calcareous sponges, and in the secondarily radially lized echinoderms, is typically and widely found in cnidarians which, with their simply organized body structure, are traditionally regarded as ancestral forms of animal life. And since they are regarded as ancestral, their radial symmetry has also been considered ancestral compared to bilateral symmetry (e.g. [5–10]). This view has gradually changed as an ever-growing amount of genetic studies have shown that orthologues of developmental patterning genes that were classically considered to be typically bilaterian may also be found in radially symmetrical cnidarians (e.g. [8,9,11–22]). What is more, it has become more widely recognized that the radially symmetric cnidarians exhibit some bilaterally symmetrical internal structures—like the arms of the manubrium or the rhopalial or the gastric pouches in the tetraradially symmetrical medusa _Aurelia_—that is, they are capable of generating bilateral symmetry as well. These two facts have prompted several scientists to re-evaluate the symmetry properties of cnidarians, suggesting that they should be regarded as originally bilaterally symmetrical organisms [23–26]. This argument is further strengthened by the recognition that several cnidarians, such as most of the anthozoans and some hydrozoan polyps, can be considered as globally bilaterally symmetrical, given their bilaterally organized internal structure (for a more detailed discussion on the distinction between locally and globally bilateral cnidarians, see [3]).

2. Axial patterning

In the past 25 years, an impressive amount of data has been gathered on the molecular mechanisms of axial patterning processes during embryonic development. Thanks to this, it has been possible to form a detailed picture of the genetic background of the organization of body axes.

The establishment of the AP (OA) axis in most animals is guided by the Wnt signalling pathway [10,27,28]. In bilateralians, the primary polarity axis is organized by the Wnt signalling system [3,27,29–31] controlling the expression of _Hox_ genes which direct the positioning of diverse structures along the AP axis [32–34]. In cnidarian models, orthologues of the AP organizer _Wnt_ [8,9,21,22,35–39] and of _Hox/ParaHox_ genes (e.g. [11–17,19,39–42]) have also been isolated. In the radially symmetrical larvae of the sponges _Amphimedon queenslandica_ (Demospongia) and _Sycon ciliatum_ (Calcispongia), an asymmetric expression of _Wnt_ [43–45] and _Transforming growth factor-B_ (TGF-B) genes [43,45] was detected, and it has been associated with the patterning of the AP axis, suggesting the possibility of an ancestral role of the Wnt signalling pathway in axis formation. A recent study has also reported that calcisponges (namely two species, _S. ciliatum_ and _Leucosolenia complicata_) express _ParaHox_ genes during axial patterning [46].

Although axial patterning in cnidarians is less clearly explored, it is known that it likely involves genes from both the NK-like gene subclass (which is a group of the ANTP class together with the _Hox, ParaHox_ and other subclasses) and the PRD class [47]. Studying the axial properties of this phylum could be promising [48] since this group has been proposed as the sister group to all metazoans [49–51]. Although _Wnt_ genes were not identified as having roles in axial patterning during embryonic development, it is interesting that 11 orthologues of _Wnt_ signalling pathway genes have been shown to be active in diverse regions of the adult ctenophore _Pleurobrachia pileus_ (including the zone around the mouth margin at the oral pole where all of these genes are expressed); and their activity has been associated with local polarization of combs in the comb rows, stem cell proliferation and neurosensory functions [52].

The patterning mechanisms of the DV axis have also been well studied. Generally speaking, it is set up by a DV gradient of the antagonistic _bone morphogenetic protein_ (BMP)—_chordin_ (chrd)—network—their _Drosophila_ correspondents are called _decapentaplegic_ (dpp) and _short gastrulation_ (sog), respectively—perpendicular to the axis established by _Wnt_ [10,30,34]. Several orthologues of members of the gene network responsible for patterning the bilateral DV axis [10,28,30,34,53–55] have been isolated from cnidarian models. These include, for example, orthologues of the genes _bmp2/4/dpp_ [18,19,26,56], _chrd/sog_ [25,26,56,57], _bmp5–8_ [20,26], _noggin_ (nog) and _goosecoid_ (gsc) [25,26]. It should be noted, however, that the conservation of neither the _Wnt_ nor the BMP systems is universal for all bilaterians: in some groups, such as _Drosophila_ and other insects, they have been replaced by other signalling mechanisms [30,58].

