Where is the Evo in Evo-Devo (Evolutionary Developmental Biology)

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COMMENTARY AND PERSPECTIVE

Where is the Evo in Evo-Devo (Evolutionary Developmental Biology)?

JOURNAL OF EXPERIMENTAL ZOOLOGY PART B MOLECULAR AND DEVELOPMENTAL EVOLUTION

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ABSTRACT

I provide a brief discussion of the present/future of Evo-Devo, reviewing opinions expressed by colleagues with different opinions/backgrounds about what Evo-Devo should be and the potential of this flourishing field and combining them with an analysis of the recent, and excellent inaugural meeting of the Pan-American Society for Evo-Devo. As an advocate of Evo-Devo and its enormous future potential, I feel that despite our different views and fields of research, we Evo-Devoists are all in the same boat and should try our best to make sure this potential is fully expressed. Therefore, I call attention to some concerns raised by other colleagues, which in my opinion are demonstrated by a quantitative analysis of the titles/abstracts of the 56 talks at this meeting. This analysis is very simple, in order to maintain the needed objectivity and minimize bias. Yet, it is profound in its implications, precisely because of its simplicity and because this meeting is clearly a major landmark for the development/future directions of Evo-Devo. The analysis shows that terms associated with development at the more molecular/genetic level were vastly overrepresented compared to terms related to evolution or to development at the whole organism level. That is, it provides support for the idea that current Evo-Devo is mainly focused on Devo, and that Devo itself is largely focused on "Geno," that is, on molecular/genetic developmental studies. This trend seems to be leading towards a loss of focus on the whole organism and on the major microevolutionary and macroevolutionary questions/theories that remain to be solved/tested. *J. Exp. Zool. (Mol. Dev. Evol.) 9999B:XX–XX, 2015.* © 2015 Wiley Periodicals, Inc.

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WHEN?

I have been thinking about writing on this subject for a while, particularly when I was doing literature reviews of Evo-Devo papers for some of the books and papers I recently published with my colleagues. However, the main catalyst was the inaugural meeting of the first American Evo-Devo society (Pan-American Soc. for Evo-Devo, Berkeley, August 5–8, 2015) not only because of the discussions held at that meeting but also because it provided a particularly timely moment to write this note. Honestly, this was one of the most interesting meetings I have attended in recent years, so the title of this paper is assuredly provocative, because the paper is not at all a criticism of the meeting or its organizers, the society or its members/council, or any other Evo-Devo society. In fact, I learned a lot in the meeting and had the opportunity to strengthen friendships and professional relationships and form many new ones.

WHY?

So why write this paper? Because apart from the truly numerous laudable aspects of the meeting, and of Evo-Devo in general, one should always aim to improve. And the meeting did provide evidence for the existence of a pronounced imbalance between the weight of Devo—and more specifically of genetics/genomics—versus that of Evo, in Evo-Devo. To be sure, I am not the first to raise this concern, and do not claim any originality for expressing it. It has been raised in different ways by various other researchers studying both plants and animals (e.g., Minelli, 2003; Stern, 2003; Klingenberg, 2004; Hoekstra and Coyne, 2007; Grover and Cronk, 2007; Moczek, 2012; Murren, 2012; Winther, 2015), but mainly shyly, almost as a whisper in many cases. These researchers have

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stressed two main problems in Evo-Devo. First, the imbalance between Devo and Evo, and particularly the fact that most of the Evo-Devo research is not even Devo research per se (e.g., embryology), but is focused specifically on genetics/genomics —"too many genes, too little development" (Moczek, 2012: p. 116). In particular, some authors argue that Evo-Devo has become more and more obsessed with new molecular methods and data, leading to a loss of interest in the phenotype and endangering the goal of studying the links between genotype and phenotype and ultimately solving questions about the origin and evolution of organismal diversity, "whereas genetic and genomic data have become abundant in the last decade, synthesis of accompanying phenotypic data lag behind" (Murren, 2012: p.1). This lag in turn makes it more difficult to study and discuss one of the most—if not the most—central issues in evolutionary biology, homology—"Evo-Devo workers have been quick to infer organ homology from a few embryonic gene expression patterns; it is now clear that such comparisons, even when they involve more than just a few expression patterns, are fraught with difficulty, particularly when they are performed in the absence of phylogenetic information" (Stern, 2003: p. 5560). The second main problem is the need for work that synthesizes the inputs of the various fields that should ideally be covered by Evo-Devo, and particularly the more recent ones such as genomics, to discuss broader, long-standing, conceptual evolutionary questions (Minelli, 2003; Groover and Cronk, 2007; Moczek, 2012). In particular, they emphasize that an effort should be made in Evo-Devo research to transcend the traditional boundaries inherited from its parent disciplines—and above all the gene/genomic centric view of development and evolution—and to move toward the development of a more comprehensive and realistic theory of developmental evolution (Moczek, 2012).

However, the discussions raised by these researchers frequently quickly become centered on evolutionary versus developmental biologists and on their personal opinions and backgrounds, and thus rapidly lose their focus on real, major problems. In this paper, I will avoid focusing on—and will thus try my best to be neutral about—the strengths of evolutionary versus developmental biology as individual disciplines, and instead focus on results from an unbiased quantitative analysis of the words used in the titles and abstracts of the recent Berkeley meeting, to avoid falling in the trap of talking instead about "impressions" and personal "feelings" about the whole subject. To be as straightforward as I can, I do come from a more Evo background; in recent years, however, my laboratory's research has been particularly focused on normal and abnormal development (Ziermann and Diogo, 2013, 2014; Diogo and Tanaka, 2014; Diogo and Ziermann, 2014, 2015; Linde-Medina and Diogo, 2014; Diogo et al., 2015a). Significantly, lately the laboratory has been immersed in the creation of a new subfield of Evo-Devo (Evolutionary Developmental Pathology and Anthropology), and right now I would define it as a "comparative developmental" lab, above all (Diogo et al., 2015b; Smith et al., 2015). So I have myself worked to integrate evolutionary biology and developmental biology, and I personally consider Evo-Devo to be the most promising and fascinating field within the Biological Sciences as a whole.

