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Genes, embryos and evolution

Alessandro Minelli[*]

Abstract: When Mendel's work was rediscovered, around year 1900, and with the subsequent progress in genetics, one could expect that the science of heredity would eventually foster a fruitful dialogue between evolutionary biology and developmental biology, but history went otherwise until the emergence of evolutionary developmental biology, or *evo-devo*. Within evo-devo we can eventually explain both the fact that phenotypes very similar to existing ones and in all likelihood functional, nevertheless do not occur in nature and also that nature often generates hardly functional 'monsters'. Both classes of facts suggest that variation, irrespective of the selective value of the different phenotypes that are produced, has an intrinsic structure with both preferred and possibly prohibited alternatives. In the long history of evolutionary change of developmental change, even the *rules* of evolution have been evolving through time, and the same can be said of the *units*, and the *processes*, to which these rules apply and even of the categories themselves – categories like individual and species.

Keywords: evo-devo; evolutionary developmental biology; genotype; individual; origins; phenotype

Evolutionary biology and developmental biology are two disciplines that specifically address problems of change of form through time. Over most of the twentieth century, these disciplines have progressively diverged, to the point that even verbatim identical questions went to have a completely different meaning within the compass of the one or the other.

Take for example the question, why do birds have wings. A developmental biologist will address the question by looking at a bird's embryo, in order to identify patterns of gene expression, waves of cell proliferation, flows of migrating cells, patterns of differential growth of the individual

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bones, and the like. When addressing the same question (or, better, what seems to be the same question), an evolutionary biologist would instead look into the modifications the forelimb of bird ancestors underwent during the transition from a dinosaur-like to a bird-like organization, as well as into the adaptive significance of possessing a pair of functional wings.

Despite the obvious fact that evolution can affect all developmental stages, not just the adult, and the not less obvious fact that the structure of modern organisms is, in terms of ontogeny, the result of a developmental schedule more or less modified in respect to the developmental schedule of the organism's more or less remote ancestors[1], the two disciplines of evolutionary biology and developmental biology have been progressing until recently without sizeable reciprocal exchange.

The evolutionary paradigm has been basically applied to explaining two aspects of the natural world: the origin of biodiversity and the adaptation to environment. To study biodiversity means, basically, to understand speciation, that is, the processes by which one species eventually gives rise to two separate species, something about which Charles Darwin started indeed speculating, but also something that remained quite less central to his major work than the title, *The Origin of Species*, would actually suggest. In fact, most of this book was devoted instead to the other major facet of evolution, that is, adaptation. It is well in the context of adaptation, much more than in respect to speciation, that the Darwinian paradigm of variation and selection does actually apply.

In Darwin's time, developmental biology was mainly a study of descriptive embryology and the similarities often found between the early developmental stages of animals widely different in the adult stage was often used (at the time, and later) as an argument to infer relatedness between two lineages[2]. Towards the end of the nineteenth century, developmental biology was already becoming a mainly experimental science, targeted to unravel the mechanisms of development[3]. This was soon to produce major advances in life sciences indeed, but this was not what evolutionary bi-

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[1] Gavin R. de Beer, *Embryos and ancestors*, Clarendon Press, Oxford 1940; Stephen J. Gould, *Ontogeny and Phylogeny*, The Belknap Press of Harvard University Press, Cambridge (MA) 1977 (trad. it. a cura di Maria Turchetto, *Ontogenesi e filogenesi*, Mimesis, Milano-Udine 2013).

[2] Ernst Haeckel, *Generelle Morphologie der Organismen. Allgemeine Grundzüge der organischen Formen-Wissenschaft, mechanisch begründet durch die von Charles Darwin reformirte Descendenz-Theorie*, vol. 1: *Allgemeine Anatomie der Organismen*, Reimer, Berlin 1866.

[3] Wilhelm Roux, *Programm und Forschungsmethoden der Entwicklungsmechanik der Organismen*, Engelmann, Leipzig 1897.

ology needed most. It needed, instead, a science of heredity: in other words, genetics, something Mendel had already founded, in the meantime[4], but for a long time unnoticed by the vast majority of biologists.

When Mendel's work was eventually rediscovered, around year 1900[5], and with the subsequent progress in genetics, one could expect that the science of heredity would eventually foster a fruitful dialogue between evolutionary biology and developmental biology, but the history went otherwise.

There were indeed two aspects to the science of heredity: on the one side, transmission genetics, that is the study of the ways genes are passed from one generation to the other, subject to continuous reshuffling due to sexual processes and to the steady challenge by natural selection; on the other side, developmental genetics, that is the study of the ways gene are expressed throughout development and eventually become responsible for the phenotypes that are produced. It happened, however, that only one of these two sides of genetics – that is transmission genetics, in the specific form of population genetics – became eventually embodied within mainstream evolutionary biology, whereas developmental genetics failed until the last two decades of the twentieth century to contribute anything of notice to the progress of evolutionary biology. In the end, together with developmental genetics it was the whole of developmental biology that for decades remained virtually foreign to evolutionary biology, and vice versa.

Historians of science have already used abundant ink to explain this fact in terms of academic or personal agendas[6]. What really matters, however, is the fact that population genetics drove evolutionary biology towards population-level phenomena. It is indeed within one species (or, at most, within sets of cross-hybridizing, closely related species) that experiments in transmission genetics could be performed. Thus, methods were developed to estimate the degree of genetic similarity, or relatedness, between individuals or populations within a species, but nothing could be said, at the time, of the genetic differences responsible, for example, for

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[4] G. Mendel, *Versuche über Pflanzen-Hybriden*, "Verhandlungen des naturforschenden Vereines, Abhandlungen, Brünn", IV, 1866, pp. 3-47.

