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EVOLUTIONARY DEVELOPMENTAL BIOLOGY (R DIOGO AND E BOYLE, SECTION EDITORS)

Introduction to Evolutionary Developmental Pathology, or Evo-Devo-Path: on Neodarwinism, Natural Mutants, Hopeful Monsters, Syndromes, Genomics, Variations, Humans, Apes, Chameleons, and Dinosaurs

Rui Diogo [1]

Abstract
During the second half of the twentieth century, few authors attempted to combine the increasing knowledge obtained from the study of model organisms and human medicine with data from comparative anatomy, evolutionary biology, "natural mutants," and variations in order to investigate the links between development, pathology, and macroevolution. However, in the last decades, there has been a renewed interest on these subjects, with the rise of Evolutionary Developmental Pathology (Evo-Devo-Path), a field that is attracting more and more attention across the globe, not only from the scientific community but also from the media and broader public. This is because this field is mainly related to a deeper understanding of developmental anomalies and disease within an evolutionary framework, paying a special attention to "natural mutants," such as cyclopic sheep, humans with severe congenital malformations, and to so-called "hopeful monsters," such as chameleons and, to a certain extent, dinosaurs, as will be explained in this issue. These are hot topics within the broader community and for the media, that have been also of main interest to biologists for a long time, for instance to renowned authors such as Étienne Geoffroy Saint-Hilaire, Waddington, Goldschmidt, Gould and Per Alberch. However, these issues became somewhat neglected with the rise of genetics and the increased focus on the "Devo" within Evolutionary Developmental Biology (Evo-Devo), in particular on molecular biology studies and therefore on experimentally produced—and not so much on "natural"—mutations. Another main, and related, reason was the prevalence of Neodarwinism within biology—sometimes defended in a quasi-religious way and using extremist ideas, such as reducing evolution to "selfish genes," that, we now know, do not correspond to the complex and multifaceted reality of biological evolution within this planet. These subjects will be discussed in this special, and very timely, issue precisely about Evo-Devo-Path, which attests the increasing interest in this field, and thus on natural mutants, "hopeful monsters," and other ideas of the authors named just above, and shows how new knowledge and tools, for instance about the cardiopharyngeal muscles and syndromes and about genomics and transposable elements, are quickly being integrated in crucial discussions within this field.

Keywords Evolutionary Developmental Biology (Evo-Devo) · Pathology · Evolutionary Developmental Pathology (Evo-Devo-Path) · Congenital malformations · Comparative anatomy · Paleontology · Teratology · Macroevolution · Evolutionary teratology

This article is part of the Topical Collection on *Evolutionary Developmental Biology*

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Introduction to Evo-Devo-Path and to this Special Issue

This very short introduction to Evolutionary Developmental Pathology (Evo-Devo-Path) is mainly based on works published by my colleagues and me in the last years within this field [1–21], as well as to my own, related, papers on how Evo-Devo became too focused on "Devo" and thus lost focus on "Evo" issues such as evolutionary mismatches, "natural

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mutants," and "hopeful monsters" [22, 23]. As this very short introduction is part of a "preface"-like, informal preamble to the special issue, and not a separate article per se, readers should consult those works for more details about the information provided here, and in particular the specific original references cited on those works.

Of the three main components of Evo-Devo-Path, pathology—and particularly human congenital malformations - has interested both erudite and lay people since thousands of years ago, including Aristotle. A key person that influenced many authors that have attempted to discuss both the reasons behind and the broader implications of human congenital malformations after the so-called scientific revolution was Goethe (1749–1832). This is because Goethe was one of the earlier more prominent defenders of internalism, which had a great impact in the Romantic German school (e.g., Oken) and *Naturphilosophie* (e.g. von Baer), as well as on non-German researchers such as Owen and Bateson. According to Goethe, internal forces (e.g., developmental ones) are the main sources for the phenotype, while the environment mainly plays a secondary role in selecting between the limited morphological diversity created by these internal forces. This idea is somewhat similar to that now defended by some proponents of the "Extended Evolutionary Synthesis." In particular, Bateson, influenced by Goethe's ideas, compiled an impressive number of studies about animal morphology, human development, variations, and defects and defended ideas that are now becoming, fortunately, again mainstream in Evo-Devo [22, 23]. For instance, he argued that variation is mainly due to internal mechanical (e.g., number of parts) or chemical (e.g., reactions leading to a certain color) factors (constraints) and that natural selection merely selects between a very constrained number of phenotypes.