It is also important to highlight that the Nodal signalling pathway, which is known for its function in coordinating left–right asymmetry in the body of bilaterians (e.g. [28,59–68]), also plays a fundamental role in axis formation. In vertebrates and echinoderms, the Nodal system...
induces both Wnt and BMP pathways to pattern the AP and DV axes [30]. Recently, it has been shown that Nodal has a crucial role in the process of lateral branching in the cnidarian Hydra [28]. Furthermore, another new study has reported that a well-developed embryo can be generated by experimentally injecting two opposing morphogen gradients into the uncommitted cells of the zebrafish blastula: BMP and Nodal [69]. Remarkably, axis regulation is not only restricted to embryogenesis: it also occurs in adult life phases, such as during agametic reproduction or regeneration [30].

However, despite the rich knowledge on the genetic mechanisms of axial patterning, the question of the phylogenetic priority of radial versus bilateral symmetry in the last common ancestor (LCA) of cnidarians and bilaterians still remains puzzling. One of the main reasons for this might be that identifying single molecules in a system does not necessarily mean that we will also be able to understand the functioning of the system. The other important cue may be the propensity of the human mind to think in abstract categories. It may easily happen that we are trying to force ideas into pre-established categories without realizing that the categories are no longer appropriate nor sufficient.

Take the example of a radially symmetrical anthozoan (Cnidaria): in the pharyngeal region, the internal structure of the body is clearly characterized by bilateral symmetry. Likewise, thinking only of our human bilateral body, a number of radially symmetrical internal structures may be observed, from the eyes and blood vessels to the diverse tubuli and vasa. Furthermore, there are other animal organs that show radial symmetry such as, for example, proboscises or siphons. We seem to act as if the symmetry of these anatomical structures was a sort of ‘default setting’, and so does not deserve attention. Similarly, we seem to neglect them as if they were unimportant in defining the symmetry properties of a body just because they are found inside it, that is, as if the symmetry of an animal only means its overall symmetry. I think that this view should change.

3. Radially symmetrical internal structures

The body of animals is teeming with radially (cylindrically) symmetrical anatomical structures. The overwhelming majority of them are tubes that transport gases, nutrients, waste products, cells and hormones across the diverse tissues, and they also serve as an interface between the body and its environment, forming barriers and regulating the exchange of materials (figure 2). Thus, biological tubes are essential for building circulatory, urogenital and respiratory systems, as well as glandular conduits, however different they may be in their precise architecture. Even portions of the gastrointestinal system are radially symmetrical in their cross section. The tubular shape with a circular cross section is an optimized form for transportation because it logically ensures the most uniform distribution of the transported materials. Spherical structures often connect to these tubes as their endings, known as acini, alveoli, ampullae and follicles.

Anatomical structures are delimited as well as internally lined by a specific tissue called epithelium. This is the most fundamental cell organization type in Metazoa [70–72]. Approximately 60% of mammalian cell types have an epithelial or epithelial-derived origin [73]. Epithelia not only cover the animal body both externally and internally, but also divide it into several compartments. During ontogenesis, the shape of the embryo and its organ systems, as well as that of the myriad biologocial tubes that weave through the organ systems, form through the patterning of the delimiting epithelial tissue. Thus, epithelial morphogenesis is crucial for
understanding the shape formation of the various anatomical structures, including tubes.

Tube formation, i.e. tubulogenesis, is an intensely studied research topic because it has a fundamental significance in medicine as well (e.g. [72,74–77]). Tubulogenesis occurs not only during embryonic development but also takes place later in life, to think only of the vascularization in developing muscles and during tumourigenesis, the vascularization of the endometrium in the menstrual cycle in placentals, as well as the formation of mammary ducts during adolescence and pregnancy in humans. Although the formation of biological tubes has been studied many times in living models (e.g. [78–82]), given that in vivo experimentation poses many difficulties [83], cell cultures are generally used to acquire insights into the details of the process. Initially, two-dimensional plate cultures were used, while more recently three-dimensional gel matrices have been developed [71,83]. They have greatly improved the possibilities of observing many subprocesses that had previously been impossible to see in three-dimensional cultures [71,83]. However, in vitro models cannot be expected to be able to fully recapitulate the much more complex in vivo tubulogenesis [71,83]. With the recent developments of stem cell research, it has also become possible to grow three-dimensional organ-like tissue structures, called organoids, from stem cells in vitro, mimicking the in vivo process even more faithfully (e.g. [83,84]). These experiments have shown that in organogenesis—including tubulogenesis—cells have an intrinsic ability to arrange themselves into a precise organization, that is, the process has a marked self-organizing nature [71,85–87]. This points to a cascade-like activation of successive morphogenetic cellular mechanisms.