[5] Hugo de Vries, *Sur la loi de disjonction des hybrides*, "Comptes Rendus de l'Academie des Sciences (Paris)", CXXX, 1900, pp. 845-847; Carl Correns, *G. Mendel's Regel über das Verhalten der Nachkommenschaft der Rassenbastarde*, "Berichte der deutschen botanischen Gesellschaft", XVIII, 1900, pp. 158-168; Erich von Tschermak, *Über künstliche Kreuzung bei* Pisum sativum, ivi, XVIII, 1900, pp. 232-239.

[6] Ron Amundson, *The Changing Role of the Embryo in Evolutionary Thought: Roots of Evo-Devo*, Cambridge University Press, Cambridge 2005.

the different shape of the bill of a parrot, a heron and a duck. This was a very serious limitation, indeed. The most attractive questions in evolutionary biology are not about the origin or the adaptive value of subtle differences between local populations of a single species, or even the kind and extent of the differences between two closely related species recently split from a common ancestor, but rather questions about the origin of major novelties[7] such as the wings of insects and birds, or the lungs of terrestrial vertebrates, or the flowers of flowering plants. These questions are traditionally called 'macroevolutionary' to contrast them with the 'microevolutionary' scenarios within which revolve the questions evolutionary biology can address with the help of population genetics[8]. A key issue thus became, whether macroevolution is simply microevolution writ large; that is, whether the origin of novelties requires special mechanisms, or can be simply explained as the effect of prolonged microevolution[9]. In other terms, the question is, whether the neo-Darwinian scenario of natural selection acting on individual variation can always be regarded as an adequate explanation for everything in evolution[10].

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[7] Gerd B. Müller, *Developmental mechanisms at the origin of morphological novelty: a side-effect hypothesis*, in Matthew H. Nitecki (ed.), *Evolutionary Innovations*, University of Chicago Press, Chicago 1990, pp. 99-130; G.B. Müller, Günter P. Wagner, *Novelty in evolution: restructuring the concept*, "Annual Reviews of Ecology and Systematics", XXII, 1991, pp. 229-256; Id., Id., *Innovation*, in Brian K. Hall, Wendy M. Olson (eds.), *Keywords and Concepts in Evolutionary Developmental Biology*, Harvard University Press, Cambridge (MA) 2003, pp. 218-227; Gerard B. Müller, Stuart A. Newman, *The innovation triad: an EvoDevo agenda*, "Journal of Experimental Zoology (Molecular and Developmental Evolution)", CCCIV B, 2005, pp. 487-503; Alan C. Love, *Explaining evolutionary innovations and novelties: criteria of explanatory adequacy and epistemological prerequisites*, "Philosophy of Science", LXXV, 2008, pp. 874-886; Armin P. Moczek, *On the origins of novelty in development and evolution*, "Bioessays", XXX, 2008, pp. 432-447; Massimo Pigliucci, *What, if anything, is an evolutionary novelty?*, "Philosophy of Science", LXXV, 2008, pp. 887-898; Ingo Brigandt, Alan C. Love, *Evolutionary novelty and the evo-devo synthesis: field notes*, "Evolutionary Biology", XXXVII, 2010, pp. 93-99; Andreas Wagner, *The Origins of Evolutionary Innovations. A Theory of Transformative Change in Living Systems*, Oxford University Press, Oxford 2011; Tim Peterson, Gerard B. Müller, *What is evolutionary novelty? Process versus character based definitions*, "Journal of Experimental Zoology (Molecular and Developmental Evolution)", CCCXXB, 2013, pp. 345-350; Günter P. Wagner, *Homology, Genes, and Evolutionary Innovation*, Princeton University Press, Princeton (NJ) 2014.

[8] The term "microevolution" was introduced by Reginald Ruggles Gates, *The mutation theory*, "The American Naturalist", XLV, 1911, pp. 254-256; "macroevolution" by Jurii Philiptschenko, *Variabilität und Variation*, Borntraeger, Berlin 1927.

[9] Stephen J. Gould, *The Structure of Evolutionary Theory*, The Belknap Press of Harvard University Press Cambridge, Mass. and London 2002 (trad. it. a cura di Telmo Pievani, *La struttura della teoria dell'evoluzione*, Codice Edizioni, Torino 2003).

[10] Manfred D. Laubichler, *Evolutionary developmental biology offers a significant challenge to the Neo-Darwinian paradigm*, in Francisco J. Ayala, Robert Arp (eds.) *Contemporary Debates*

The neo-Darwinian formula ‘variation and selection’, however, was perhaps itself worth revisitation. Indeed, over the last couple of decades, attention has been called upon two classes of apparently odd, counterintuitive facts. On the one side, there are phenotypes very similar to existing ones and in all likelihood functional, which nevertheless do not occur in nature. On the other hand, nature continues to generate, under circumstances we can also produce (or re-produce) in the lab, a whole array of unlikely, hardly functional ‘monsters’. Both classes of facts suggest that we cannot take unlimited and readily available variation for granted, but also indicate that variation, irrespective of the selective value of the different phenotypes that are produced, has an intrinsic structure with both preferred and possibly prohibited alternatives. I will illustrate the case through three examples[11].