Étienne Geoffroy Saint-Hilaire (1772–1844), who has been described as the "father of evo-devo", was also influenced by Goethe. For Étienne, "monstrosity" was at a high, special level among anatomical anomalies, differentiating from all the dominant characters defining each species. His intention was to consider "monsters" without prejudices and study them through the identifiable and classifiable facts. Thus, it was necessary to also think beyond the deviation from the original shape. By means of Étienne's theory of the unity of organic composition—or the continuity of organization between beings—"monstrosity" was discussed within an overall frame of the organization plan through rules, including the "principle of connections" or the "balancement of organs." That is, for him, order exists in the apparent disorder, which leads to establish a classification grouping individuals under the heading of common deformities. These links between development and deviation of form were experimentally studied by Étienne and further explored by his son, Isidore Geoffroy Saint-Hilaire (1805–1861), who introduced the term "teratology" as the science of anomalies within organismal organization. A current definition of teratology underlines a "discipline devoted to the study of congenital morphological anomalies, their causes and teratogenesis"; its study has emerged within a comprehensive theoretical framework of the organization of life, with the ability of features to be passed from one species to another through transformation.

Already in the twentieth century, authors such as Waddington further discussed developmental perturbations and their effects on the phenotype and implications for "monstrosity." Specifically, he coined the term "canalization" for those features of developmental pathways that lead to the production of standard and discrete phenotypes despite environmental or genetic influences that would otherwise disrupt development. That is, canalization buffers physiological and metabolic systems against environmental and genetic perturbations, and by doing so allows genetic/developmental variability to build up within the genotype, even though such variability is not expressed phenotypically. Unfortunately, authors often refer to Waddington's notions of homeostasis, canalization and genetic assimilation, but not so much to his concept of homeorhesis. Waddington proposed for living systems the term homeorhesis, meaning stabilized flow, that is, the stabilization of a progressive system acts to ensure that the system goes on altering in the same sort of way that it has been altering in the past, i.e., in a way any steady state refers to homeostasis and any stabilized state as homeorhesis. In other words, homeorhesis can in theory lead to major, organized changes by stabilizing them, and may be useful to explain the occurrence of saltatory evolution, being somewhat related to the current notion of "facilitated variation" within evolutionary biology.

Importantly, these ideas are also related to one of the most emblematic, and extreme, examples of an internalist view of evolution, Alberch's ill-named "Logic of Monsters." According to this theory, there is often a parallel between the variation/defects in normal/abnormal individuals of a certain taxon (e.g., modern humans) and the usual wild-type configuration seen in other taxa (e.g., species of lizards or amphibians or dinosaurs). Such a parallel was also noted at the beginning of the nineteenth century by Meckel, who stated that the constant involvement of certain organs together in congenital malformations allows the conclusion that their development is coordinated under normal conditions. This parallel is achieved through regulation of a conserved developmental program (e.g., a set of genetic and/or epigenetic interactions) such that the structure of these internal interactions constrains the realm of possible variation upon which selection can operate. In principle, such internal constraints can break down in the evolution of some clades, but while in most clades, this would lead to death of the embryos due to internal selection; members of other taxa might eventually survive until adulthood.

The internalist framework of the "Logic of Monsters" thus contrasts with the more externalist view of Neodarwinists (see

below), and in particular of adaptationists, who defend that the current form of organisms is above all explained by the external environment in which they live, and not by internal factors. For instance, frogs and salamanders tend to lose/reduce digit I and digit V, respectively: the first digit to be lost/reduced is the last to form in the development of each taxon. Such a pattern seems to be mainly due to developmental constraints, because for instance, the reduction/loss of digit I is seen in frogs that live in very different environments and that are exposed to markedly different external factors. Another example provided by Alberch concerns mammals, and specifically St. Bernards dogs, which usually have an extra (6th) digit probably related to their larger size and larger limb buds—smaller dogs of other species almost never have an extra digit and often even lack some digits—and not because the presence of a 6th digit is adaptive per se.

