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Debate / Débat

How can we understand the construction of an organism?

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Abstract

Since a dozen years, biology is in a state of permanent technical and conceptual excitement. The pendulum is swinging back from the selectionist populationist biology of Darwin – the organism is a black box: viewed from the outside – to the mechanistic embryology of Aristotle – viewed from the inside of the organism – leading to a new interpretation of old concepts. This short text tries to get to the meaning of these events by putting them in historical and epistemological perspectives, through such concepts as teleology and differentiation, on the way describing several paradoxes: experimental results yield a detailed description of purposeless mechanical devices, explaining Nature, which, to us, appears purposeful. **To cite this article:** A. Weydert, *C. R. Biologies 327 (2004)*.

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Résumé

Depuis une dizaine d'années la biologie est bouleversée du point de vue technique et conceptuel. C'est le grand retour de l'embryologie explorée par des techniques modernes. Ce court texte essaie de placer dans une perspective historique et épistémologique ces bouleversements à l'exemple de deux concepts, la téléologie et la différenciation, en rappelant de vieux paradoxes et en proposant de nouvelles solutions. **Pour citer cet article :** A. Weydert, *C. R. Biologies 327 (2004)*.

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1. Introduction

In January 2001 a meeting organized in honour of Nicole Le Douarin (*The Embryo and the Time*) brought together Rudy Raff, Denis Duboule, the since deceased André Adoutte, and both Antonio Garcia

Bellido and Lewis Wolpert, who have defended over the last 30 years the concepts of compartment (and syntagmata) and of morphogenetic gradient to allow an understanding of the organism's logic of construction. The meeting was a marked triumph of the mechanistic teleology over the vitalism still detectable in Hans Spemann.

The question has become: how can we understand the construction of an organism? rather than: how is

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an organism constructed? The difference between both formulations is the introduction of the subject. Why? In biology, as long as one is dealing with nucleotide sequences, digestion by restriction enzymes, PCR, or even cell cultures and gene inactivation, reasoning is straightforward, linear, technical, mistakes can be done, but they may be detected quickly, they are material mistakes and an eventual consensus may soon be found to correct them. However, the interpretation and the meaning of the results of such experiments for embryology and evolution require concepts and reasoning integrating several different levels of complexity and missense, sophism, *petitio principii*, paradoxes can be easily smuggled in surreptitiously, i.e., one has to be careful concerning the reasoning methods: this is why embryology fascinates some and repels others.¹

Thus we are faced with two elements: the ‘object’ and the ‘understanding subject’. The separation subject–object in Europe goes back to the 6th century BC: the subject is excluded from the objective world and, secondly, the world can be understood. This made science possible [1]. Our understanding resources are the concepts fabricated by the activity of our brain and our brain has been constructed to ensure two macroscopic operations: survival and reproduction (predator, prey). Our brain is able to assess the distance, the speed, the weight, and the strength of a prey or a predator. The brain has not been constructed for resolving mathematical or quantum theory problems [2–4]. When we leave the domain our brain has been constructed for during evolution and within which the produced concepts are relevant, and we use these concepts and faculties (capacity of abstraction, induction, deduction generated by the ratiomorph apparatus of Rupert Riedl [5]), i.e., the underlying neural circuitry, and try to apply them outside their relevant domain, then we run the risk of surprises, antinomies, paradoxes.² Understanding the living organism means that we have to understand ourselves, the subject, im-

plicated in the object, is self-referenced. The concepts required to understand the living organism are paradoxical. How can they be resolved?

2. The paradoxes and their solutions

Outside biology there are paradoxes in philosophy, e.g. the synthetic a priori judgments and the antinomies of pure reason (causality,³ time, space⁴). In 1941, Konrad Lorenz, holding Kant’s chair in Königsberg, gave the following interpretation of synthetic a priori judgments: a priori for the individual, a posteriori for the species, as a result of the learning process by the ratiomorph apparatus that has integrated them [5]; this had already been recognized by Ludwig Boltzmann [6–8]. Then there are the paradoxes in logic, e.g. “Cretans are never anything but liars, dangerous animals, all greed and laziness, this is a true statement”, a Cretan says, analysed by Bertrand Russell and Kurt Gödel.