The first example if the neck of the giraffe. This animal has become a favourite example in evolutionary biology, since the time Lamarck[12] first used it to illustrate his concept, that bodily modifications produced by repeated use may become hereditary. In the present case, the shorter neck of old-time giraffes was frequently stretched in the effort to reach the branches of acacias, precious source of food during the dry season in the savannah. This effort would have produced a slight elongation of the neck, a change that the giraffes of the past would have transmitted to their offspring. Repeated over a long chain of generations, this change would produce, in the end, the long-neck giraffe of today. To Lamarck’s giraffe we can contrast a Darwinian giraffe, whose populations have always included individuals with quite short necks alongside other giraffes with longer necks. Most of the time, the individuals with longer neck would have enjoyed higher chances of surviving and transmitting to their offspring the longer neck they had inherited from their parents. A continuous selection in favour of longer necks would have progressively brought to an increase in the average neck length, up to the present condition.

Reasonable as it may look like, this Darwinian scenario is nevertheless incomplete from an important point of view. It tells us nothing about the

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in Philosophy of Biology, Wiley-Blackwell, New York 2010, pp. 199-212; Alessandro Minelli, *Evolutionary developmental biology does not offer a significant challenge to the neoDarwinian paradigm*, ivi, pp. 213-226; Massimo Pigliucci, Gerard B. Müller (eds.) *Evolution: the Extended Synthesis*, MIT Press, Cambridge (MA) 2010.

[11] Alessandro Minelli, *Forme del divenire*, Einaudi, Torino 2007 (Engl. transl. *Forms of Becoming*, Princeton University Press, Princeton (NJ) 2009).

[12] Jean Baptiste P.A. Lamarck, *Philosophie zoologique*, Dentu, Paris 1809.

way a giraffe can make a shorter or a longer neck or, at least, a shorter or longer neck skeleton.

In principle, we can think of two different ways to elongate a neck skeleton, that is, either by increasing the number of the cervical vertebrae supporting it, or by making these bones longer while keeping their number unchanged. Of course, a mixed strategy would also very likely work. The critical point is, that what is offered to natural selection are simply necks of different lengths, irrespective of the number and shape of the vertebrae supporting them. Selection does not care for the actual mechanism that provides variation. Variation, however, is constrained. In fact, there are seven cervical vertebrae in the neck of a giraffe, exactly the same number we find in the much shorter neck of a deer, a cat, a human being. To very marginal and minor exceptions, all mammals have seven cervical vertebrae, irrespective of the degree of elongation of the neck. Virtually no number variation is possible. Elongating the seven cervical vertebrae is, therefore, the only available way to make the giraffe's long neck.

Another interesting case of 'forbidden numbers' is provided by centipedes. More than 3,000 species are known in this group, most of which have either 15 or 21 pairs of legs; others have larger numbers, even so high as 191, but there is no adult centipede with an *even* number of leg pairs[13]. This is particularly puzzling in the cases where members of the same species can have different numbers of leg pairs, for example 39, 41, or 43, but no specimen is ever found with an intermediate even number such as 40 or 42. We can hardly imagine that this is the effect of selection. How could selection ever discriminate between centipedes with 100 pairs of legs and others with 101? To be sure, in this case too the 'missing' phenotypes are not missing because of their poor performances, but because they cannot be currently produced. However, if selection alone cannot provide an explanation, neither does genetics alone. Genetic variation is possibly responsible for the fact that some specimens have 39 pairs of legs, others have 41, still others 43, but to explain the lack of intermediate phenotypes we must rather look into the developmental mechanisms through which the existing phenotypic variation is produced.

In other instances, these mechanisms do not seem to have any difficulty producing maladaptive, unlikely phenotypes, thus showing that natural selection prolonged over millions of generations has not been able to

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[13] Alessandro Minelli, Stefano Bortoletto, *Myriapod metamerism and arthropod segmentation*, "Biological Journal of the Linnean Society", XXXIII, 1988, pp. 323-343.

eradicate these sources of ‘monsters’, such as four-winged fruit-flies, or fruit-flies with an extra pair of legs growing in the place of the antennae. Monsters, indeed, occur in nature, even in the absence of human action. But these monsters have nothing in common with fantasy-borne creatures like the winged dragon or the chimera. Real-world monsters are strictly lawful, to such an extent that a careful study of the rules by which their weirdness is channelled has provided, all along the twentieth century and up to our days, one of the most powerful approaches to understanding what we are used to call the normal, or standard, development of an animal species.

Monsters are lawful[14], in that they do not borrow body parts from other species, but only show excess, or defect, in expressing organs which, per se, would be easily recognizable as legitimate parts of a normal animal of the same species. The two legs growing on the head of some mutant fruit-flies, at a site where their normal kin have the usual pair of antennae, are indeed fruit-fly legs, as the two extra wings of the four-winged mutant fruit-flies are, again, nothing else than fruit-fly wings: more specifically, a very good copy of the other, normal pair of wings borne by the same fly. Nothing to be compared to a chimera with a goat’s head raising from the back of a lion’s body, whose tail is replaced by the anterior half of a snake. Next to species-specificity, the abnormal parts of a monster’s body do obey another set of rules, those constraining position. In a fruit-fly, an extra pair of legs can be found replacing another pair of body appendages, such as the antennae, but will never sprout out, for example, from the dorsal side of the abdomen. Similarly, only one, precise place is available for the two extra wings of the tiny four-winged monster, i.e. the place usually occupied by the halteres, another kind of appendages related to flight (and, indeed, regarded as derived from normal wings, a change that happened at the base of the lineage of the dipterous insects). The main message we can derive from the study of these monsters is, again, that a deep knowledge of development is required, if we want to know how animals can evolve. This is actually the intellectual background from which the science of *evo-devo*, or evolutionary developmental biology, is eventually emerged[15].