In fact, as I have discussed in recent papers [22, 23], apart from the rise of genetics, and the focus on molecular biology studies and therefore on experimentally produced—and not so much on "natural"—mutations in the second half of the twentieth century, and in the past decades within Evo-Devo, an other, related, major reason for the decreased focus on topics such as "natural" mutants and "hopeful monsters" during that time was precisely the prevalence of Neodarwinism within Biology and within Evolutionary Biology in particular. One of the articles of this special issue, authored by me, therefore focuses on this crucial topic. This is because, as explained in that article, Neodarwinism was - and continues to be - often defended in a quasi-religious way, and produced extremist ideas—such as the one that evolution is basically about "selfish genes"—that, we now know, do not correspond at all to the reality of the complex, multifaceted evolution on this planet. Such Neodarwinist extremist ideas, and in particular the almost fundamentalist way in which they were defended by so many prominent and highly influential scholars, created a major difficulty for a more holistic, and much more accurate, understanding of evolution, and in particular of macroevolution, and the key role played by both normal and abnormal development. In particular of how abnormal development, together with natural variations, has played a crucial role for the rise of not only new species but also above all of innovations and completely new types of forms.

Fortunately, this scenario seems to be slowly changing, with a renewed interest in Evo-Devo-Path in the last few decades, as explained by Diaz in one of the articles of this special issue. He explains, in that article, that Evo-Devo Path is becoming a crucial bridge between the study of evolution and morphological disparity and the field of medicine, with the renewed interest on "natural mutants" and "hopeful monsters" and their links to the understanding of human pathologies in the age of genomics. Similarly, the recent increase of interest about natural variations, and in particular their biological origin and their implications for the understanding of our own evolution and for medicine is exemplified by another article of this special issue. The article, written by Boyle and myself, shows how muscles lost in our adult primate ancestors still imprint in us, and discusses the links on muscle evolution, development, variations, and pathologies. One other paper of this special issue, written by Guinard, further introduces us to the historical context of the rise of Evo-Devo-Path, which he defines as "Evolutionary Teratology," and explains how we are now finally starting to break though the mold of the Neodarwinist synthesis paradigm.

Guinard proposed, some years ago, the concept of "Evolutionary Teratology" based on the notion that current and extinct wild-types of certain taxa arose through deviations of "normal" development that could be seen as developmental anomalies. For him, those deviations are not necessarily drastic; that is why he made a distinction between his conception and some of the notions related with Goldschmidt's "Hopeful Monsters." Goldschmidt introduced the concept of developmental macromutations—i.e., mutations of important developmental genes that can produce significant phenotypic effects—to explain macroevolution. Although the vast majority of such mutations would be disastrous ("monsters"), there may be one macromutation leading to the adaptation of an organism to a new way of life—a "Hopeful Monster." Therefore, macroevolution would occur mainly with the rare success of "Hopeful Monsters" rather than by an accumulation of small changes in populations. However, as explained by Guinard, this notion is often misinterpreted as the achievement of "perfection" in a jump (extreme saltationism), and Goldschmidt is often used as a "straw-man." The examples that have been provided by Guinard in the last years have stressed how pathological features of one taxon (e.g., humans) are often seen as the normal phenotype of another taxon (e.g., dinosaurs), thus nevertheless supporting some of Goldschmidt's ideas and thus contributed to the resurgence of ideas defended by Étienne and Isidore Geoffroy Saint-Hilaire, more than 150 years ago: "monstrosity is no longer a blind disorder but another order, also regular and subject to laws." In fact, one could also add that the criticism of Goldschmidt's Hopeful "Monsters" by Neodarwinists was facilitated by a biased, anthropocentric view of evolution. This is because in humans, any "macromutation" such as a chromosomal mutation tends to lead to the death of individuals, well before they reach sexual maturity and thus before being able to leave descendants, except in cases such as trisomy 21 (associated with Down syndrome). However, in many other animals, and particularly in other organisms such as plants, similar macromutations very often do not have the same dramatic effect as they have in humans, leading to healthy and viable organisms, as evidenced by the huge chromosomal diversity seen in not only different taxa but also in cases within a same taxon. In this regard, one of the scholars that has been also more active within the field of Evo-Devo-Path, through both her studies of the anatomical malformations and variations of