The most frequently used three-dimensional models for studying tubulogenesis are cells from the canine kidney, the human mammary gland and lung, and the murine kidney and mammary gland [83]. As clarified by these models and by other in vitro and in vivo studies on different animals such as Drosophila (e.g. [75,80–82]; reviewed in [71–74,88–94]), zebrafish (e.g. [78]; reviewed in [73,76,88,90,93,94]) and the nematode C. elegans (e.g. [79]; reviewed in [73,74,88,91,93,94]), the details of tube formation differ according to both the organism and the organ in which it takes place. However, some commonalities seem to underlie the basic processes of the birth and the development of biological tubes. Tubes may initiate their formation via several mechanisms. Wrapping and budding are ways to create lumina from pre-existing spaces and from already polarized cells (this means apicobasal polarization); while in focalized contact with membrane repulsion, cell hollowing, cord hollowing and cavitation, the lumen of the tube is formed de novo, from formerly not polarized cells [72–74,83,90,91]. Plasma membrane invagination has recently been proposed as a distinct type of de novo luminogenesis [93]. These modes of lumen formation are not exclusive [71,74], and at least some of them may also act synergistically [95]. Importantly, examples can be found in which if one way of lumen formation is blocked, then another mechanism begins to operate, showing the robust drive of epithelia to form lumina [96] (see also [72,73]). The detailed presentation of tubulogenetic mechanisms—additionally including the machinery of cell–cell and cell–extracellular matrix (ECM) interactions, the polarization of cells, cyst formation, luminogenesis, elongation, branching, as well as the role of tip cells or epithelial–mesenchymal and mesenchymal–epithelial transitions—falls beyond the scope of this paper; instead, I refer the reader to some excellent papers and the references therein [71–74,76,78,79,82,88–94,97].

Tube formation takes place as a result of an interplay between the epithelium (or endothelium, a specialized epithelium of blood vessels), soluble factors, the surrounding cells and the molecules of the ECM [73,83,89]. Lumino genesis during tube formation is orchestrated by two domains that act as sources of signals. Those coming from the ECM establish one axis for lumen positioning, while signals from the neighbouring cells, through cell–cell contact, determine a second axis [72]. These mechanisms provide the spatial coordinates for the generation and the correct positioning of the apical membranes of the cells forming the tube [72]. However, the exact mechanisms as well as their molecular background are still a long way from being precisely mapped [76,90,91,93]. Nonetheless, some basic elements can be outlined. Several signalling pathways are involved in epithelial and/or endothelial tubulogenesis, such as hepatocyte growth factor [71,73,74,75,83,86,88,93], epidermal growth factor [75,82,83,85,88–90,94], fibroblast growth factor (FGF) [75,83,87,88,90,94], Wnt [75,76,85,89,90], TGF-β/BMP [73,75,83,85,89,90], Robo/Slit [75,76,88–90], Hedgehog (Hh) [75,90,94], Notch [75,76,83,85,88–90,94] and vascular endothelial growth factor [76,83,88,89]. According to the given model and the given organ, a vast number of other different molecules have been identified as being involved in tubulogenesis (for more detailed descriptions, see [72–83,85,87,90,92,94]).

Eyes are salient animal organs which have radially symmetrical components. The optic cup is the retinal primordium from which the eyes develop. A major advance in the field of stem cell culture research allowed the observation of complex early eye morphogenesis in vitro in three-dimensional embryonic stem cell culture, optic cups and the fully stratified neural retina tissue can self-develop, unravelling a robust, intrinsic self-organising programme of optic cup formation [84,86], reminiscent of that of biological tubes. But how do all these mechanisms induce the formation of structures with an organization as complex as that of a developing embryo with its rapidly growing organs and organ systems? The internal anatomical structures as well as the whole body plan are built according to the information encoded in the genome: there are genes that ultimately control their formation and, by definition, their symmetries. However, to better understand morphogenetic processes, instead of considering the enormous number of genes that have been identified as involved in morphogenesis one by one, we should examine their networks as specific sets of genes, devoted to specific goals. Thus, in order to understand the functioning of these genes, it is crucial to decipher their regulation.

