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For a new dialogue between theoretical and empirical studies in evo-devo

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Despite its potentially broad scope, current evo-devo research is largely dominated by empirical developmental studies, whereas comparably little role is played by theoretical research. I argue that this represents an obstacle to a wider appreciation of evo-devo and its integration within a more comprehensive evolutionary theory, and that this situation is causally linked to a limited exchange between theoretical and experimental studies in evo-devo. I discuss some features of current theoretical work in evo-devo, highlighting some possibly concurring impediments to an effective dialogue with experimental studies. Finally, I advance two suggestions for enhancing fruitful cross-fertilization between theoretical and empirical studies in evo-devo: (i) to broaden the scope of evo-devo beyond its current conceptualization, teaming up with other variational approaches to the study of evolution, and (ii) to develop more effective forms of scientific interaction and communication.

Keywords: evolutionary theory, evolutionary models, developmental variation, structured variation, scientific communication

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[. . .] it is only theory that will allow us to convert data to knowledge.
(Brenner, 2010, p. 207)

What Evo-devo Is about and Its Main Current Focus

As a general statement, evo-devo is the idea that in order to explain evolution, development must be considered (Hall, 1992; Amundson, 2005). Including information about developmental processes provides more complete explanations of observed evolutionary patterns, by evaluating not only the variation sorted by natural selection, but also what kinds of variation can possibly arise from developmental systems (Müller, 2007).

The rationale behind this claim is the idea that "traits do not reside in genes but emerge during development" (Moczek, 2012, p. 109), and that variation produced during development can significantly affect the direction of evolution. This is because such variation is *structured*, rather than isotropic, and thus *instructive* (i.e., able to influence the direction of evolution) rather than merely permissive (i.e., only necessary for evolution under natural section).

Despite this potentially broad scope, current evo-devo research, at least what is usually recognized under this "umbrella term" (Minelli, 2015), is largely dominated by empirical developmental studies, among which developmental genetics or, at best, comparative developmental genetics prevails, whereas comparably little role is played by theoretical research. The result of a cursory survey on the recent evo-devo literature will support this claim.

Emulating the bibliometric approach of Fawcett and Higginson (2012), I have estimated the percentage of "theoretical" papers in the last 5 years' (2010–2014) issues of three influential evo-devo journals [*Evolution and Development*, *Evo-devo*, *Journal of Experimental Zoology (Molecular and Developmental Evolution)*] and in the contributions to the last three editions of the congresses of the European Society for Evolutionary Developmental Biology (Paris 2010, Lisbon 2012, Vienna 2014). This was implemented by automatic filtering for specific keywords, followed by a manual check for contextual meaning. As a proxy, a journal paper, or a congress contribution was scored as "theoretical" when the term "theory" (plus related terms like "theoretical," "theoretically," etc., but excluding generic reference to "evolutionary theory," "Darwinian theory," etc.) or the term "model" (plus related terms like "modelistic," "modeled" etc., but excluding empirical uses such as "model system," "model organism," etc.) was present in the title or in the abstract. I found that the frequency of "theoretical" works was 6.0% ($n = 717$) for journal articles and 11.3% ($n = 1238$) for congress contributions. This contrasts with the results of Fawcett and Higginson's (2012) survey, where a similar sampling search on more general evolution and ecology papers, despite adopting a less inclusive keyword set (only the character string "model*" was searched for) gave a figure of 22.2% "theoretical" papers ($n = 28,068$).

This does not come as a surprise for one who works in the field, but it is not at all obvious why this should be the state of affairs. In fact, the theoretical implications of the evo-devo approach to evolution are not small (Müller, 2007). For Sears (2014), evo-devo even requires a paradigm shift in evolutionary biology, from the traditional research emphasis on the sorting of phenotypic and genetic variation, mainly by natural selection, to a new emphasis on the production of that variation by developmental processes. Why, then, should theoretical studies be so under-represented in evo-devo research? A possibly correlated fact about evo-devo is that, despite more than three decades of productive research (Haag and Lenski, 2011), with a number of studies demonstrating how development can significantly bias the generation of phenotypic variation at different levels of biological organization, the concept of *developmentally biased variation* has not yet been widely accepted into mainstream evolutionary biology (Sears, 2014).