A group of 23 co-authors just published an account of the progresses and contributions of the discoveries of Evo-Devo to a wide range of disciplines, such as evolutionary biology, paleontology, developmental biology, neurobiology, cellular and molecular biology, phenomics, human health and disease, ecology, agriculture and food sciences, and even science education (Moczek et al., 2015). Before reading the next paragraphs, readers are strongly encouraged to read that account, as I subscribe to the major points discussed there, and they put in a broader perspective the problems mentioned below. That is, they stress the fact that we are all in the same "boat," (Evo-Devo) which is already a splendid and flourishing boat, we are all proud to be Evo-Devoists and the purpose of calling the attention to these problems is simply to try to enhance the functioning of the boat.

HOW?

So and how did these problems arise in the first place? The major problem—at least according to many Evo-Devoists, including myself—is that in the last few decades Evo-Devo has become more and more dominated by Devo, and particularly by molecular studies. This has led to a loss of focus on the original, broader, long-standing evolutionary questions, and issues that those molecular studies were supposed to help solve, or at least address. As stressed by Moczek et al. (2015), one of the reasons for this imbalance is inertia, that is, the inheritance of some of the parent disciplines of Evo-Devo, particularly of the gene/genomic centric view of development and evolution to which many evolutionary biologists strongly subscribed, particularly at the time of the Modern Evolutionary Synthesis. Moczek cannot be accused of being an Evo radical, as he works on many Devo subjects and was moreover the first author of the overtly optimistic Evo-Devo paper co-authored by the 23 authors mentioned just above.

If one of the reasons for the imbalance would be such inertia, could it be that we are not seeing a trend at all toward a reduced focus on Evo, or at least on the organism? Perhaps there was never really a focus on the organism in Evo-Devo, from the start. However, I would argue that there was. There are actually two different versions about the most crucial events leading to the origin of Evo-Devo, what is interesting itself because they reveal themselves the different ways in which evolutionary biologists and developmental biologists see the evolutionary history of Evo-Devo. Probably, as usually, both views are essentially correct, and reflect themselves how Evo-Devo was a complex multidisciplinary discipline from the beginning. One view, defended mostly by researchers with an Evo background, is that researchers such as Gould and Alberch were the "fathers" of Evo-Devo (Rasskin-Gutman and De Renzi, 2009), by combining

the study of the evolutionary patterns (e.g., paleontology) with the study of developmental changes (e.g., embryology), for instance by arguing that changes in developmental timing (heterochrony) can lead to major evolutionary changes. Gould's 1977 book "Ontogeny and Phylogeny" is in particular seen by many as the main landmark leading to the birth of Evo-Devo. On the other hand, many developmental biologists tend to stress instead more the discoveries of homeotic genes and, in particular, of similar developmental genetic toolkit genes in a wide range of taxa—explaining for instance how very different forms evolved from common Bauplans—as a major landmark in the origin of Evo-Devo. Interestingly, this later view begins to be now more often seen as the dominant view, being for instance expressed in the recent reviews of Organ et al. (2015) and Moczek et al. (2015) on Evo-Devo, its achievements and its promising potentials, which will be discussed in more detail below. For instance, Moczek et al. (2015: p. 199) specifically state that "Evo-Devo was made possible in large part by the emerging power of molecular biology to contrast gene sequences, and subsequently gene functions, across taxa." Be that as it may, both views do recognize that in its earlier stages Evo-Devo did have a strong focus on Evo and on the organism: Gould and Alberch were mainly interested in the links between organismal evolution and organismal development (embryology), and the discoveries of homeotic genes lead researchers to talk about the links between conserved genetic toolkit genes, Bauplans, and organismal diversity, as beautifully reflected in the title of Carroll's book "From DNA to diversity: molecular genetics and the evolution of animal design" (Carroll et al., 2011).

If there is effectively an increasing imbalance between Devo and Evo in Evo-Devo, and a decreasing focus on the organism, one of the reasons for this trend might be simply that when new methods are being discovered—particularly in the areas of genetics/genomics and molecular biology—it is logical that more interest and funds are directed toward exploring those new methods. Evo, and Evo-Devo as a whole, have to take advantage of those new methods. We cannot just stop in time and praise the good old days. Perhaps developmental biologists, and molecular biologists in general, can simply argue that the major reason for the imbalance is that the molecular angle offers many more potential leads to do interesting work and/or to explore new avenues of research, and that it is the organismal/evolutionary branch that has to improve and think about other ways to promote new, viable research programs yielding novel insights on major Evo-Devo questions. Be that as it may, even if this is the case, this does not mean that Evo should become a second division component, or a "follower," of a first division, "driver" Devo. In my opinion, one of the major reasons for this imbalance is that a substantial part of the younger generation of Evo-Devoists comes from an almost exclusively developmental —and often even molecular—background. How many graduate courses, or PhD/Master programs, have really integrated in a fair and balanced way Evo and Devo in a true Evo-Devo context, in recent years? This situation markedly contrasts with the more hybrid, less gene/genomic centric background of the researchers who helped to reinstate the links between Evo and Devo in the 1970s and 1980s (e.g., Gould, see Gould, '77, 2002, and Alberch, see Rasskin-Gutman and De Renzi, 2009) and the Evo-Devoists who emerged later and are now at top positions in Evo-Devo societies (e.g., Sears, Galis: see below).