4. Gene regulatory networks

A biological structure, such as body parts, as well as the whole body, is built thanks to the aligned action of the so-called gene regulatory networks (GRNs) [98–101]. They determine which protein-coding gene will be transcribed, and when, in which cells and how much protein will be produced. The transcription of protein-coding genes is directed by regulatory sequences of the DNA. The different types of regulatory regions (for example, enhancers, promoters, silencers, insulators and so on; e.g. [102]) are activated by the binding of specific proteins called transcription factors (TFs). The binding of a proper
combination of the given TFs to the regulatory regions can either activate, modulate or inhibit the transcription of the target gene. Thus, the gene of a TF regulates (through its product, the TF) another regulatory DNA sequence—for example an enhancer—which, receiving all the necessary input from its TFs, in turn regulates the transcription of a coding gene. It can thus be seen that regulatory genes regulate both each other and non-regulatory genes. The picture is further complicated by the fact that a regulatory gene responds to multiple inputs and, similarly, it provides input to multiple other genes. Thus, the ensemble of the interactions among the regulatory genes forms a GRN [98,99]. The different GRNs and GRN subcircuits are activated and deactivated successively, in given developmental stages in the given tissues. The GRNs function embedded in and interlocked with a system involving the dynamic exchange of molecular information through morphogen gradient formation and cells–surface contacts. These systems may also form reaction–diffusion systems (e.g. [103]) generating spatio-temporal oscillators of GRNs (e.g. [104,105]). Excellent illustrations of this phenomenon include the FGF/Sonic Hedgehog-mediated branching morphogenesis of the mammalian lung [106,107] as an example of development of cylindrical structures, and the Notch/lunatic fringe-mediated segmentation of paraxial mesoderm during somitogenesis [108,109] as an example of a bilaterally organized pattern formation.

The changes by mutation in the structure of the GRNs cause changes in the morphological characters of the animal [98–101,110]. Importantly, it is now widely recognized that the evolution of animal form is mainly due to these changes in the regulatory genome [34,98–102, 110–112]. If one considers two diversifying animal taxa and counts the known number of regulatory changes in relation to those occurring in protein-coding exons, the former out-numbers the latter [102,110]. For example, it has been calculated that while the conservation for coding sequences is nearly 33% between humans and the cephalochordate Amphioxus, for conserved non-coding sequences (which are often identified as regulatory regions), this proportion is less than 1% [113].

Since the diverse regulatory genes are activated in different tissues, in different molecular combinations, in different developmental stages and for different purposes, a mutation in a specific regulatory region can avoid pleiotropic effects, i.e. it does not necessarily affect the whole phenotype [34,102,114,115]. Thus, the evolutionary process has a great many opportunities, through mutations that take place in the regulatory regions of the DNA, to experiment with new morphological variations.

The GRNs are highly complex systems but they share some important common features. One of these features is that the GRNs have a hierarchical structure [98–101]. The top and the bottom of the hierarchy are well characterized. The GRN subunits which are found at the core of the developmental programme (in other words, at the top of the GRN hierarchy), controlling the developmental patterning of the embryo, including the establishment of the progenitor fields for developing body parts, are named ‘kernels’ of the GRN [98–101]. They determine the phylum- and superphylum-level features of the animal, establishing, among other key characteristics, the basic spatial coordinates in the body plan [98,101]. The kernels are evolutionary inflexible genetic systems: they do not tend to change over hundreds of millions of years [98,99,101]. The so-called ‘plug-ins’ form a versatile genetic tool in the developmental programme. They are conserved GRN subcircuits which are repeatedly co-opted for different developmental purposes during evolution, thus their connection into the whole genetic network is evolutionarily flexible [98,99]. The well-known signal transduction systems such as Wnt, TGF-β, FGF, Hh and Notch are prominent examples of plug-ins [98]. The function of the kernels and the plug-ins is entirely regulatory [98]. Another unit in the developmental genetic programme is constituted by the ‘input–output (I/O) switches’. These are subcircuits which permit or block the functioning of other GRN subcircuits [98,99]; for example, several Hex gene functions act in this way in development [98,99,101]. The alterations in the deployment of the plug-ins and the I/O switches cause class-, order- and family-level divergences in the morphological properties of the body plan [98]: since they operate at many levels of the GRN hierarchy, the magnitude of the evolutionary changes their alterations cause depend on where in the GRN hierarchy they reside [99]. Finally, the GRN subsystems called ‘differentiation gene batteries’ consist of protein-coding genes and their immediate regulatory genes: they control cell-type-specific functions, and they carry out the terminal, fine-scale operations on the construction of body parts [98–101], determining, for example, integumental properties [98,99]. They reside at the periphery of the developmental process, so they constitute the bottom of the GRN hierarchy [98–101]. The developmental gene batteries are evolutionarily labile subnetworks: their changes mostly underlie the processes of speciation [98,99,101].

