Perspective

An Evo-Devo Perspective on Analogy in Biology

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Abstract: To explain the amazing morphological and biomechanical analogy between two distantly related vertebrates as are a dolphin and a shark, an explanation exclusively framed in terms of adaptation (i.e., in terms of the Darwinian survival of the fittest) is far from satisfactory. The same is true, of course, of any other comparison between structurally similar, but phylogenetically unrelated organisms. A purely evolutionary argument does not throw any light on how the developmental processes of their ancestors could eventually evolve in such a way as to eventually produce these peculiar phenotypes (the arrival of the fittest). How does Nature play with animal and plant form? To address the issue of the evolution of possible forms, we cannot ignore that these are products of development. This invites adopting the integrated perspective, currently known as evolutionary developmental biology, or evo-devo. Paths through the maze of living forms are not satisfactorily explained in terms of pure geometrical transformations or of the adaptive value of the phenotypes eventually produced. The emergence of form is largely dependent on the intrinsic evolvability of the developmental processes that translate the genotype into phenotypes. As a consequence, development makes analogous structures more likely to evolve than a pure adaptationist argument would ever suggest.

Keywords: analogy; comparative biology; evolutionary developmental biology; evolvability; genotype; homology; phenotype

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1. Nature and Art

Are there universal laws of biological form? This is not the kind of question a researcher in life sciences is likely to address. Current studies of biological form focus instead on its adaptive significance or its developmental or evolutionary origin (whatever the word 'origin' may eventually mean).

Less demanding versions of that question, however, may guide fruitful research programs, the viability of which has become much more solid since the last decades of the past century, due to technical progress in the field of molecular and developmental genetics, as well as to conceptual developments that have involved at least two major disciplines of the life sciences: Developmental biology and evolutionary biology.

Indeed, the existence of pervasive structural commonalities even between *prima facie* disparate living forms has attracted the attention of the students of animals and plants since the time of Aristotle and Theophrastus at last. These recurrent patterns have not simply offered reliable criteria on which to establish a zoological or botanical classification, but have also frequently been the target of speculations about their causes.

2. The Comparative Method in Biology

2.1. Homology and Analogy

Comparative anatomy as an explicit research programme emerges at the beginning of the XIX century, largely through the efforts of Georges Cuvier (1769–1832) and Etienne Geoffroy Saint-Hilaire

(1872–1844) [1]. However, an excellent, explicit exercise in comparative anatomy had been already performed by Pierre Belon (1517–1564) about 250 years before: Pages 40 and 41 of his *Histoire de la nature des oyseaux* [2] feature, indeed, two woodcuts, representing a human skeleton and a bird skeleton, respectively, with the individual bones labeled with a letter code that flags their precise correspondence between the two vertebrates. For example, the human humerus is labeled 'N' and the same letter is used for the corresponding bone in the bird, despite the fact that this bone is here part of a wing's skeleton rather than of an upper arm's. In a less detailed but equally compelling graphical exercise, Petrus Camper (1722–1789) convincingly showed [3] that the overall architecture of the human body can be precisely matched onto that of a quadruped (in Camper's drawing, a horse). This was only a few years before the great French anatomists mentioned above begun their extensive comparative studies that eventually brought to the understanding that the similarities observed between different kinds of animals are not all of the same nature. Butterflies have wings, as birds have, but this circumstance just tells us that butterflies and birds are two groups of flying animals; their wings, like the remaining of their bodily structure, are so different, that the shared possess of flight organs does not suggest any particular degree of 'affinity' between the two groups, whatever 'affinity' may mean in pre-evolutionary biology. To the contrary, the detailed similarities found among the skeletons of vertebrates (especially, among those of the four-legged terrestrial ones), despite the wildest disparity of the overall body shape and the animal's life style, are suggestive of affinities that support classifying all these animals in the same group. This is, for instance, how Vertebrata emerged as one of the main divisions (*embranchements*) of the animal kingdom in Cuvier's classification [4].

Terms, such as homology and analogy, were often used by these authors, but with variable meaning, a circumstance that can easily cause misunderstanding in a less than attentive reader. For example, Geoffroy Saint-Hilaire's *théorie des analogues* [5] was actually about what we currently call homology rather about the kind of similarity long called analogy.