I am not saying that developmental biologists know less about evolutionary biology than evolutionary biologists know about developmental biology and particularly about molecular biology. Probably, I would even argue the contrary because many of the Evo terms and concepts (e.g., adaptation, natural selection, gradualism, fitness) are much easier to grasp or at least much better known by the general public than the more specific jargon of developmental molecular biology (e.g., enhancer, transcriptome, exome, cis/trans isomerism). In fact, I think that is why evolutionary biologists—for instance, those working in Natural History museums, in fields such as paleontology or physical anthropology—often tend to remain in fields that are exclusively related to evolutionary biology and to venture less into developmental/molecular research. In contrast, young developmental biologists often tend to be more easily driven to/integrated into Evo-Devo, in great part because this field is already mainly focused on Devo, in a process that can become self-perpetuating. The general consensus at the Berkeley meeting was that the vast majority of the attendees, particularly the younger ones, came from developmental, often molecular, backgrounds. Of course, a much broader historical account of the expansion of and recent trends in Evo-Devo should be given to fully explore and discuss the "how" of the Devo versus Evo imbalance. Some extensive historical accounts of the multidisciplinary field of Evo-Devo have already been published (Laubichler and Maienschein, 2007), and it would be very interesting to expand them to include the trends that have occurred over the last few years. However, that is not at all the main goal of this paper. It is instead to simply call the attention of Evo-Devoists to this imbalance in the most neutral, unbiased way that I can, and to avoid falling in the trap of "my field is better than yours" type of arguments, which can only be distracting and ephemeral.

WHAT?

So what is the problem really about, and what is the evidence—obtained from the Berkeley meeting and a review of recent opinion/perspective/review papers on Evo-Devo by other authors—that it does exist and might affect the future of this field? It is always a challenge to write such perspective/opinion papers calling attention to a certain problem without being accused of being biased, trying to be controversial, taking things out of context, or using "straw man" examples. Therefore, to avoid this I will simply (i) use two recent papers by Organ et al. (2015) and

Moczek et al. (2015), devoted Evo-Devoists—as I am—praising Evo-Devo and its enormous potential as a discipline—as I do; and (ii) contrast the concept of Evo-Devo put forth in these two reference papers with what is said in recent opinion/perspective papers about Evo-Devo by other authors and particularly with the results of a very simple, objective, unbiased quantitative analysis of the number of times certain key Devo and Evo terms were used in the titles and abstracts of all the 56 talks of the recent Berkeley meeting. Therefore, no one can say that the two key references are outdated, or that their authors are biased or "anti-Devo," or that there was "cherry picking" of only certain talks to support a priori assumptions or confirm a particular position. In fact, I was myself completely surprised when I started to check, just out of curiosity, some of the numbers that will be given below, by the depth of the imbalance between Evo and Devo in current Evo-Devo that they bring to light.

Organ et al. (2015) explain that, before Darwin, embryologists struggled to connect their observations with the *morphological* diversity of life, and that only much later, in the last few decades of the 20th century, homeotic *genes* were discovered and developmental *genetic* toolkit genes were found to explain how so many splendid forms evolved from common *Bauplans* (see above). According to these authors, Evo-Devo now describes how genetic change is manifested through development to produce the *forms* on which natural and sexual *selection* act, connecting the genotype with the *phenotype*, from genetics to embryology, to *anatomy* and *phylogenetics*. I have no doubt that Evo-Devo has contributed enormously to our knowledge of these diverse topics, and that it has the potential to expand this knowledge much more. But does current Evo-Devo research really correspond to this idea of what this field should be? From a search of the terms I italicized just above, or of similar terms, within the titles and abstracts of the 56 Berkeley talks, it appears that this is not the case. Of all these terms, which are by far the most used? The ones with, or derived from, "gene" (i.e., gene/tic, geno-type/me/mic): 204 times. So, what about the "phenotype/phenotypic"? 33 times only, or only about 1/7 as often. Could this be because researchers are using terms such as morphology, or anatomy, or other similar terms instead? Strikingly, within a discipline that is supposed to be in great part focused on helping us understand how form/morphology, including Bauplans, originated and changed during evolution, the term "morphology" and all its derivatives were used only 37 times, "anatomy/anatomical" only two times. What about "Bauplan/Bauplans," which are said to be so important for, and are much better understood due to, Evo-Devo? Zero times. These numbers provide further support for those researchers who argue that the study of the phenotype and of the organism as a whole is lagging dangerously behind in current Evo-Devo (Murren, 2012 see above), to the detriment of another major goal of this field, to study the links between the genotype and phenotype.