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[14] I. Geoffroy Saint-Hilaire, *Histoire générale et particulière des anomalies de l’organisation chez l’homme et les animaux ou traité de teratologie*, Baillière, Paris 1832-37.

[15] Rudolf A. Raff, Thomas C. Kaufman, *Embryos, Genes, and Evolution: The Developmental-Genetic Basis of Evolutionary Change*, Macmillan, New York (NY) 1983; Brian K. Hall, *Evolutionary Developmental Biology*, Chapman & Hall, London 1992; Wallace Arthur, *The emerging conceptual framework of evolutionary developmental biology*, “Nature”, CDXV, 2002, pp. 757-764;

Uniquely placed at the crossroad between two traditional disciplines such as developmental biology and evolutionary biology[16], both of them targeted to the study of change, evolutionary developmental biology is indeed taking shape as the *science of the change of change*, focussing on evolution as the outcome of modifications of developmental processes.

Critically important, in allowing a fresh dialogue between two disciplines that had proceed without exchange for an all too long time span, has been the explosive progress in developmental genetics over the last three decades. Unexpected to most, a rapidly increasing number of genes expressed during early developmental stages and directly involved in shaping an animal's bodily architecture were found to be the same in animals as different as a mouse and a worm. Same genes involved in marking the main body axes, that is, in distinguishing what is back and what is belly, what is front and what is rear[17]. Same genes involved in placing here or there the brain, the eyes, the heart. In front of this evidence, we can not look at the evolution of animal form with the same eyes as before. Rather than as a consequence of the arising of many new genes, the evolution of body architecture, including what is generally defined as the origin of the main evolutionary lineages, or phyla, is to be explained in terms of novel uses of the old genes, that is, in terms of changes in gene regulation or gene networking[18].

In the meantime, an unprecedented acceleration in the development of new analytical techniques has been revealing a wealth of information about the molecular nature of genes, also allowing something of which the older students of evolution could only dream, that is, the direct comparison of genes (and, more recently, of whole genomes) between distantly related organisms, at a scale of comparison enormously larger than the

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Gerard B. Müller, *Evo-devo as a discipline*, in Alessandro Minelli, Giuseppe Fusco (eds.) *Evolving Pathways. Key Themes in Evolutionary Developmental Biology*, Cambridge University Press, Cambridge 2008, pp. 5-30.

[16] Rasmus G. Winther, *Evo-devo as a trading zone*, in Alan C. Love (ed.), *Conceptual Change in Biology: Scientific and Philosophical Perspectives on Evolution and Development*, Springer, Dordrecht 2015, pp. 459-482.

[17] J[onathan] M.W. Slack, P[eter] W.H. Holland, C.F. Graham, *The zootype and the phylotypic stage*, "Nature", CCCLXI, 1993, pp. 490-492.

[18] Enrico Coen, *The Art of Genes: How Organisms Make Themselves*, Oxford University Press, Oxford 1999; Sean B. Carroll, *Evo-devo and an expanding evolutionary synthesis: a genetic theory of morphological evolution*, "Cell", CXXXIV, 2008, pp. 25-36; Sean B. Carroll, Jennifer K. Grenier, Scott D. Weatherbee, *From DNA to Diversity: Molecular Genetics and the Evolution of Animal Design*, first ed., Blackwell, Malden 2004 (trad. it. di Patrizia Malaspina, *Dal DNA alla diversità: evoluzione molecolare del progetto corporeo animale*, Zanichelli, Bologna 2004).

species-level horizons hitherto accessible through the traditional tools of population genetics.

At the very heart of these dramatic developments there was, anyway, the gene. No wonder that some of the architects of the burgeoning evolutionary developmental biology have been inclined to describe the new science as nothing more than the comparative aspects of developmental genetics[19]. Let's investigate the differences in gene networking and gene expression between different species or lineages, and we will have the key to the evolution of animal form. We know, however, that not everything is in the genes[20].

The most convincing example of complex patterns generated by reference to structural (morphological) templates rather than encoded in genes, is provided by a group of unicellulars, the ciliate protozoans. There are thousand of different species of ciliates, each with its specific and often elaborate pattern of cilia. These organelles, used by the ciliates in gathering food and also in locomotion, are often arranged in regularly spaced but not strictly equivalent rows. Several ciliates are large enough – in the order of one millimetre – to allow manipulations with reasonable simple tools. It is possible, for example, to gently insert a micromanipulation tool into the superficial layer of the cytoplasm, in such a way as to cut all the ciliary rows at mid-length, and then to rotate one cell half in respect to the other along the main cell axis, in such a way that the half-rows in one cell half loose conotinuity with the corresponding half-rows in the other[21]. This condition stimulates the growth of these half-rows, each of which will orderly add new elements into the opposite cell half, until the manipulated cell eventually possesses a duplicated number of ciliary rows. Nothing, in the meantime, happens at the level of genes. The experimental treatment only affect the cytoplasm; more specifically, its cortical layer.