Explicit definitions were provided at last by Richard Owen (1804–1892), in the Glossary of his *Lectures on the Comparative Anatomy and Physiology of the Invertebrate Animals* [6]. According to Owen, a homologue is "the same organ in different animals under every variety of form and function", whereas an analogue is "a part or organ in one animal which has the same function as another part or organ in a different animal." These definitions have provided a firm link between the two different (and often, but not necessarily, opposite) notions of similarity already identified by the French school of comparative anatomy and the terms under which these notions have been largely known since then, at least up to the time the advent of phylogenetic systematics [7,8] caused a deep rethinking of concepts and methods in comparative biology.

On a closer look, in Owen's definitions there was a term that could not fail to cause serious problems of interpretation. What does it actually mean that a butterfly's wing has the *same* function as a bird's wing? Indeed, the mechanics of flight are quite different in the two kinds of animals. Still more embarrassing is the following question: What does it mean that a bird's humerus is the *same* part of the skeleton as a human's humerus?

Efforts to reformulate the two concepts in less abstract terms were soon to follow. Focus, however, has been increasingly stronger on homology rather than analogy, for different reasons. First, different degrees of similarity between homologous organs are likely the expression of more or less strictly conserved developmental processes; knowledge of the latter, in turn, has been steadily progressing since the early times of comparative embryology in the first half of the XIX century (e.g., [9]). Second, different degrees of similarity between homologous organs are likely correlated with more or less ancient divergence between the evolutionary lineages to which the species we are comparing belong; this perspective becomes sensible as soon as an evolutionary perspective on life comes to light, starting with Darwin's *Origin* [10]. In the case of analogy, instead, a tentative explanation of the similarity could only be suggested in terms of adaptation, that is, by postulating that distantly related organisms sharing analogous traits have been evolving under similar selective regimes.

This is the way we are used to explain, for example, the morphological and biomechanical similarity between two large and robust swimmers, such as a dolphin and a shark. But this kind of explanatory hypothesis is neither stringent nor easy to test. This has caused a progressively fading attention to analogous similarities between living organisms. However, as we will see below, conditions have emerged of recent that encourage renewed interest in analogy.

The subsequent history of the concept of homology and the bewildering range of qualifications and related notions proposed thus far have been summarized in a number of essays and reviews, e.g., [11–22], to which the interested reader is referred.

At this point, it is sensible to move back in time once more, to pay attention to an approach to the comparison of forms that was not so strongly influenced, as Cuvier's was instead, by the need to find a solid foundation for the classification of animal species in groups of different ranks and above all at the highest level, the *embranchements* (Vertebrata, Articulata, Radiata, Mollusca), between one and the other of which Cuvier [4] denied the possibility of a structural comparison. Importantly, this shift of attention leads to focus on the cultural environment in which, roughly in the years of Cuvier and Geoffroy Saint-Hilaire, a study of biological form took shape in Germany, for which the very term of *morphology* was coined (the first use of this word in a printed text is probably by Burdach in the year 1800 [23]; cf. [24]). In particular, Burdach (1817) saying is worth mention, that we truly know a form only when we know how it comes out of first principles [25]. But these principles were not those of function, around which Owen will later try to consolidate the notion of analogy, neither those of development, to which Geoffroy Saint-Hilaire [26] had already looked as a possible foundation of what, with Owen, will become the notion of homology; even less those of phylogeny, since the biology of the period has not yet taken the path of the Darwinian evolutionism (and the Lamarckian version is not able to impart a significant change to the comparative method). This science of form [27] is the morphology of Goethe, according to whom this discipline "soll die Lehre von der Gestalt, der Bildung und Umbildung der organischen Körper enthalten" (should contain the doctrine of the shape, formation and transformation of organic bodies), thus developing as "Betrachtung der Gestalt sowohl in ihren Teilen als im Ganzen, ihren Übereinstimmungen und Abweichungen ohne alle andere Rücksichten" (contemplation of the figure both in its parts and in the whole, their correspondences and deviations without any other considerations) [28]. This is therefore the morphology according to which, in botanical declination, *Alles ist Blatt* (everything [in a plant] is leaf) [29], thus opening the way to a comparative morphology in which equivalences are not only sought between anatomical parts of different organisms (as had been done already by Belon, when he compared—bone after bone—the skeleton of man with the skeleton of the bird), but also between different anatomical parts within the same individual: An easy job, when serial structures are involved, even if subtly different from each other, as are the vertebrae of the same vertebral column, but not so when the morphologist's intuition is tempted to compare a leaf with a petal, a petal with a stamen; and, indeed, a leaf with a segment of the stem of a plant, or a vertebra with a bone of the vertebrate skull. Unfortunately, the progressive (and obviously justified) success of the evolutionary reading of the living world has led to the development of comparative morphology almost as a servant at the service of phylogenetic reconstruction, leaving little room for other approaches and interpretations. In the long run, this led to obscure German 'romantic morphology' until its recent and still incomplete reappraisal [30]. In a recent paper, Riegner (2013) [31] has suggested that this morphology can be reinterpreted in a way, such as to make it compatible with evolutionary dynamics and even likely to contribute significantly to the still emerging field of evolutionary developmental biology (evo-devo). This, in my view shareable passage consists in placing the accent on the dynamic, rather than the static, character of the typological thought that informs the German morphology of the early nineteenth century.