In this view, the manifestation of the hierarchy in the GRN is that the earlier activated subcircuits have more pleiotropic effects on the phenotype than the terminally acting GRN subsystems which configure fine-scale processes [98]. It is important to emphasize, however, that the above-described hierarchy has little to do with the commonly used, social-sense hierarchy, in which the upper levels directly control the lower levels. The hierarchy of GRNs is much more like an ecological succession, in which the first settling group prepares the ground for the second, which, in turn, acts in the same way for the third group, and so on. Thus, the hierarchical organization of the GRNs can be best described as a diverse timing of separate GRNs and GRN subcircuits during development. In this conception, it is simply because of their prior activation that earlier operating GRN modules have more pleiotropic effects than the more terminal ones [98]. Accordingly, the simple fact that they come later in a series does not mean that the later activated GRN subsystems are inherently inferior to those activated previously.

Another prominent feature of the GRNs is that their structure is highly modular [98–101]. From the evolutionary point of view, this also means that the genetic linkages that act between certain GRN subsystems are more likely to change than those which are found inside of these GRN subunits: clear examples are the previously mentioned plug-ins [99]. This structure makes it possible for the evolutionary process to redeploy the subcircuits, reorganizing the GRN [99–101]. The redeployment of whole, pre-existing, genetic systems satisfying new developmental purposes is a known process in experimenting new evolutionary pathways [3,34,99,101,116,117].

This process confers a third important quality on the GRN: its mosaicity [100,101] (the term mosaicity indicates...
that a system is composed of subsystems whose functional connectedness does not necessarily mirror either their phylogenetic relationship or their antiquity). An important consequence of the mosaic nature of the GRNs is, for example, that the evolutionary age of the diverse subcircuits is not necessarily connected to their order of activation. This is indeed the case in several instances: some GRN subunits activated at the periphery of the developmental process are very ancient [100, 101]. Thus, the GRNs have to be viewed as historically, structurally and functionally modular genetic systems [100].

From the point of view of symmetry properties, the above-mentioned notions imply that the earlier activated GRN subunits that determine the symmetry features of the overall body plan should not necessarily, in principle, be considered either more ancient or of a higher order than the later activated, symmetry-determining, body-part-specific subcircuits.

Naturally, if a spatial domain is established in a developing embryo, then the subsequently operating GRN subcircuits must be activated within that domain, so the number of regulatory steps (sets of regulatory proteins) that can potentially be activated in that region will decrease [101]. This process is called developmental canalization [101], and it is very much in line with the aforementioned succession-like activation of GRN subunits.

5. A new paradigm

Based on the previously discussed ideas, it seems clear that the ‘radially symmetrical’ cnidarian body can be viewed as a combination of radial and bilateral symmetries, just like the ‘bilaterally symmetrical’ bilaterian body. Thus, one can conclude that animals may be regarded as being both bilaterally and radially symmetrical at the very same time [118]. It is not hard to conceive that the animal genome—speaking of course, over a geological time scale—keeps the capability of expressing both symmetries and deploys them for different purposes according to the function and the physical environment of the given body part and of the body. The influence of physical factors on the changes between symmetry types during evolution has already been proposed as being of crucial importance [3].

In this context, the old debate on the symmetry of the cnidarian–bilaterian LCA also loses its sense: the LCA most probably had both symmetries [118]. The LCA is hypothesized to have been a genetically complex animal [10, 119, 120] possessing a nearly complete genetic toolkit for animal biochemical and developmental processes [119]. Thus, we can suppose that it very probably could express both radial and bilateral symmetries—similarly to its cnidian and bilaterian descendants [118]. Not incidentally, this is a more parsimonious explanation than the convergent acquisition of bilateral symmetry in Cnidaria and Bilateria [3].