What will happen when the manipulated cell will undergo division? Will it give rise to two daughter cells like itself, both provided with doubled ciliary rows? Or will the anomaly disappear, following the structural

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[19] Walter J. Gehring, *Master Control Genes in Development and Evolution. The Homeobox Story*, Yale University Press, New Haven-London 1998.

[20] H. Frederik Nijhout, *Metaphors and the role of genes in development*, "BioEssays", XII, 1990, pp. 441-446; Evelyn Fox Keller, *The century of the gene*, Harvard University Press, Cambridge (MA) 2000 (trad. it di Sylvie Coyaud, *Il secolo del gene*, Garzanti, Milano 2001); Massimo Pigliucci, *Genotype→phenotype mapping and the end of the 'genes as blueprint' metaphor*, "Philosophical Transactions of the Royal Society B", CCCLXV, 2010, pp. 557-566.

[21] Vance Tartar, *The Biology of* Stentor. Pergamon, Oxford 1961.

rearrangements that necessarily accompany cell division? Unexpectedly – at least if we assume that phenotype is strictly controlled by the genotype – the modified cell morphology is preserved and transmitted to the progeny for an indeterminate number of generations. In a sense, it has became hereditary, despite the fact that nothing happened at the level of the gene. To be honest, it must be said that this is possible, in ciliates, because of the peculiar mechanics of cell division in this group of unicellulars. Their complex ciliary architecture does not go lost when the cell divides, but each daughter cell inherits a part of the mother cell's originals ciliature, which acts as a template from which the whole parental pattern is rapidly restored. Something like the semi-conservative replication of a double-strand DNA molecule – except that, in the present case, the faithful replication of a complex form is accomplished without any involvement of the DNA.

For several reasons, in multicellulars like humans we can hardly expect to find a gene-independent morphogenesis comparable to what happens in ciliates. Nevertheless, there are plenty of examples, among animals and plants alike, of nontrivial morphological patterns, some of which are likely of great adaptive value, which are virtually inexpensive in terms of genetic information. For example, in the production of the intricate network of blood vessels in a vertebrate, genes are known to control aspects such as the identity of a given vessel – whether it becomes a vein or an artery. There are also genes causing a vessel to branch or, to the contrary, to anastomize with another vessel, but the actual detailed pattern is dictated by purely environmental cues and this explains the often conspicuous differences in the vessel pattern, not simply between individuals but also between the left and the right half of the body[22]. Again, genes have very little to do with generating the wonderful symmetry of a lily, or a coral polyp. It is rather in departing from symmetry that genes have a precise role, as in producing bilateral-symmetry flowers such as those of orchids or legumes, or the asymmetric shape and arrangement of our internal viscera[23].

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[22] Kenta Yashiro, Hidetaka Shiratori, Hiroshi Hamada, *Haemodynamics determined by a genetic programme govern asymmetric development of the aortic arch*, "Nature", CDL, 2007, pp. 285-288.

[23] Mariana Mondragón-Palomino, Günter Theißen, *MADS about the evolution of orchid flowers*, "Trends in Plant Sciences", XIII, 2008, pp. 51-59; Michael Levin, Amar S. Klar, Ann F. Ramsdell, *Introduction to provocative questions in left-right asymmetry*, "Philosophical Transactions of the Royal Society B", CCCLXXI, 2016, 20150399; A. Minelli, *Plant Evolutionary Developmental Biology*, Cambridge University Press, Cambridge 2018.

These few examples are probably sufficient to show how different are biological systems in respect to those key properties, such as the control of genes over the production of form, which are at the core of developmental biology and evolutionary biology alike. This diversity testifies to a long history of change, and to the fact that we cannot safely generalize to all organisms from what we see in any individual system, be it human or amoeba, fruit-fly or plant. Eventually, to understand life's unceasing history of change we need to pay equal attention to the history of the individual (its ontogenetic development) and to the history of the lineage to which it belongs (its evolution).

If we take our perspective broad enough, we will easily discover how fragile are the very concepts through which we are accustomed to describe both the development and the evolution of the living beings. Are we sure that the rules of the game have always been the same? Are we sure that we can always use, in analyzing life, those categories that seem to work so fine when applied to man and to the animals most similar to it? There is hardly anything of importance that escapes from change and this circumstance should recommend caution when extrapolating far away either in temporal or in phylogenetic terms. This will bring us, in the end, to wonder how confidently, in biology, we may ask questions about origins.

How safely can be extrapolate to events very deep in time the rules of the game we see at work in living matter today? Despite the difficulties raised by facts like the idiosyncratic distribution of segment numbers in centipedes, or the gene-independence of the morphogenesis of ciliary rows in ciliate protozoans, we must acknowledge that evolutionary biology has been very largely successful in explaining biodiversity and adaptation in what we can describe as neo-Mendelian and neo-Darwinian terms. In other words, by applying the Darwinian paradigm of evolution (basically, although not exclusively, selection on naturally occurring heritable variation) coupled with an increasingly precise understanding of the mechanisms of inheritance centred on Mendel's concept of gene, biology has shaped a powerful interpretative model within which a sheer diversity of biological phenomena can be effectively analyzed.

There is a problem, however, in that the confidence we have in the validity of this model is partly empirical rather than theoretical. Does its success in interpreting the phenomena of present day's life guarantee that the rules of the game were exactly the same in an earlier phase of life's history on Earth? The most critical point is perhaps about the nature and the degree of the relationships between genes and phenotypes. Since the early '90s, Stuart Newman and Gerd Müller have been developing an interesting argument against the tacitly assumed principle that the degree of genetic determination of phenotypes has not sensibly changed throughout the history of life[24].