There are several possible explanations for this fact, beyond the opinion that some evo-devo claims are not supported by compelling evidence (e.g., Futuyma, 2015). Nunes et al. (2013) argued that by primarily focussing on variation across broad phylogenetic scales, evo-devo shows some limitation in revealing the most basic (molecular) causes of developmental evolution, and encounters difficulties in integrating with population genetics. Thus, they advocated a complementary "micro-evo-devo" approach, centered on the genetic and developmental basis of intraspecific variation. In a different perspective, Moczek (2012, 2015) noted that much research in contemporary evo-devo remains confined within a traditional framework that views traits and trait differences as being caused by genes, with the environment relegated to the role of mere external context within which development and evolution unfold. He argued that several theoretical frameworks are already in place to foster a systemic integration of the role of the environment in evo-devo. An alternative, or an additional reason for the undervaluation of evo-devo is that its achievements are easily perceived as too circumstantial in nature to be relevant in a general sense. Actually, a mass of research seems to suggest that developmental influences on evolution are system-specific (Sears, 2014), and the search for general principles of biased variation of developmental origin is still in its infancy (Minelli and Pradeu, 2014). Last, but not least, it is not at all clear how evo-devo should be formally integrated in the current evolutionary theory (Müller, 2007), not even in its more pluralistic, recently proposed version dubbed "extended evolutionary synthesis" (Pigliucci and Müller, 2010).

A common element among these shortcomings seems to be a deficiency of theoretical work in evo-devo, possibly causally linked to a limited exchange between theoretical and experimental studies in the same field, which represents an obstacle to its wider appreciation and integration within a more comprehensive evolutionary theory. I argue here that for evo-devo to get out of this sort of theoretical marginalization, it is necessary to engage in more theoretical work, fostered by a more effective interexchange with empirical studies. But before analysing the state of the art and its possible causes more in depth, and reasoning how to implement this exchange, a preliminary note is needed.

Different readers may have distinct opinions on what constitutes a theoretical work, and it could be questioned that my argument is based on too narrow a view, by focussing on theoretical developments formulated through some kind of (mathematical) formalism. This standpoint apparently disregards so called evo-devo "conceptual" advances (Arthur, 2002), as for instance the concepts of "facilitated variation," "developmental modularity" and "developmental systems drift," to mention but a few (Müller, 2014). Actually, while acknowledging the importance of conceptual developments in any theoretical work, in my view these cannot stand as independent theoretical products with respect to formal models. On the contrary, formal, and conceptual formulations should be viewed as complementary, intimately interconnected aspects of the same theoretical construction. Stand-alone, only verbally expressed concepts, well founded on data as they may be, are in general not sufficiently accurate, quantitative, or predictive to be considered a theoretical finished product. At the same time, not every modeling-based or computational study in the field should necessarily be considered a theoretical contribution to evo-devo, in particular when it does not directly address any general questions in the evolutionary theory. For instance, mathematical modeling of specific developmental processes, or formulating and testing hypotheses on specific evolutionary events in the history of life, are not theoretical works in the sense of interest here, if they deserve that label at all.

Theoretical Work in Evo-devo

Highlighting a shortage of theoretical evo-devo works does not equate to saying that works involving formal (e.g., mathematical) modeling, or based on some degree of biological abstraction do not exist.

As a matter of fact, theoretical work in evolutionary biology distinguished by marked attention to variation and its properties is a lively and multi-branched field of investigation. Current lines of research range from purely mathematical approaches, elaborating on general evolutionary equations and showing why and how development should enter into any truly general theory of evolution (Rice, 2004, 2011), through systems-biology approaches based on mathematical modeling of gene regulatory networks (Crombach et al., 2012; Jaeger and Monk, 2014), and computational studies on the origin of innovations at the level of basic biological systems, such as metabolic networks or regulatory circuits (Wagner, 2011; Payne and Wagner, 2014), to mathematical modeling of the evolution of morphogenesis, as in that of mammal dentition (Salazar-Ciudad and Jernvall, 2010; Salazar-Ciudad and Marín-Riera, 2013).