An exercise of this kind can be useful, as a starting point from which to address the frequent situations in which a resemblance, even if not coarse like the relationship between the wing of the bird and the wing of the butterfly or similar textbook examples, however escapes explanation in terms of common descent. This is the topic of the following section.

2.2. Homoplasy

All adult insects—with the exception of many of those living in caves or deep fissures of the soil, and some parasites—have a pair of large faceted eyes, generally in a lateral position on the head. In some flies, however, the head has a hammer-like shape and the eyes are located right at the end of the two side 'arms', therefore very far apart. This peculiar condition is characteristic of a family of flies, the Diopsidae, which for this reason are called the eye-stalked flies, but is also found in a number of species belonging to seven other families. It is therefore very probable that the transition between a normal head and a hammer head occurred independently at least eight times, while the opposite transition (from hammer head to normal head) must be considered less probable and perhaps never happened. In any case, the last ancestor common to all these hammer-headed flies certainly had a normal head: In terms of phylogeny we cannot therefore consider their peculiar condition as homologous between the different families concerned. However, the distribution of these eight families within the phylogenetic tree of the Diptera is not random at all. They all belong to a group of Diptera (Acalyptratae) deeply nested within the evolutionary radiation of this insect order; more specifically, four of these families belong, together with six other families whose representatives are all provided with a head of normal proportions, with the same superfamily of Acalyptrata, i.e., the Tephritoidea. This phylogenetic clustering of the different families of dipterans with pedunculated eyes suggests that, with remarkable probability, the peculiar morphology of their head has appeared repeatedly within the Acalyptrata, due to the existence of some condition, in the members of this lineage, that facilitated the evolution of stalked eyes, a condition that instead seems not to be shared by the remaining Diptera. What this condition might be is not known today, however looking for it would be a reasonable subject of research. This reasoning is based on the idea that the emergence of an evolutionary novelty is in some way conditioned by a different distribution of the probabilities of change in different directions (*evolvability*), a notion on which we will return shortly.

The similarity among these flies belonging to different families, but all united by the possession of pedunculated eyes, is currently called a *homoplasy*. The term was introduced by Lankester [32] to cover all instances of independent acquisition of similar attributes in distinct lineages. Within homoplasy, many authors distinguish today three different kinds of change: Parallelism, convergence and reversal [33].

Parallel evolution is the independent development of similar characters in two or more lineages with common ancestry. The characters concerned were not present in the ancestor, but the descendants have inherited from the latter the potential to express them. When this shared potential to evolve in parallel similar phenotypes is interpreted in terms of shared possession of specific sets of genes, or gene networks, this translates into the notion of deep homology, to use a term introduced by [34] and currently quite popular, despite the fact that this pattern of evolution is hard to reconcile with the traditional notion of homology in its many declinations. In other instances, the similarity between two lineages cannot be traced to any commonality in their common ancestor. In this case, the descendants are more alike than their common ancestors, and this is described as *convergent evolution*. This distinction, however, is somehow arbitrary [35], more than the distinction of either parallelism or convergence from *reversal*. In this last case, a trait shared by two species was already present in their last common ancestor and was maintained through the generations in one of the two lineages, whereas in the other it was temporarily lost, but evolved again.

The pervasiveness of homoplasy has long been underestimated. Strict focus on homologies, as a basis on which to reconstruct phylogeny and arrange plant and animal species in a 'natural' classification, led to consider homoplasy simply as noise to be identified and then best ignored. Instances of parallelism, convergence and reversion are, however, a legitimate and important topic of study. Between the end of the last century and the early years of this, some important reviews (e.g., [35,36]) showed convincingly how frequent these patterns are in nature.

3. Does Adaptation Explain Everything?

A critically important refreshment of our perspectives on evolution can be obtained as soon as we realize that natural selection explains why a given phenotype is maintained throughout the generations, or how it changes through time, but fails to explain two important classes of phenomena: On the one hand, the fact that likely functional phenotypes very similar to existing ones are apparently 'forbidden' in nature, on the other hand, why and how unusual phenotypes whose survival chances are nil or nearly so continue to be produced. A couple of examples will clarify the issue, eventually suggesting how to adjust our perspective on evolution and eventually disclosing a way to revisit analogy.