human fetuses and newborns including those with trisomies, and her developmental work on the cardiopharyngeal field, is Ziermann, who is the author of an article in this special issue. Specifically, in this article she combines data obtained from these two different, but related, lines of research.

Another scholar that has also been very prominent within Evo-Devo-Path research is Esteve-Altava, who is the co-author of another article on this special issue. Esteve-Altava has published several papers with me and other colleagues, on the links between mathematical network theory, systems biology, evolutionary biology, and anatomical sciences. In particular, he has been a key player in the development of a new tool to study the links between evolution, development, and pathology: Anatomical Network Analysis. I will not describe the methodology employed in anatomical network analyses in detail here, as that has been done in various recent papers, including some cited in this paper. I will thus instead provide a single example to illustrate the potential of this methodology, as well as an extreme case of developmental constraints that strongly supports Alberch's Logic of "Monsters." Anatomical network analyses of the muscles and their contacts in the most common—so-called "normal"—configuration of the adult human head have revealed that there are three main muscular modules: an "ocular/upper face" module including facial muscles of both the left and right sides of the head; a "left orofacial" module including left facial muscles; and a "right facial" module including right facial muscles. The same modules are also found in human newborns. Strikingly, in an extreme case of congenital malformation seen in a cyclopic human fetus with trisomy 18 studied by our colleagues and me, the very same three muscular modules are present despite the severity of the head defects and the cyclopic condition, showing that there is in fact a "logic" (order) even in such cases of extreme developmental deformities. Anatomical, neurological, and pathological studies of humans further support the idea that these particular facial muscle modules are in fact deeply entrenched in the evolution, development, and overall organization of our heads. For instance, studies in humans and nonhuman primates suggest that the innervation of the face is bilaterally controlled for the upper part and mainly contralaterally controlled for the lower part and, accordingly, in humans, paralysis of the upper face is often bilateral while of the lower face is often unilateral. This is in line with the facial muscle modularity revealed by our network analyses. Recent studies on modularity, for instance about the modular heterochrony of dermal vs. endochondral bones, have also provided examples of strong internal constraints, and pointed out how in many cases such constraints can have a crucial role in vertebrate macroevolution.

A multifaceted scholar,—as are the other authors of the articles of this special issue, which is not surprising because Evo-Devo-Path is precisely the result of a more holistic, interdisciplinary view of the links between evolution, development, pathologies, and variations—Esteve-Altava, is now developing new lines of research. This is precisely shown in the paper published in this special issue by Barteri and him, which concerns transposable elements. These are mobile genetic units that, within mammalian genomes, produce genomic structural variation in evolution, development, and disease. They review several congenital malformations in which transposition has modified, deleted, or added new regulatory regions (genomic and epigenomic) in genetic regulatory networks, including heart defects, ciliopathies, anomalies of kidney, and urinary tract, and skeletal malformations such as polydactyly and craniosynostosis, and show that the mechanisms by which transposition causes congenital malformations are a window to understand how development is regulated and can lead to new insights on the evolution of morphological traits.

Their paper, as well as the other papers of this special, and very timely, issue therefore not only attest the increasing interest in Evo-Devo-Path but also show how new knowledge and tools, for instance about the cardiopharyngeal muscles and syndromes and about genomics and transposable elements, are indeed quickly being integrated in crucial discussions within this field. The primary aims of this special issue are, accordingly, to provide the historical background of the rise of this field and to highlight the strength of studying developmental anomalies within an evolutionary framework to understand morphological diversity and disease by connecting the results of such recent works using such tools, in order to pave the way for further and much needed work regarding abnormal development, variations, and macroevolution.

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Compliance with Ethical Standards

Conflict of Interest Rui Diogo declares nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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