In this sense, the ‘primitiveness’ of Cnidaria can also be put in a new context. If their complex genome is capable of constructing both symmetries, the overall radial body symmetry might not be a primitive feature but a useful adaptation to their specific lifestyle. If evolution can be regarded as an optimum-seeking algorithm, and the appearance of a successful group as the finding of a local optimum, then it seems feasible that in cnidarians, the process simply found a local optimum sooner than, for example, in insects or in vertebrates, which appeared later in evolution. In this view, they should by no means be regarded as primitive [121]. For instance, comparing a visual and a tactile zooplanktivore (a fish species and a cnidian species), it has been shown that high visibility and low prey density favour visual predation, while in low visibility and high prey density tactile predation gains advantage [122]. An insightful paper [123] pointed out that when also taking into account energy balance in function of body carbon content, in terms of factors such as feeding benefits versus respiratory losses, growth and reproduction rates, clearance rates (water volume cleared of prey per time unit) and swimming costs, the overall bioenergetic performance of jellyfish is similar to that of fish. However, despite providing evidence that the combination of the feeding system and lifestyle of jellyfish can be optimized to a degree where it efficiently competes with that of fish, the authors use the term primitive for describing cnidian-type lifestyle and feeding. This might be a legacy from past textbooks, with which not everybody necessarily agrees [121]. Even when used with the intention of indicating similarity to an ancestral state, the term primitive unfortunately bears a negative connotation, also indicating a certain inferiority. However, primitive should not be confused with simple. The problem is similar to comparing a beautiful folk song with a Beethoven symphony. Which is simpler, is not questionable. But which is more pleasant or better?

It is also important to note that when speaking about entire animal groups (not just specific traits), even simplicity becomes relative. It may be the case that the clades whose members are traditionally described as simple are viewed in a distorted way: examining every animal through a ‘bilaterian lens’ [4] certainly biases our judgement, because instead of looking for unique traits in non-bilaterians, we often limit ourselves to looking for the presence or the absence of bilaterian traits (for a wider discussion, see the recent paper by Dunn et al. [4]). As the authors state [4, p. 289] ‘We cannot array animals from simple to complex, because there is no single axis of complexity. Organisms have a mix of simple and complex traits, but many are currently hidden to us [...]’. [...] Different animal groups have different complex traits, and complex traits are gained and lost all across the animal tree.’

6. Concluding remarks

Symmetry-establishing GRN kernels, being very conservative gene subcircuits, are, by definition, evolutionarily ancient. The extreme conservation of the kernels also indicates an important phenomenon: conservation means that a strong purifying selection is acting on the DNA sequences at hand [99, 102, 115], weeding out the eventual mutations. This is partly due to the recursively wired, tightly bound internal structure of the kernels [98, 99, 101], but is also the result of developmental canalization [101]. For both phenomena, mutations in the early activated, domain-specifying GRN subunits are more likely to produce potentially deleterious effects on the phenotype, and thus these levels of the GRN hierarchy are less likely to change [98, 99, 101]. But, notwithstanding this, the fact that the kernel is under the effect of continuously acting and strong selective forces is also exactly what we would expect if the given structures determined by the kernels were highly constrained functionally (i.e. they physically interact constantly and intensely with the
environment). For the above-discussed symmetrical biological structures, as well as for the whole body [2], this is indeed the case: their symmetries are connected with high functionality. So in addition to the internal structure [98,99,101] and the developmental canalizing effects of the kernels as causes of their evolutionary stability [101], I suggest we also add that, in the case of symmetry, the constantly acting selective forces are mainly constituted by the functional constraints which biological structures must obey. This is a further step towards the ‘demystification of the body plan’ (expression from [101]).

The question of the extent to which the developmental GRNs could channel the evolution of animal form [34] is an intriguing problem. The repeated deployment of ancestral GRN variations during animal evolution may obviously be caused by the eventuality that the evolutionary process operated through the use of already existing and efficient genetic solutions to diverse evolutionary challenges, progressing along the channel of least resistance [34]. De Robertis [34] argues that, as a corollary to these constraints produced by developmental GRNs, the existing body plans may be only a subset of the many possible animal body plans that could have been successful if they had had the chance to be built during evolution. In my opinion, however, this canalization may only refer to the different constructive details of body plans, but not to their basic symmetry properties. Symmetry endows a structure with important and fundamental biomechanical attributes, constituting an intimate connection between the physical environment and the body (and minor anatomical structures): thus, it serves as a geometrical basis for the various body plans. And taking into account that, both theoretically and practically, there are only two types of fundamental body symmetries which are optimal in locomoting animals in the macroscopic world [2], the potential existence of many basic animal body plans does not seem probable.

The genome of most animals can express both radial and bilateral symmetries, which are the two possible local optima in the morphospace of theoretical body geometries, and are tightly linked to the function of the given structure (see also [2]). These notions together support the idea that radial and bilateral symmetries seem to be obligatory patterns in the evolution of animal body plans [2], and that the most important limits to the evolution of animal symmetry were—and are—ultimately settled by the physical environment of planet Earth.

Competing interests. I declare I have no competing interests.

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