A first lesson can be learned in the fly room, that is, in the laboratory where geneticists keep their bottles full of fruitflies (*Drosophila*), for one century a favorite model organism in the study of heredity. Natural selection has not been able to eradicate the developmental mechanisms that generate four-winged fruit-flies, or fruit-flies with an extra pair of legs growing in the place of the antennae—eventually, two kinds of 'monsters' the study of which has been crucially important for the advancement of developmental genetics. The form of monsters preserves structural order despite the lack (or serious impairment) of adaptive function; thus, a study of their morphogenesis is a kind of exercise in *Naturphilosophie* from which we may learn about the constraints that also apply to the related 'normal' forms [37].

The other example is offered by the neck of the giraffe, first used by Lamarck [38] to illustrate his concept, that modifications produced by repeated use may become hereditary. Let's replace this Lamarckian giraffe with a Darwinian one, a giraffe whose populations include individuals with necks of different degrees of elongation. Most of the time, the giraffes with longer neck will have higher chances of surviving and transmitting to their offspring the long neck they have inherited from their parents. This Darwinian scenario provides a likely explanation for the evolutionary trend towards a progressive elongation of the neck in the giraffe's lineage, however, it does not tell much about how a giraffe's shorter or longer neck is actually built. Let's restrict the obviously much more complex problem to the question of how to build neck skeletons of different lengths. In principle, a neck skeleton could be elongated either by increasing the number of the vertebrae supporting it, or by making longer vertebrae while keeping their number unchanged; a mixed strategy would also very likely work. Quite probably, natural selection does not care for the actual mechanism that provides variation: What matters is the length of the neck rather than the number or shape of the bones that support it. Variation, however, is constrained. To change the shape of the vertebrae is actually much easier than to change their number. Eventually in the neck of a giraffe there are seven cervical vertebrae, exactly the same number as those supporting the much shorter neck of a deer, a cat, or a human being. If the extraordinary elongation of the giraffe's neck is a product of directional selection operating over thousands of generations, we must admit that selection is blind in respect to the mechanism producing variation in neck length. Evolution, however, is not satisfactorily explained unless we take into account, besides natural selection, also the processes responsible for the production of variation. These processes are those of development and in the case of the giraffe they are generous in producing dramatic differences in the shape (thus, in the degree of elongation) of the cervical vertebrae, but seem totally unable to generate variation in their number.

Summing up, in the case of the fruitfly 'monsters' developmental mechanisms give rise to individuals with survival value close or equal to zero, whereas in the case of the giraffe developmental mechanisms are unable to provide variation (in the number of vertebrae) acting on which natural selection would have produced functionally advantageous phenotypes. It is thus clear that a satisfactory understanding of phenotypic change as occurring in nature can actually be obtained only by the joint contributions of evolutionary biology and developmental biology: The Darwinian survival of the fittest [10] presupposes the existence of more and less fit phenotypes, all of which can be tested by selection only if development has produced them: The Darwinian perspective must thus be complemented by a consideration of the arrival of the fittest [39].

This is actually the intellectual background from which the science of *evo-devo*, or evolutionary developmental biology, has eventually emerged (e.g., [40–43]).

Uniquely placed at the crossroad between the two parent disciplines [44], both of them targeted to the study of change, evolutionary developmental biology is indeed taking shape as the science of the change of change, focusing on evolution as the outcome of modifications of developmental processes [42,45–49].

4. Evolvability

As forcefully argued by Hendrikse et al. [50], *evolvability* is the proper focus of evolutionary developmental biology. There is no agreement, however, on how this term should be best defined, perhaps as "the ability of particular features of systems to facilitate change" [51] or as "the tendency of a genotype or lineage to generate genetic variability and produce or maintain phenotypic variation over evolutionary time, enabling it to pursue diverse evolutionary trajectories" [52] (p. 19). Taking a given phenotype, and the corresponding genotype, as the arbitrary starting point of an evolutionary walk through the landscape of forms, I suggest that evolvability can be defined as the set of phenotypes that can be reached from that origin, with the probability of change associated to any of them. Accordingly, there will be easy (i.e., highly probable) transitions and less easy (i.e., less probable) ones, and also changes with zero probability [53,54].

In the last three decades, there has been increasing interest in the study of the genotype→ phenotype relationships, or genotype→phenotype map (e.g., [55,56]). There is abundant evidence, by now, that we cannot equate small vs. large genotypic differences with small vs. large differences in the corresponding phenotypes. Gross generalizations would be ill-advised.