However, some might argue that we are focusing here too much on the phenotype, or specifically on morphology, and that there is much more to organismal evolution than morphology. But this is not borne out by the data: "evolution" and all its derivatives (e.g., "evolutionary," "evolutionarily," etc.) were used only 137 times, 1/3 less that "gene" and its derivatives, clearly demonstrating the dominance of genetics/genomics, and the shrinking of Evo, and even of non-molecular (e.g., organismal; embryology) Devo, within the field. In fact, in the vast majority of the 137 cases in which the term "evolution" or its derivatives were used, it was in the context of genetic/genomic evolution. Notably, the terms "organism/organismal" were only used 13 times in total. Strikingly, and at least for me also surprisingly, even the terms "selection/selective" and "adaptive/adaptation/adapted," which are at the very core of evolutionary biology and can apply to both molecular and organismal evolution, were only used 14 and 13 times, respectively. Although I tend to see evolution from a more "internalist" perspective myself—and I recognize the huge contributions of Evo-Devo that have brought me and many others to a greater appreciation of internal constraints, for instance—one should not neglect the importance of natural selection and the study of adaptations and their links with the environment (see below). And what about the use of "phylogenetic/phylogeny/phylogenetically," which is considered by both Organ et al. (2015) and Moczek et al. (2015) to be one of the major contributions of Evo to Evo-Devo, and a tool that should be widely used by Evo-Devoists and by developmental biologists in general? Seven times, only. Within all the titles and abstracts of 56 talks that does not really seem to be enough. These numbers are even more remarkable when one compares the number of times these key, general, broadly applicable evolutionary terms are used with the number of times that some molecular/developmental terms are used: for example, "patterning" and its derivatives (in the context of, e.g., gene expression) were used 67 times, "expression" in this context was used 82 times, "enhancer/enhancers" 22 times, "signaling" 28 times, and "transcript" and its derivatives 31 times.

So the take home message thus far is that, not only were each of these molecular terms used more than any specific evolutionary or phenotypic term, but even very precise, particular—but clearly important, no doubt—molecular terms such as (gene) "expression" were used almost as many times (82) as all the evolutionary and phenotypic terms listed so far all together (a total of 92 times for phenotype, anatomy, morphology, Bauplan, organism/organismal, selection, phylogeny, selection and adaptation, and all their derivatives). To be honest, and avoid biases and sounding unfair, I should clarify that during a few of these talks I did hear the word "Bauplan," for instance. It is logical that some terms not used in the titles/abstracts are used in the talks themselves, as there is much more information been given/discussed in the talks. So I am not arguing that these terms/issues were completely ignored in the meeting. However, if one counted

the number of times I heard the terms "transcript" or "enhancer" and their derivatives, it would be far more than 31 and 22 times, respectively, so the proportionate use of terms in abstracts/titles does reflect, in a rough way, what was really happening in the meeting overall, and it is the more objective, easy to measure, and thus less biased way of performing these comparisons. In fact, in a way the meeting was very upfront about this imbalance between Devo and Evo, by the very choice of the titles of the two inaugural keynote plenary talks, in which genes are clearly the main actors: "Gene co-option and the evolution of novelties" and "Gene networks modules regulating natural diversity in leaf shape." As I will explain below, this is not at all a criticism of the organizers of the meeting who, I think, actually made a laudable effort to include talks from researchers from a wide range of backgrounds and discussing a vast range of taxa—including both plants and animals, for instance—and subjects, from genetics to paleontology. But this line-up of talks does reveal a striking imbalance in current Evo-Devo, which contrasts with the somewhat idealized view of the current status of Evo-Devo given, for instance, in recent paper of Moczek et al. (2015). I think that the authors of this paper, and even the people who have questioned the route that Evo-Devo has taken in the past years/decades (see above), will probably be surprised by some of the numbers given above.

So, let us go back to the way Evo-Devo is described in recent papers of Organ et al. (2015) and Moczek et al. (2015). Organ et al. (2015) state that hypotheses in Evo-Devo are often robustly evaluated because, unlike in evolutionary biology, they are usually amenable to direct experimentation. This is, I agree, a major contribution of Devo to Evo-Devo. The authors explain that this strategy of testing hypotheses through direct experimentation uncovers the mechanisms responsible for shaping animal morphology over macroevolutionary time, in species both modern and extinct, for instance, combining knowledge about evolutionary changes of Bauplans (allometry) and timing of developmental events (heterochrony) and their links with adaptive radiations. They assert that combining proximate and ultimate hypotheses is a hallmark of Evo-Devo, and that paleontological evidence is extremely useful to frame and test hypotheses, for instance, to inform the polarity or direction of character evolution or hypotheses about developmental and evolutionary constraint and extinctions, or mosaic evolutionary patterns. For instance, they state that this combination should help us understand which molecular mechanisms might be related to acceleration (e.g., peramorphosis) or deceleration (e.g. paedomorphosis, neoteny) of development and to relate these phenomena to both molecular and morphological rates of evolution. However, despite their visibly optimistic view of Evo-Devo, the authors do recognize that these approaches unfortunately are often lacking in current Evo-Devo.