The fact that genes are involved in seemingly simple processes such as producing tissue spheres and tubes, or subdividing a tissue rod into a regular series of segments does not mean that living tissue, per se, requires specific gene expression in order to perform those elementary morphogenetic processes. Spheres, tubes and segmented rods can be directly produced by generic (other than genetic) processes of which the physicochemical, visco-elastic properties of living matter are directly and specifically responsible. If so, the corresponding morphogenetic events which now undergo under the control of genes are, perhaps, sovradetermined[25].

To be sure, this does not mean that this genetic control is irrelevant. With the involvement of the expression of what are now true 'developmental genes', these spheres, tubes and segments are probably produced more consistently, that is, their genesis is probably protected from fluctuations in environmental conditions that could profoundly affect the regularity of their occurrence, and this may have in turn important consequences on the short- or long-term survival of an organism of which spheres, tubes and segments are temporary or definitive features. However, in Newman and Müller's scenario, evolution would not have proceed always as in present-day organisms, mainly by natural selection acting on phenotypic variation corresponding to their differences at genetic level, expressed throughout development. Rather, this modern kind of evolution has perhaps smoothly replaced, to an ever increasing extent, a pre-Mendelian evolution where the role of genes was secondary to what directly depended on the structural properties of living matter.

This vision of evolutionary rules changing through the aeons is attractive but, admittedly, it has not yet been articulated enough as to allow for adequate testing. However, to realize that the rules of the evolutionary game may have evolved themselves throughout the history of life, there is no need to flirt with such 'heterodox' scenarios. Commonly shared opinion among leading developmental geneticists is that the complex networks of inhibitory and inductive effects among genes and gene products that are nowadays involved in controlling morphogenesis in all animals

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[24] Stuart A. Newman, *The pre-Mendelian, pre-Darwinian world: Shifting relations between genetic and epigenetic mechanisms in early multicellular evolution*, "Journal of Biosciences", XXX, 2005, pp. 75-85.

[25] Gabor Forgacs, Stuart A. Newman, *Biological Physics of the Developing Embryo*, Cambridge University Press, Cambridge 2005.

but a few most primitive groups, like sponges, are themselves the product of evolution[26].

If the *rules* of evolution have been evolving through time, the same can be said of the *units*, and the *processes*, to which these rules apply.

Critically important, this statement is not intended here to apply to the individual instances of a given category of biological objects or phenomena, but to the categories themselves. This thought may have dramatic consequences for our views on living nature.

That a species will inevitably change through time and will perhaps eventually split into two separate species, is a notion at the heart of the Darwinian view of life. That an individual will change its form, its behaviour, its physiological performance throughout development, and will perhaps produce offspring similar to itself, but anyway distinct from it, is nothing but a truism in developmental biology. The change I am speaking of here is *not* this change at the level of the species or the individual, but a more pervasive change that questions the very existence of our cherished biological *categories*, the species and the individual.

It may well be true that most of the living world today is composed of individuals belonging to species, but this is not true of all of life. There are, indeed, organisms which do not belong to species other than by the fact that we call them by ‘scientific’ species names in the Linnaean tradition[27]. There are, also, organisms about which it would be arbitrary to say whether we are confronted with one individual or with two or a million individuals. We can also argue, that problems with applying these important biological categories, the individual and the species, would have been quite more frequent in respect to ancient forms of life. In other terms, those forms of biological organization to which we can sensibly apply the concept of individual, or the concept of species, are themselves products of evolution. Neither the individual nor the species are necessary categories of life; they are, instead, historically determined forms of organization that came into being, probably many times independently, along the history of life on Earth.

Sooner or later, the individual and the species proved to be stable or robust enough as to became entrenched as widely occurring levels of or-

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[26] Eric H. Davidson, *The Regulatory Genome: Gene Regulatory Networks in Development and Evolution*, Academic Press, Oxford 2006.

[27] Michael T. Ghiselin, *Species concepts, individuality, and objectivity*, “Biology and Philosophy”, II, 1987, pp. 127-143 Alessandro Minelli, *The ranks and the names of species and higher taxa, or, a dangerous inertia of the language of natural history*, in Michael T. Ghiselin, Alan E. Leviton (eds.) *Cultures and Institutions of Natural History. Essays in the History and Philosophy of Science*, California Academy of Sciences, San Francisco (CA) 2000, pp. 339-351.

ganization. Nothing, however, can guarantee their universality, neither protect them from the risk to be lost again, temporarily at least, to give rise to others forms of organization. The target of this paper being evolutionary developmental biology, rather than evolutionary biology, I will leave the problem of species aside[28], to devote instead a few thoughts to the fleeting nature of the individual (as category) and to the evolutionarily negotiable nature of what we would perhaps like to take as uniquely defined developmental events.