A simple iteration of a developmental process of modest complexity can give rise to highly structured fractal patterns or to other phenotypes of no lesser intricacy. Commonality between developmental processes operating at different scale is less obvious in the case different body axes are involved, such as an animal main body axis vs. its appendages [57], or a plant's stem vs. its leaves [49]. However, without assuming this hypothesis of *paramorphic relationship* between axes of different order within the same organism [57], it would hardly be possible to explain, for example, why animals with segmented body, e.g., arthropods, have also segmented limbs, while the appendages of animals with unsegmented body, like mollusks, are never segmented [57]; or, why the branching pattern of trees is so often mirrored by the branching pattern of the veins in each of their leaves [49].

However, we shall not assume *a priori* that all elegant patterns observed in living nature are produced by the simplest mechanisms. For example, the earliest segmental pattern observable in a *Drosophila* embryo is the set of seven regularly spaced stripes of expression of the so-called primary pair-rule genes. Interestingly, these stripes are produced synchronously. An elegant (in the mathematical sense of the adjective) way to obtain this pattern would be if the positions at which the seven stripes are produced were obtained by one mechanism only, but this is not the way in which the pattern is actually obtained. Each and any stripe is under separate regulatory control: This means indeed that Drosophila embryo is *Making stripes inelegantly* [58].

Approaching evolution from the perspective of evolvability may help explain the occurrence of strikingly similar phenotypes in very distantly related animals. Selective advantage can explain why a given phenotype is maintained throughout generations, but does not explain where the same phenotype first came from. Moreover, strictly similar phenotypic traits of species sharing the same environment and life-style are possibly maintained by similar selective pressures acting on them, but this argument cannot be applied to the amazing morphological similarity sometimes existing between very distantly related species. For example, the unmistakable raptorial appendages into which are modified the forelegs of the common praying mantis (*Mantis religiosa*) are not exclusive to the mantid lineage (ca. 2400 species described to date), because appendages with very similar morphology have evolved in another two arthropod lineages, i.e., in the Mantispidae or mantid lacewings and in the Stomatopoda or mantis shrimps. The first are insects strongly resembling true mantises, but not

closely related to them: It may suffice to say that mantispids undergo complete metamorphosis with larval stages followed by a pupa and eventually by the adult, the only stage which resembles true mantises, while the latter develop through a series of stages quite similar to the adult (raptorial legs included), apart from size and presence of wings. Stomatopods, a lineage of marine crustaceans, are still further away from mantises, in the tree of life.

The argument for a strong role of selection in the evolution of strict similarities between distantly related organisms is more convincing in the case of mimicry. This peculiar adaptive similarity occurs in two main forms. In Batesian mimicry, the color pattern (sometimes also the overall body shape) of a poisonous or strongly distasteful 'model' is found also in a 'mime': Potential predators avoid attacking the mime as they avoid attacking the protected model. In Müllerian mimicry, two or more different species, each of which is provided with protective devices, such as poison, bad smell or powerful mandibles, share the same color pattern (sometimes also the overall body shape), thus resulting, in the eye of a predator, as a potential prey to be avoided because of a whole set of dangerous weapons it would be ready to use. Thus, the selective advantage of these similarities are hardly a matter of dispute, but this does not explain their origin. It is possible, however, that the evolution of mimicry between distantly related groups has been facilitated by the availability to both models and mimics of similar pattern units more likely to be expressed and to be modified in parallel ways, due to shared developmental constraints. Marchini et al. [59] have explored this hypothesis in a comparison between (stinging) wasps and (inoffensive) hoverflies that are considered to be their Batesian mimics. Each element of the insect's skeleton can occur in a number of alternative chromatic patterns, differing in the distribution of black vs. yellow areas on the surface of the 'tile'. Eventually, a very different combination of elements could generate an overall black-and-yellow pattern that an observer would probably regard as the same, but similar 'tiles' are present, in corresponding parts of the body of wasps and their mimics, more frequently than a random selection would produce, thus supporting the hypothesis of biased evolvability.

Paths through the maze of living forms are not satisfactorily explained in terms of pure geometrical transformations or of the adaptive value of the phenotypes eventually produced. The emergence of form is largely dependent on the intrinsic evolvability of the developmental processes that translate the genotype into phenotypes. As a consequence, development makes analogous structures more likely to evolve than a pure adaptationist argument would ever suggest.

Conflicts of Interest: The author declares no conflict of interest.

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