However, while these theoretical lines of investigation continue flourishing and accumulating significant results, the dialogue between empirical and theoretical studies remains somehow limited, or, to use a metaphor already exploited for the relationship between evolutionary and developmental biology in evo-devo (Minelli and Fusco, 2008, p. xvi), there does not seem to be enough "cross-fertilization" between the two approaches. While theoretical works closely associate with experimental results through mathematical modeling and computer simulation and, on the other front, theory-driven experimental works are certainly part of evo-devo research (e.g., Grieneisen et al., 2012), more often than not the interaction between theoreticians and experimentalists is implemented within the same research group. There is nothing wrong with this, on the contrary this is great, but unfortunately this is not a model, either in term of research group mission or in terms of research group composition, that can easily be exported to most university departments and research institutes. To be really effective and pervasive, interactions should definitely be developed between groups, at the level of the community as a whole. Only in this way, theoretical development could take the form of a wide-ranging collective enterprise.

The great leap forward of the Modern Synthesis in the 1930s and 40s was catalyzed by the mathematical work by R.A. Fisher, S. Wright, and J.B.S. Haldane, and since then mathematical models of evolutionary theory have continued to mature (Servedio et al., 2014). It is not an isolated opinion that a next step toward a theory of developmental evolution should pass through a similar process of theoretical formalization. Rice (2011) anticipates that any theory mechanistically connecting developmental and evolutionary processes will necessarily involve mathematical descriptions of the same processes at the population level.

Indubitably, there are evolutionary biology fields, as for instance molecular evolution (Kimura, 1983) and population genetics (Hartl and Clark, 2007), that are naturally better disposed to mathematical formalization than the evolution of developmental systems, but this should not be taken as an excuse. Evo-devo claims cannot remain limited to verbal arguments, as evolutionary processes and the resulting patterns are often complex, and in verbal chains of arguments there is much room for error and oversight (Servedio et al., 2014).

Current Impediments to an Effective Dialogue

The difficult relationship between theoretical and experimental studies is not only true for evo-devo. For some time, several authors have been pointing out this problem in biology in general (e.g., Hillis, 1993; Peck, 2004; Brenner, 2010; Servedio et al., 2014), nonetheless, its expression in evo-devo has specific features. As possibly always the case in any relationship, the causes of the scarce interaction between theoreticians and experimentalists can be found in the behavior of both partners. Here, is a short list of potentially concurring causes.

Variation Is Overlooked in Many Developmental Studies

Love (2010) observed that developmental studies in model organisms are usually carried out by establishing a set of normal embryonic stages, which allow researchers in different laboratories to compare their experimental results. However, normal stages are a form of idealization, because they intentionally ignore known variation in development. Variation of different origin is a constitutive feature of developmental processes, but developmental staging in model organisms typically downplays variation in ontogeny, especially variation associated with environmental variables, limiting their range of values in laboratory conditions, and overlooking many effects of developmental instability and phenotypic plasticity (Fusco and Minelli, 2010).

Quantitative Approaches Are Underrepresented in Developmental Studies

Cooper and Albertson (2008) argued that quantitative developmental studies are comparatively rare, with respect to studies concerning qualitative descriptions of how anatomical traits are affected by the disruption of specific genetic pathways. In the study of morphogenesis, mathematical descriptions of anatomical form during development are seldom adopted, and morphological variation within treatment groups is rarely taken into account. Interestingly, this occurs despite suitable analytical techniques, commonly applied in other areas of morphological research, have long been available and have proved to be very effective (Mayer et al., 2014).

Other authors have illustrated the potential of several quantitative methodologies in different areas of developmental biology, as for instance in the study of developmental patterning in association with mathematical modeling (Lewis, 2008; Oates et al., 2009; Morelli et al., 2012), or in the study of the genetic and developmental basis of phenotypic variation within species, through quantitative trait loci (QTL) mapping and genome-wide association studies (GWAS) (reviewed in Nunes et al., 2013).

All these contributions, through examples from experimental studies which span a wide range of developmental processes and organismal systems, show how quantifying ontogenetic data and accounting for developmental variation can result in a deeper understanding of the processes under investigation. A key point, for the argument developed here, is that a quantitative approach "allows the iterative dialogue between theory and experiment that is required to understand the complexity of the developing embryo" (Oates et al., 2009, p. 518).