Is this latter statement supported by what was seen in the recent Berkeley meeting? The answer is a robust, and even distressing, yes. As explained above, "morphology" and all its derivatives were only used 37 times, "anatomy/anatomical" 2 times, and "Bauplan" 0 times. What about "macroevolution" and all its derivatives? Strikingly, only three times. "Pattern" and its derivatives were used only 11 times in an evolutionary sense, in another clear example of the profound imbalance between Evo and Devo in Evo-Devo, because as explained above "pattern" and its derivatives were used 67 times in a developmental context, so about six times more. "Allometry/allometries" were used only four times, and "polarity," "direction," and "mosaic" and all their derivatives were not used at all in a macroevolutionary context. Even "homology" and its derivatives, terms that are at the very core of evolutionary biology and supposedly also of Evo-Devo as they can be applied to both the phenotype and genotype (Moczek et al., 2015; Organ et al., 2015), were used only nine times. As a reminder, the term "gene" and its derivatives were used 204 times, "expression" 82 times, "enhancer/enhancers" 22 times, "signaling" 28 times, and even a very specific—but extremely important, I am not questioning that—molecular term, "transcript" (and its derivatives), was used 31 times. This gene/molecular-centric aspect of current Evo-Devo is also clearly reflected when we compare the number of times "module/modular/modularity" were used in a molecular vs. a phenotypic context: 8 versus none at all. These numbers are particularly significant because Organ et al. (2015) give many examples to show why we absolutely need a phylogenetic framework and should use fossil and organismal data as much as possible to inform us about, test, and discuss Evo-Devo hypotheses and mechanistic developmental hypotheses, in particular. In fact, although their optimistic, positive paper was not intended to be a criticism of Evo-Devo at all, in a way it does reflect the fact that Evo-Devo is losing its focus on the phenotype, the tempo of evolution, and one of the most central issues in evolutionary biology: the evolution of morphological diversity. This is because, in theory, there should be no need to promote, or even create, the term "Macroevolutionary Developmental Biology," as they do in their title, as the Evo in Evo-Devo should refer—and should have referred since the beginning—to both micro- and macroevolution. They state that the best way to integrate data from paleontology/evolutionary biology with the new information obtained in developmental/molecular works would be to use phylogenetic comparative methods, and they do recognize that this method is unfortunately seldom applied in Evo-Devo.

One of the most striking facts I observed during the meeting was the lack of studies or even discussions about the tempo of evolution. Temporal information was almost completely lacking, and thus issues related to rates/acceleration/deceleration of evolution or gradualism versus punctuated equilibrium were almost—but not completely—kept out of the picture. It is as though we are so obsessed with knowing in detail the novel molecular data about certain taxa and the fancy new techniques to study them that we are losing focus on the whole picture: how we put together that new molecular and mechanistic data with

the broader Evo patterns and processes needed to gain a comprehensive understanding of both the tempo and mode of evolution. Numbers? "Fossil/fossilized/fossils" were only used nine times, "extinct" three times, and temporal terms such as "years" (as referring, e.g., to millions of years) only four times; "punctuated" one time, and "gradual/gradualism," "cladogenesis," and "anagenesis" were not used at all; as mentioned above even "phylogeny;" and its derivatives were only used seven times.

Might it be that the Evo is still represented very strongly in Evo-Devo, but its focus has been more directed toward the study of microevolution, rather than macroevolution? On the one hand, it is true that the founders of Evo-Devo were mainly interested in macroevolution, and namely its links with the discoveries of *Hox* genes and a better knowledge of developmental phenomena such as heterochrony, as emphasized by influential authors like Carroll et al., (2011) and Gould ('77), respectively (see below). On the other hand, one cannot forget that the Modern Evolutionary Synthesis was actually more focused on microevolution—geneticists, particularly population geneticists, played a major role in that synthesis—and on creating a more genetic/genomic centric view of evolution as a whole, a goal which seems to have been at least partially inherited by current Evo-Devo. Thus, do we see a prevalence of microevolution over macroevolution in current Evo-Devo? According to the numbers compiled from the titles/abstracts of the 56 talks at Berkeley, this does not seem to be the case. As noted above, "selection/selective/selected" and "adaptive/adaptation/adapted" were only used 14 and 13 times, respectively. Moreover, other terms that are at the very core of microevolution were even less frequently used, or not used at all: "speciation" three times, "fitness" four times, and "allopatry," "sympatry," and even "geographic" (as in, e.g., geographic isolation) and all their derivatives were not used. In fact, it seems that Evo-Devo is not focusing enough on either the tempo of evolution, that is, the changes across time, or on their geographical context, that is, the changes across space. Therefore, a clarification needs to be made. One could argue that a gene-centered focus can still be considered to be part of Evo, as genetics play a crucial role in evolutionary biology, and sub-fields such as population genetics, for instance, were particularly important for the Modern Evolutionary Synthesis, as noted above. But as explained here and above, the genetic themes that were the focus of NeoDarwinists, including population genetics, are not at all the main focus of Evo-Devo. Instead, the "Geno" part of Evo-Devo to which I refer to in this paper concerns instead to very specific genetic concepts within the field of developmental biology, such as transcriptor factors and gene expression in embryos, for instance. Therefore, the "Geno" to which I refer is part of the Devo within Evo-Devo, and not of Evo.