First, the individual. Physical integrity and genetic homogeneity are arguably two solid pillars of individuality. Apparently at least, there seems to be no difficulty applying these concepts to the living beings we encounter in our daily life: to our fellow humans, of course, but also to the other mammals, and birds, fish, and also butterflies and mosquitoes. On a second thought, however, doubts may creep in as soon as we are confronted with physically separate organisms which are nevertheless identical from a genetic point of view, as are monozygotic twins, or plants grown from cuttings obtained from the same parent plant. Physical distinctness, however, will generally emerge in these cases as a sufficient ground for acknowledging individuality to each of these genetic replicates. Other cases, however, are much trickier. The strawberry, for example[29]. Thin and virtually leafless stems, the runners, grow horizontally on the soil surface until, some centimetre distance from the mother plant, they develop a new vertically growing stem and, correspondingly, a new set of roots. A new strawberry plant is forming. Eventually, the runner will die out and the two plants will become physically separate (but they will remain genetically identical anyway). At this stage, to deny their individuality would be uselessly fastidious and obviously disputable; however, so long as they were connected by a fresh, living runner, were they already ‘full’ individuals in any definable sense? Their status, to be sure, was not that different from that of the body (or bodies?) of Siamese twins, painfully conjoined in a very odd condition that challenges our cherished categories not less than it troubles our feelings and thoughts[30].

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[28] Alessandro Minelli, *Taxonomy faces speciation: the origin of species or the fading out of the species?*, “Biodiversity Journal”, VI, 2015, pp. 123-138; Frank E. Zachos, *Species Concepts in Biology. Historical Development, Theoretical Foundations and Practical Relevance*, Springer International Publishing Switzerland, [place not stated] 2016.

[29] John L. Harper, James White, *The demography of plants*, “Annual Review of Ecology and Systematics”, V, 1974, 419-463.

[30] Bernabé Santelices, *How many kinds of individual are there?*, “Trends in Ecology & Evolution”, XIV, 1999, pp. 152-155; Jack Wilson, *Biological Individuality: The Identity and Persi-*

Next to the individual, even if perhaps not so critical for our worldview and the serenity of our judgement in the praxis, there is no shortage of developmental categories that on a close inspection emerge as the products of history rather than as universals. This is commonplace, indeed, when we study the developmental schedules of different animal species comparatively. For example, let's open a window onto the variegated world of arthropods, that is the insects and their allies.

A butterfly's life cycle may represent a convenient term of reference, with its sequence of stages from the egg to the adult, through a series of larval instars and the motionless pupa, during which many larval organs are literally demolished while those typical of the adult, like the wings and the reproductive organs, grow and differentiate into their final state. Within this long series of changes, two events would offer themselves as sound reference points around which to organize a comparison of the developmental schedule of different insect (or arthropod) species. One of these events is 'birth': actually, the event of hatching from the egg. The other event is the final moult to mature (adult) butterfly. However, things are far from clear-cut[31]. At the time of hatching, many arthropods are well equipped to start an active life immediately, but other species, when emerging from the split egg chorion, are still embryonic in their organisation, their appendages are nothing more than unarticulated bulges and a moult is required before the little animal can start moving around, eating, sensing and growing. Thus, while in the former case emerging from the egg largely corresponds to the transition from embryonic to post-embryonic condition, this is not true in the second case. Interestingly, even among mammals there are difficult cases in categorising stages and major developmental events.

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stence of Living Entities, Cambridge University Press, Cambridge 1999; Peter Godfrey-Smith, *Darwinian Populations and Natural Selection*, Oxford University Press, New York 2009; Thomas Pradeu, *The Limits of the Self: Immunology and Biological Identity*, Oxford University Press, Oxford 2012; Id., *Organisms or biological individuals? Combining physiological and evolutionary individuality*, "Biology and Philosophy", XXXI, 1016, pp. 797-817; Alessandro Minelli, *Individuals, hierarchies and the levels of selection – a chapter in Gould's evolutionary theory*, in Gian Antonio Danieli, Alessandro Minelli, Telmo Pievani (eds.) *Stephen J. Gould: The Scientific Legacy*. Springer, Milan 2013, pp. 73-83; Giuseppe Fusco, Alessandro Minelli, *Biologia della riproduzione*, Pearson Italia, Milano-Torino 2018 (Engl. transl., *The Biology of Reproduction*, Cambridge University Press, Cambridge 2019); Alessandro Minelli, *Biological individuality – a complex pattern of distributed uniqueness*, in Antonino Pennisi, Alessandra Falzone (eds.), *The Extended Theory of Cognitive Creativity*, Springer Nature Switzerland, Cham 2020, pp. 185-197.

[31] Alessandro Minelli, Carlo Brena, Gianluca Deflorian, Diego Maruzzo, Giuseppe Fusco, *From embryo to adult. Beyond the conventional periodization of arthropod development*, "Development Genes and Evolution", CCXVI, 2006, pp. 373-383.

Consider kangaroos and the other marsupials. At the time of parturition, baby kangaroos are extremely small and so poorly differentiated that many zoologists do not hesitate calling them larvae, rather than juveniles. Others will argue that they should be better called free embryos, or the like. Is there any solution to this terminological conundrum? Yes, perhaps: not a solution favouring the use of one of these terms over the others, however, but one acknowledging that all of them (embryo, larva and so on) refer to conditions subject to evolution and thus open to problems if we try to fix them within those defining traits that obviously work within the limited, and historically circumscribed, set of animals most closely related to man.

Another difficult although useful concept it 'adult', even if we limit our considerations – as I necessarily do here – to obvious biological (functional) aspects, without extending into those specifically human aspects of growing to adulthood that so dramatically impinge upon our social behaviour and responsibilities. Broad-scale comparisons across the animal kingdom will easily show how diverse can be the relationship between becoming adult, in the sense of achieving the definitive body shape, and reaching maturity, in the sense of becoming fully equipped for sexual reproduction.