If quantitative approaches in developmental biology are important for the study of development *per se*, they are even more fundamental for evo-devo, which sees developmental processes as the real target of selection (Fusco, 2001), and in developmental repatterning a common form of evolutionary change (Arthur, 2011). Quantitative developmental data can effectively enhance our understanding of the processes by which phenotype development evolves.

Nonetheless, in many ways, modern developmental biology retains a typological outlook, and intraspecific variation in developmental pathways and their regulation have overall received little attention (Cooper and Albertson, 2008; Nunes et al., 2013).

Many Theoretical Studies Are Difficult for General Biologists

In consideration of the little training in mathematics of an average biologist, analytical derivations and the formalism adopted by many theoretical models may be hard to follow for those who are not expert in mathematical model construction.

Fawcett and Higginson (2012) showed that the citation rate of articles in ecology and evolutionary biology is negatively associated with the density of equations in the text. More importantly, equation-dense papers tend to be more frequently cited by other theoretical papers, but significantly less so by non-theoretical papers. This is a clear picture of the fact that communities of math-inclined biologists and experimental biologists do not easily meet. Evo-devo practitioners, either theorists or experimentalists, do not seem to represent an exception.

Haller (2014) noted that although both empirical and theoretical approaches to scientific research are essential to scientific progress, the interactions between the two practices seems to be problematic. He conducted a survey on more than 600 scientists (mainly ecologists and evolutionary biologists) about the relationships between theoretical and empirical work. The resulting scenario was a lack of mutual reliance, understanding, and interaction between empiricists and theorists, despite a vague general desire of closer interactions.

Although a greater mathematical literacy of biologists might be desirable, it is a fact that excessively technical presentations of mathematical models reduce the comprehension by general biologists, and it is a shared opinion that the time investment required for many biologists to understand what is going on in computational models is not always worth the payoff (Hillis, 1993). In other words, the apparently scarce interest of empirical biologists in theoretical studies may reflect a somehow rational stance, when the latter are not endowed with empirical support, as it is too often the case (Gibbons, 2012). In an apology for "non-mathematical biology," E.O. Wilson (2013) went so far as to asses that "The annals of theoretical biology are clogged with mathematical models that either can be safely ignored or, when tested, fail." I personally do not share Wilson's view, but I suspect that many evo-devo biologists may do so. Thus, irrespective of any personal opinions on his objection, this draws attention to the existence of deeply divergent views of the matter that cannot be ignored.

Enhancing Cross-fertilization between Theoretical and Empirical Studies in Evo-devo

I have two suggestions for promoting a more fruitful dialogue between theory and experiment in evo-devo: to broaden the scope of evo-devo beyond its current conceptualization, and to develop more effective forms of scientific interaction and communication.

From "Developmentally Biased Variation" to "Structured Variation"

If evo-devo represents an extension of the Darwinian theory of evolution (Pigliucci and Müller, 2010), rather than a completely different evolutionary theory, as very few would argue, what place should it take in a more inclusive theory of biological evolution? Besides rhetoric, this question remains substantially unanswered, as it is not at all clear how evo-devo can formally articulate with the massive edifice of the standard theory. Also, the relationships between developmental evolution and the extant models of evolutionary dynamics, especially those developed in the context of population genetics, have not been completely clarified.

The obvious locus for evo-devo seems to be the question of variation, i.e., the problem of the origin, structure, and maintenance of variation. Evolution is a process which both generates and sorts out variation (Fusco, 2001). The production of variation (through mutation, recombination, development, etc.) and the sorting of variation (through natural selection, random drift, etc.) are not independent components of the process, but the study of their interactions has been mainly restricted to population genetics models, where the descriptors of evolving systems are the genotypes (or alleles) and their frequencies, and additive genetic variance is often the only kind of variation considered (Rice, 2004). From an evo-devo perspective, this appears as a partial, incomplete description of the evolutionary process. However, neither is evo-devo, as currently understood, immune to a kind of conceptual short-sightedness by focussing on a too narrow view of phenotypic variation.