A review of the recent literature makes it not so surprising to find that Evo-Devo is not paying as much attention as it should to the geographic context, or to the environmental factors in general. Although authors have pointed out that Evo-Devo and Ecology have already established some promising links—including the attempt to create Eco-Evo-Devo—and that each discipline has contributed to the other, it is often assumed that this is one aspect where Evo-Devo urgently needs to improve (Abouheif et al., 2014). Evo-Devo needs to take ecological data more into account to better understand the links between phenotype, genotype, and the environment as a whole. Paradoxically, it is often said that one of the major achievements of Evo-Devo was the contribution to a better understanding of developmental plasticity and its importance for both macro- and microevolution, whereas the vast majority of the experiments performed in Evo-Devo in general and in Devo in particular aim to reduce that plasticity and eliminate the "environmental noise." This paradox was pointed out in a recent paper whose title clearly reflects the broadly accepted view that not enough has been done to integrate Evo, Devo and ecology: "Eco-Devo-Devo: the time has come" (Abouheif et al., 2014). It is now time to move beyond the exclusive study of the links between geno-and phenotype—even if that study itself is also very incomplete because of the scant importance given to the phenotype and the whole organism (see above)—and to start promoting more laboratory research into the true developmental plasticity of organisms and the interactions between genotype, phenotype, and environment. For many decades, Evo-Devoists and molecular and developmental biologists in particular have mainly focused on laboratory experiments in which they try to reduce plasticity and variability to a minimum to standardize their procedures and allow comparisons with results from other laboratories. For instance, millions of mice and other model organisms are kept in laboratories around the world following very similar protocols for each taxon, for example, using specific, "standard" temperatures, and so on. This is completely justifiable when one seeks to perform a systematic, standardized, comparable study of, for example, the phenotypic consequences of knocking out gene A in developmental stage B of an embryo of a taxon C. However, by minimizing plasticity, variability and "environmental noise" we are departing somewhat from what really happens in the wild, and particularly from the type of holistic observations that led to Darwin's theory of evolution by natural selection in the first place. That is why researchers are stressing more and more the necessity of not only including ecological data obtained in the field into the equation but also expanding laboratory experiments to include variable conditions and not minimize "noise," but instead to try to replicate more accurately the true natural conditions in which organisms live, feed, strive, and die (Ledón-Rettig and Pfennig, 2011). Moreover, authors are also emphasizing the need to incorporate more information from the study of natural variations and defects, including pathological data, and not to regard such variations and defects in a negative way (as "noise") but instead to appreciate the enormous potential that they have to illuminate our understanding of both normal development and the origin of novelties (Guinard, 2014). Guinard's recent call for an

"Evolutionary Teratology" (Guinard, 2014) subfield reflects this need and is in a sense in line with the creation of the "Evolutionary Developmental Pathology" subfield of Evo-Devo that is being promoted by our laboratory and other colleagues (Diogo et al., 2015; Smith et al., 2015), which is in turn influenced by the type of research that has been done by Galis et al. (2007) (e.g., Van Dongen et al., 2009; Bots et al., 2014), in which humans themselves—and particularly their natural variations and anomalies—are used as the main model organisms/case studies.

Lastly, could it be that this lack of focus on evolution mainly concerns issues that have been often the focal point for researchers, such as paleontologists, ecologists, and comparative anatomists, who traditionally have been more involved in the study of adult forms and their interactions with the environment? That is, current Evo-Devo may be more interested in approaching evolution and discussing major conceptual evolutionary questions/theories from a more developmental, but still organismal, perspective? After all, it is often assumed that one of the main forces leading to the creation of Evo-Devo was the integration—by, for example, Gould ('77, 2002) and Alberch (Rasskin-Gutman and De Renzi, 2009) (see above)—between the evolutionary patterns observed in the studies of adults by such researchers, and the developmental processes (e.g., heterochrony) studied by developmental biologists. As noted above, recent paper of Organ et al. (2015) emphasized how this integration is crucial to link major evolutionary changes with specific changes in the timing of ontogenetic events, and also to study evolvability and constrained evolution by better understanding the molecular mechanisms leading to those patterns. So perhaps what happened is that many Evo-Devoists opted to follow this line of research founded by researchers such as Gould and Alberch, and thus to concentrate mainly on these developmental aspects of macroevolution. Let us see if such a trend is, therefore, reflected in the titles/abstracts of the 56 Berkeley talks. Amazingly, even "heterochrony," a key term that played a central role in the foundation of Evo-Devo—and that refers exclusively to the study of changes of developmental timing, that is, it is above all a Devo term—was used just two times. The almost complete lack of focus on such issues is also reflected in the scarce, or nonexistent, use of related/similar Devo terms that were so important in the very first attempts to link morphological diversity with ontogeny by authors such as von Baer, in the 19th and 20th centuries, and then by some of the first prominent Evo-Devoists, and that according to Organ et al. (2015) should also play an role in current Evo-Devo: "acceleration" (both in a Evo and even in a Devo context) was used one time; "peramorphosis," "deceleration," "paedomorphism," "vestigial," "atavism," "phylotypic" (stage), and "hourglass" (in a Devo context) were not used at all. "Neoteny," a related term that has been suggested to have played a particularly crucial role in human evolution and in the origin of major clades and evolutionary history of many taxa, including salamanders, lungfishes, and many amniote groups (Gould, 2002), was not used at all. Even terms that are at the very core of evolutionary biology such as "constraint/constrained/constraints" and "evolvability," and that according to Moczek et al. (2015) are now better understood because of Evo-Devo and are illustrative showcases of the power of this field, were barely used at all, seven and two times, respectively. The numbers given in this paragraph do seem to provide support for the "too many genes, too little development" criticism of some authors (Moczek, 2012: p. 116). That is, the problem is even deeper than the Evo shrinking in Evo-Devo: the Devo itself is more and more becoming in fact "Geno," with a huge focus on genetics/genomics/molecular biology and a vanishing interest in embryology and in organismal Devo per se.

WHO?

If you made it this far and agree with at least some of the points raised in this paper, you might been wondering: so, who is to blame for the imbalance between the huge weight given to Devo—and I would say in particular to Geno (genetics/genomics)—in Evo-Evo? My answer would simply be nobody specifically. First of all, no criticism can be made of the organizers of the meeting at Berkeley, or of any other previous Evo-Devo meetings organized elsewhere (e.g., Euro-Evo-Devo society). As noted above, this was one of the most interesting meetings I have attended, and one can clearly appreciate the enormous effort of the organizers to try to provide a fair balance between the different backgrounds of and taxa studied by Evo-Devoists. A clear example is the choice of having an "animal" talk and a "plant" talk in both the two opening and the two closing talks.