In biology, trying to understand the construction of an organism means trying to understand two paradoxes: the paradox of teleology (finalism in Latin), i.e., a cause is acting from the future to the present, or the effect precedes the cause going back to Antiquity, and the paradox of differentiation, i.e., the part is as large as the whole, as recently formulated (19th century).

² Within a discipline, e.g., physics, the position and the velocity have a different meaning in Newton’s mechanics than in quantum mechanics (W. Heisenberg).

³ Causality has been considered as due to laziness of mind (Hume), when we see that A is followed every time by B, we say that A is the cause of B, this allows to anticipate, then through I. Pavlov (conditioned reflexes) and D. Hebb (synaptic enhancement for neurone assemblies) we come to the current conception of neurophysiology and to the metabolic and morphological modifications of the synapses as a basis for causality and learning. The elementary particle is described as a function of probability-and therefore a possibility to exist-and since the nature of microscopic physics’ laws is statistical, a permanent causal chain cannot be linked to an individual particle.

⁴ The theory of relativity implies a reassessment of the concepts of space, time and from the point of view of ontogeny, the construction of space is investigated by neurobiology.

¹ I knock out a gene (level: DNA, homologous recombination) and obtain a phenotype (level: protein–protein interaction), how can I explain the phenotype? Not by answering the question: How was the operation done? By homologous recombination (level DNA), but by explaining the role of the protein in the signal transduction pathways, in the chromatin, in a gradient, in epigenesis, answering the question: Why this phenotype? How does the protein work (level: protein)?

2.1. The paradox of teleology (finalism)

Aristotle was preceded by the Presocratics and one of them, Anaximander (600 BC), explains the origin of man through evaporation of humidity by the sun and says that man at the beginning was like a fish [9], and by the Hippocratean physicians who proposed, in order to understand the development of human embryo, to compare it with a chicken embryo and therefore make two hens sit on twenty eggs and to open every day an egg starting from the second day [10].

Aristotle is the heir of the Presocratics, the pupil of Plato, the tutor of Alexander the Great. He is a philosopher and a biologist, particularly an embryologist, biology covers one third of his *opus*. In embryology he proposes epigenesis in order to explain development and becoming (the greatest crux in Greek philosophy) and not preformation: first the heart forms (*punctum saliens*) then development proceeds sequentially like the plaiting of Orpheus' net: mesh by mesh. Current interpretation would equal a mesh to a compartment of Antonio Garcia-Bellido. The notions and the terms of potential, potentiality are still in use to day, Latin terms translated from the Greek (δύναμις). Aristotle may have used the concepts of embryology in philosophy [11].

He was struck by the permanence, the similarity of organisms, what we now would call genetics, heredity, species, *Bauplan*: man generates man, a horse never generates a donkey, hence the idea of a mechanism copying an internal form. Children are like parents. Aristotle discusses Empedokles's solution for reproduction: the union of the form of the father and that of the mother gives the form of the child ($1 + 1 = 1$). How can this be explained? Empedokles proposes that the semen of each parent carries a complementary half: two complementary half forms give a complete form ($1/2 + 1/2 = 1$). He compares this to a σύμβολον, i.e., an object broken into two parts, and each person has one complementary half, which allows both persons to recognize each other [12]. It is difficult not to think of the two halves of the chromosomal set, one paternal half and one maternal half, or of the two complementary DNA strands of Watson and Crick. Empedokles also introduced analogy (hairs, leaves, feathers, scales); he is the father

of natural selection and Darwin considered himself as his successor [9,13–15].