The key point is that while evo-devo claims that development can bias the production of phenotypic variation, it is not true that the structure of variation, its instructive role, must come from development exclusively.

Firstly, development, even extending its significance to include unicellular organisms' progression through their cell cycle, is only a segment of an organisms' life cycle, which can include more than one developmental process and as many reproductive phases, as in the case of a fern or a jellyfish, which have multi-generational life cycles (Minelli and Fusco, 2010). Each different segment of a life cycle can provide variation for evolutionary change, and the articulation of life cycles in segments can itself vary and evolve, as the diversity of life cycles in the tree of life shows.

Secondly, there are biological processes other than development that can be source of anisotropic phenotypic variation, and which are the subject of several independent lines of investigation. These are standard mutation and recombination through the constrains imposed by standing genetic architecture (e.g., Hansen, 2006; Rajon and Plotkin, 2013), epigenetic effects (e.g., Richards et al., 2012; Mesoudi et al., 2013), different forms of biased transmission (e.g., Dalton and Carroll, 2013; Wilson et al., 2014), and not fully appreciated effects of several kind of stochastic events (Lenormand et al., 2009; Beatty, 2010; Vogt, 2015).

What is needed is thus a comprehensive "theory of variation," for which a natural place within a more inclusive theory of evolution already exists. Moving forward from the limited concept of "developmentally biased variation," evo-devo could act as a center of aggregation and organization for a "nebula" of approaches and sources of variation, to consolidate a more comprehensive research area, centered on a concept which we can tentatively dub *structured variation*.

In a well-known article, Lewontin (1970) indicated three fundamental "principles" for Darwinian evolution: (i) phenotypic variation, (ii) associated differences in fitness, and (iii) heritability, and the same three principles emerges from the most general equations describing evolutionary change (see Okasha, 2006). Several quantitative and qualitative aspects of variation with the potential of influencing evolutionary processes have been somehow overlooked, but the teaming up of different variational approaches to the study of evolution can effectively contribute to reappraising the fundamental role of variation in evolutionary theory.

Actively Searching for a Dialogue between Theory and Experiment

In explaining the several potentials of computational approaches to developmental patterning, Morelli et al. (2012) remarked that "the key to success [in the understanding of developmental processes] is an open dialogue between experimentalist and theorist." However, and these are my own words, empirical studies are too rarely theory-inspired or theory-oriented, and too many theoretical studies are self-supporting or cross-referential only within a set of similar theoretical works, in substantial disregard of empirical data, or at least leaving most empirical data unexploited. This may sound as an overstatement and may not correspond to a widely shared perception of the matter, but it can help seeking new ways of interaction, or enhancing the too limited communication channels existing to date.

On the side of research planning, empirical developmental studies should pay more attention to quantitative aspects and to the type and amount of variation that is associated with developmental processes. Beyond descriptive works, whose importance does not need to be defended here, more space should be devoted to hypothesis-driven experimental studies, aimed at solving theoretical questions. The more general the hypothesis, the better. At the same time, theoretical studies should try to keep more in contact with empirical observation. The level of description and model type should be matched to the best available data, and the model should produce explicit, testable predictions (Morelli et al., 2012).

On the side of research communication, every effort should be made to produce theoretical papers that are accessible to a wider and more diverse audience. In the age of on-line publication, there are certainly technical solutions to the problem of making a paper understandable at different levels of detail. This could be done not merely through the use of appendices (which not always are particularly effective), but through the implementation of genuine hypertexts, adopting for instance systems of in-text drop-down boxes whereby a reader can optionally reveal the desired details of the paper (Kane, 2012). Needless to say, some effort is required from experimentalists as well, which should devote time to cultivating their theoretical skills and to try to understand the key message of abstract argumentations.

Evo-devo is not a theory, and neither is it a new version of evolutionary theory. It is a field of studies, but more than that, it could be a direction of theoretical development for the theory of evolution. I have argued that pursuing this objective needs more theoretical work, in an effectively dialectic exchange with empirical studies. I think the time is ripe for a new, fertile interchange between experimental and theoretical works in biology, as fertile as it has been and still is for other scientific disciplines.

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