In the vast majority of insects the beginning of the adult condition is very clearly marked by the last moult, which is generally accompanied by major and often dramatic changes in respect to the immediately previous stage, but this moult does not necessarily correspond to the achievement of sexual maturity. For example, a female mosquito will not be able to bring her eggs to maturity without taking, as adult, a couple of generous blood meals. On the other hand, a few members of the same insect order, the two-winged Diptera, can reproduce when still in a larval condition. These contrasts are examples of heterochrony, that is, of differences in the timing or rate of development of different body parts among different and even closely related species. In a sense, if we take the developmental schedule of one of the species under comparison as a point of reference, we can sensibly say that in the other species the different body parts are either younger of older.

Thus, 'age' emerges as another only apparently obvious concept, whose practical application can be marred with difficulties. In this respect, a most dramatic example is provided by a little parasitic crustacean, *Hemioniscus balani*. The first half of his post-embryonic life is a conventional growth punctuated by a few moults, until the animal reaches a first condition of sexual maturity. Interestingly, at this stage all *Hemioniscus* are male. What happens next is completely different for the anterior respectively the posterior half of the body. Only the latter, indeed, continues to moult and grow, eventually becoming a sexually mature female, following five additional moults. The anterior half, instead, remains literally 'frozen' in the size and shape it had developed at the time the animal was mature as male. There are thus reasons to say that the two halves of this animal will eventually have a different physiological age[32].

To be sure, the notion of age evolved, in our mind, as a descriptor to be used in respect to man, where it obviously works. It works also when applied, for example, to livestock. Similarly, in ordinary life people do not need to quibble about the relationship between adulthood and sexual maturity. Things are very different, however, as soon as we begin investigating nature in a comparative way, and extending the scope of our study to organisms increasingly different from man, from mammals, from vertebrates.

With its specific focus on the historical (evolutionary) modification of the patterns of developmental changes all organisms undergo throughout life, evolutionary developmental biology is uniquely confronted with a necessary revisitation of all these important concepts. Thus, it is becoming more and more evident how extensively these concepts need to be qualified and circumscribed in their application. To follow the old saying, that no rule is without exception is, arguably, a bad way to do science. To the contrary, exceptions to a rule should suggest that the relevant rules are others than those we had accepted at first.

The units, or modules[33], which are sensibly the seat of relevant processes, either in development or in evolution, do not necessarily coincide with the units we identify in terms of our traditional concepts like individual, larva, adult, age. There are many kinds of dynamics in nature, each one with its range of action. A tornado does not see the boundaries between town and countryside. Similarly, the fact that organs such as heart and eye are very well defined in anatomical and also functional terms does not mean that in development there should be specific ontogenetic modules called cardiogenesis or ophthalmogenesis[34], neither is there any certainty that the heart or the eye are really units of evolution.

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[32] Marie Goudeau, *Contribution à la biologie d'un crustacé parasite:* Hemioniscus balani *Buchholz, isopode épicaride. Nutrition, mues et croissance de la femelle et des embryons*, "Cahiers de Biologie Marine", XVIII, 1977, pp. 201-242.

[33] Gerhard Schlosser, GünterP. Wagner, *Modularity in Development and Evolution*, The University of Chicago Press, Chicago-London 2004.

[34] Alessandro Minelli, *Perspectives in Animal Phylogeny and Evolution*, Oxford University Press, Oxford 2009.

The possible consequences of this extensive revisitation of key concepts in biology, necessitated by a comparative perspective on change, developmental and evolutionary alike, may extend well beyond the technical province of scientific research. Specifically, it may affect our way to frame questions about origins.

The Origin of Species, the title of Charles Darwin's major work, seems apparently to guarantee a place (and, indeed, a central one) in evolutionary biology for questions about origins. But this would be a wrong conclusion. Biological species are defined in respect to the other species that live in the same segment of evolutionary history, not in respect to their ancestors (or their descendants, if any). In their mostly gradualist mood, evolutionary biologists do not allow, generally, for abrupt changes along the chain of generations[35]. Thus, *no species can change into another species*. In addition to going extinct, only the following are its possible fates: either to split into two separate species, or to continue evolving, steadily changing its character but still preserving a continuity somehow comparable to that an individual organism. Some evolutionary biologists and some philosophers of science claim, indeed, that a species is, ontologically, an individual, and there seem to be some merit to this view[36].

Problems with investigating the origins of evolving systems are mainly due to the pull of present. We move by categorizing the world in which we live by selecting items (be these particular species or particular forms of biological organization) in which we are interested, and we start moving back in time with the hope to discover eventually *the* critical event by which that species, or that form of biological organization, abruptly came into existence. This applies to ontogeny and well as to phylogeny. But in front of the continuity of life since time immemorial, and of the unceasing diverging and endless intertwining of the innumerable threads of biological organization, we cannot be too confident in extending the use of our categories beyond the more familiar, traditional scope at the service of which older generations of humans tentatively, but increasingly successfully, applied them for centuries.

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[35] Walter J. Bock, 2004, *Species: the concept, the category and taxon*, "Journal of Zoological Systematics and Evolutionary Research", XLII, 2004, pp. 178-190.

[36] Michael T. Ghiselin, *A radical solution to the species problem*, "Systematic Zoology", XXIII, 1974, pp. 536-544; David L. Hull, *Are species really individuals?*, "Systematic Zoology", XXV, 1976, pp. 174-191.

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