As I also stressed above, the choice of the two opening key lectures—"Gene co-option and the evolution of novelties" and "Gene networks modules regulating natural diversity in leaf shape"—does reflect, in a very straightforward manner—the current gene-centric reality of Evo-Devo. But in my opinion, the choice of these talks, and of all the other 54 talks for that matter, does not reflect a specific purpose or agenda of the organizers. In fact, the President (Ebouheif) of the Pan-American Soc. for Evo-Devo did a PhD in a Department of Ecology and Evolution, and the Vice President & President-Elect (Sears) comes originally mainly from an Evo background. Also, for a long time the President of the Euro-Evo-Devo society was a researcher with a Evo—actually a comparative/functional morphology—background (Galis) who I profoundly admire. And the current President of that Society (Muller) is someone who surely cannot be accused of having a gene-centric view of evolution, very much the contrary. Therefore, the choice of talks presented in previous Evo-Devo meetings, and in the Berkeley meeting to which this paper refers in particular, reflects instead the fact that despite their excellent, laudable effort to provide a fair balance between disciplines, the organizers had to work with what is available within the current reality of Evo-Devo, as evolution works with the available traits (tinkering). Moreover, the organizers did a very good job of including a series of workshops and panel

discussions to allow everybody interested to discuss—and have their say about—the major challenges and aspects to be changed/improved in Evo-Devo. For instance, among these there was a "Future of Evo-Devo" panel discussion and a "Theory in Evo-Devo" panel discussion, reflecting the open, democratic spirit of the organizers, and their willingness to listen to their peers.

This paper, and particularly my decision to publish it at this time, is actually in part the result of that meeting, and various portions of it were inspired by discussions that I had with, or heard from, other attendees during the meeting. One of the specific aspects pointed out during those two panel discussions was the need to further integrate the new developmental—mainly molecular/genetic—data into broader discussions of major evolutionary theories and long-standing conceptual questions. As noted above, this has also been stressed in the recent Evo-Devo literature. It is also reflected by the analysis of the titles/abstracts of the 56 talks of the meeting: the terms "conceptual/conceptualize" were used only one time, and "theory/theories" were not used at all. Therefore, on an optimistic note, the occurrence of this meeting, and particularly of its workshops/panel discussions, and the quality and multidisciplinarity of the persons promoting, organizing, and leading these meetings and their respective societies can only give us hope for, and confidence in, an even better future for Evo-Devo. This effort should be combined with an active effort, by all of us, to promote a better balance between Evo and Devo within Evo-Devo, and to address the reasons that contributed to the current imbalance.

For instance, many evolutionary biologists, particularly those studying adults and above all those studying adult members of fossil taxa—for example, paleontologists, physical anthropologists—tend to remain in their own fields, unlike some of the earlier more prominent Evo-Devoists, such as Gould. However, in recent years there are more and more exceptions to this rule, in part due to the fast growth of many sub disciplines within developmental and particularly molecular biology and—in what can be seen as a paradox—of the increasing importance of these sub disciplines within Evo-Devo. As the saying goes, "if you can't beat them join them," and the increasing influence of Devo and particularly of Geno and the increasing emphasis—and in many cases obligation—on including mechanistic components in grant proposals, for instance, is forcing evolutionary biologists to learn/use more Devo and Geno. One the one hand, this is good because it promotes further integration of Evo and Devo which, contrary to the saying, should not be seen at all as enemies, but instead as natural partners, as they were seen for long periods in the 19th century and first decades of the 20th centuries and fortunately again with the blossoming of Evo-Devo. On the other hand, we should be very careful not to let the saying turn into a reality, by having Evo become a second division, almost subservient "poor brother" that desperately needs the "rich brother" Devo in order to get attention (e.g., publishing in high impact journals) or pay its bills (e.g., applying for grants).

A problem that might arise from this current scenario is the forced/artificial use, by researchers that are purely developmental and/or molecular biologists, of evolutionary terms in the titles of their publications and/or grant proposals that have no true connection to evolutionary biology or Evo-Devo, just to make them more appealing for journal/grant reviewers. Studies that merely compare the developmental/molecular biology of a few species are not necessarily evolutionary studies. This was stressed above, using the quantitative analyses of the titles/abstracts at the Berkeley meeting: the large number of times that the term "evolution" and/or its derivatives are used in such titles/abstracts is inflated when compared with the number of times where evolutionary issues/theories (e.g., about selection, adaptation, developmental plasticity, heterochrony, or macroevolution) were truly mentioned/discussed in the respective abstracts/talks. A related problem is the pressure for younger generations to be experimentalists and "empiricists," that is, to produce "new data" by themselves, in a field that has become too big for one to produce enough data if one wishes to propose a novel integrative concept. In Evo-Devo, "original" work means that one performs experiments and produce such "new data," but the work by those who synthesize data in a novel way, and produce new ideas, is also original, and should be valued as much as the empirical approaches are. I myself recently felt this pressure—despite being a mid-career, awarded, tenured associate professor with several current grants—when a grant reviewer listed, as one of the very few weaknesses of an Evo-Devo grant proposal, that I had "several (too many) review papers" (!). If Evo-Devo is all about doing new experiments and producing new data endlessly, in a completely disconnected way, without any effort to synthesize/make sense of the obtained data and to integrate them with data already available from other fields, then it would really fit a Red Queen model: running so fast, to do not move at all, going anywhere. On the other hand, one should also recognize that it might be that Evo is not catching up to provide new, synthetic ideas that can be tested through molecular/developmental techniques. That is, maybe some evolutionary biologists have been/are too occupied with rather vague ideas and moving targets (e.g., homology, cladistic algorithms, and so on) that Evo has not come to build a theoretical framework within which molecular/developmental researchers can take a full advantage of the new, powerful technological tools available to them.

But having said that, it should be stressed that there are in fact numerous reasons to be optimistic. For instance, the new discoveries of preserved non-adult specimens of a wide range of fossil taxa and/or new methods of studying them have provided a new impetus to integrate paleontological and developmental analyses, and has namely led to the creation of a new subfield: Developmental Paleontology (Sánchez-Villagra, 2012). Moreover, apart from including the study of non-adult specimens in paleontolological studies, recent works are exploring the study of embryos of experimental lab specimens/mutants

of model taxa—for example, chickens—to predict undiscovered transitional morphologies in the fossil record—for example, the transitions between non-avian dinosaurs and birds (Bhullar et al., 2015). These works are an illustrative example of how Evo and Devo can be used in a balanced, interactive way in Evo-Devo, with Evo studies informing Devo works by, for example, helping in the search for specific developmental mechanisms that might have lead to particular evolutionary changes, and the results of these latter works then inform Evo studies by helping to predict and find particular fossil forms (Bhullar et al., 2015).

Furthermore, although Evo-Devo has often found it difficult to fully include comparative anatomy as a major actor within its research programs, as stressed by Minelli and many others (Stern, 2003), it has, ironically, indirectly contributed to the renaissance of this anatomical field (Diogo et al., 2015; Moczek et al., 2015). This is because for a long time Evo-Devoists, and particularly developmental/molecular biologists, have mainly concentrated their studies on a limited number of model organisms, which are distantly related (e.g., mice, birds, frogs, and zebrafish, within vertebrates). Because many of these studies aimed to study the relationships between the phenotype and genotype, particularly before the rise of genomics and the study of genomic networks, there was a need to go back to some of the original descriptions of the embryos, and also adults, of those model taxa. Unfortunately, this was not always done in the best way. Instead of seeking out closer relationships with comparative anatomists, developmental biologists sometimes have preferred to undertake by themselves less careful analyses of the phenotype of their model taxon or, more often, even less meticulous anatomical comparisons between that taxon and other model taxa (Diogo and Abdala, 2010). Such analyses are essential to extrapolate the data obtained from, for example, experiments using one model taxon to what is seen in/known about other model organisms, and particularly to apply the obtained data to better understand human evolution, anatomy, and medicine, for instance, and they are plagued with difficulties even for well trained comparative anatomists. But the rising interest in those model organisms and their anatomy has indirectly led comparative anatomists to compare them and then try to themselves correlate the data obtained from those comparisons with those from the emergent developmental studies. This is another reason why researchers who worked mainly on adult morphology—included myself, at the earlier stages of my career—are now more and more interested in developmental and molecular data. But an effort should be made to further promote this interest in genetics and genomics and stress its importance to young comparative anatomists, paleontologists, and physical anthropologists and others, from very early stages of their academic/research careers. This should include courses and lab rotations in PhD/Master programs, and ideally whole components of their thesis research.

Similarly, developmental biologists should make an effort to work more closely together with, and use the methods developed by, evolutionary biologists, as stressed by authors such as Minelli (2003) and more recently by many other authors, including Organ et al. (2015). A recent paper examined this question in some detail, from a broader perspective, and particularly using the conceptual framework of trading zone, with a title that again reflects that we are still far from living in wonderland—which we as Evo-Devoists all aim for—concerning the relationships and balance between the Evo and Devo in Evo-Devo: "Evo-Devo as a Trading Zone" (Winther, 2015). Namely, Winther raises some deep questions: "Evo-Devo exhibits a plurality of scientific "cultures" of practice and theory. When do these cultures act—individually or collectively—in ways that actually move research forward, empirically, theoretically, and ethically? When do they become imperialistic, in the sense of excluding and subordinating other cultures?" (Winther, 2015: p. 459). The latter sentence goes in line with the call of attention above of not falling into the trap of having one "culture" being subservient of another, but Winther is not referring merely to Evo and Devo. His analysis is more profound and refers instead to various types of "cultures", including "styles" (e.g., mathematical modeling, mechanism, and history) and "paradigms" (e.g., adaptationism, structuralism, and cladism) within these two major components of Evo-Devo. What I particularly like about Winther's paper, and is more relevant for the purpose of the present one, is the advice he gives us to fully explore the potential of Evo-Devo as field that can, and should, "progress through a radical plurality of perspectives and cultures . . . characterizing the internal structure of each is necessary for understanding how they collaborate or compete, and how they are fragmented or integrated, in the rich interdisciplinary trading zone of Evo-Devo" (Winther, 2015: p. 459). That is why the present paper should in no way be seen as a criticism of an individual field, person, or research program, but instead as a contribution to expanding this trading zone where Evo-Devoists from all backgrounds and "cultures" can further collaborate and make a concerted effort to turn Evo-Devo into an even more complete, balanced, and fascinating scientific field. This effort should ideally lead to the creation of more Evo-Devo societies and journals, and above all graduate courses and PhD/Master programs as well as summer schools that are not Evo, or Devo, or even Geno (genomics/genetics) and Eco (ecology), but are simply, and cohesively, Evo-Devo. That way, students will have the possibility to be themselves, from very early career stages, part of each of these different "cultures," which will then, with time, be no longer seen as so "different" and "strange", but instead as highly interconnected and balanced fields within the multidisciplinary, pluralistic Evo-Devo.

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