According to Aristotle, an explanation requires four causes: the material cause (bronze, wood), the formal cause (the form of the statue, of the table), the efficient cause (the hammer, the saw) and the final cause (the goal of the sculptor, of the carpenter). Final cause is a free translation of the Greek expression: τὸ ὄν ἐνεκα, i.e., what for, the reason why, thus Aristotle gives an operational definition rather than a substantial one. We, however, are speaking of teleology (from τέλος, goal, a term sometimes used by Aristotle) or finalism (end, completion). Democritus turns to chance in order to explain. Aristotle says that the organisms are too complicated to be explained by chance, a goal directed principle is required, i.e., the teleological principle. What does teleological causality correspond to? It corresponds to the development of a grain of wheat towards its goal, its purpose, its completion, its τέλος, i.e., adult wheat, pup to dog, egg to bird, as if there were something inside the organism: vital force? Soul? *Bildungstrieb*? *Gestaltungskraft*? *Lebenskraft*? Entelechia? *Élan vital*? guiding it to its goal, to its end.⁵ Consequently, internal teleology is a concept derived from everyday experience. Aristotle's teleology may be interpreted as a provisional, heuristic, global concept before being resolved into a mechanism due to the efficient causes of the internal constraints, i.e., the signal transduction machinery [16]. These internal constraints are responsible for the fact that the organism during evolution does not adopt any possible form, but only some discrete forms, hence the metaphors of Galton's polyhedron [17], Waddington's creode (chreode, necessary path [18]) and all along the 2500 years this opposition can be found: chance/directiveness, i.e., accidental/purposeful or order/disorder, from Democritus/Aristotle to Mendel, Morgan/Driesch, Spemann via Lemery/Winslow [19] or in terms of disciplines: biochemistry, molecular biology/embryology, physiology. Only recently the concepts of compartment, of gradient and the signal transduction pathways merged together.

⁵ Herrmann Helmholtz eliminated the 'Lebenskraft' by demonstrating the impossibility of a 'perpetuum mobile' in measuring body heat (*Über die Erhaltung der Kraft*, 1847).

Karl Ernst von Baer proposed to resolve the paradox of teleology in his answer to Darwin (*Über Darwin's Lehre*, 1876) by distinguishing: subjective, external teleology, the goal is determined by an external agent (sculptor, architect, God, external principle of development) and objective, internal teleology e.g. the development of an organism based on an internal principle of development [20]. The organism has been compared to a machine, a clock, a computer. Here is what Jacob von Uexküll says [21]: “The mechanism of any machine, such as a clock, is always designed in a centripetal manner, i.e., all the parts of the clock – hands, springs, wheels – must first be completed before being assembled on a common support. On the contrary, the growth of an animal, like the triton, is always organized in a centrifugal manner starting from the germ; first a gastrula, then new buds form, which develop differentiated organs. In both cases, there is a *Bauplan*: in the case of the watch the *Bauplan* controls a centripetal process, in the case of the triton, a centrifugal process. Following the plan the parts are assembled under entirely opposite principles.” There appears to be a sort of linguistic confusion here, if there were two different terms for designating the two meanings of teleology, the issue might be clarified and sophisms more easily prevented.

Another paralogism may *con permesso* be quoted here: I think therefore I am, which may be transcribed into: I am thinking, therefore I am existing. In the first part “to be” is used as a copula and therefore in a predicative way, in the second part “to be” means to exist, to live. The conclusion is illegitimate, since the existence of an entity cannot be inferred from a predicative property (*ambulo ergo sum*, P. Gassendi in [22]). The same word (to be) has two different meanings. Languages with two different words for these two different meanings avoid this paralogism [4, 23,24].

In the Middle Ages, the Catholic Church used Aristotle as well as Plato for its own benefit, since they are teleologists, and their manuscripts have been saved and celebrated – not to the same extent in the case of Democritus – among others in order to demonstrate the existence of God.

Immanuel Kant (1724–1804) has written, besides the *Critique of Pure Reason* and the *Critique of Practical Reason*, the *Critique of the Power of Judgment*

(1790, *Kritik der Urteilskraft* [25]) of which the second half is devoted to the critique of the power of teleological judgment [26]. One of the best-known definitions is that the living organism is means and end (*Mittel und Zweck*) i.e., the organism is altogether cause and effect (a loop, a feedback system).

From Kant, a powerful stream of teleomechanism flowed in Germany through J.F. Blumenbach, C.F. Kielmeyer, T. Döllinger, K.E. von Baer, T.L.W. Biscohoff, C. Bergmann, R. Leuckart, R. Virchow, J. Müller, J. Liebig and many others up to the *Entwicklungsmechanik* of Wilhelm Roux (of French Huguenot descent), Hans Driesch and Hans Spemann. The climax of this trend is the discovery of the Spemann-Mangold (née Pröscholdt) organizer in 1924. The morphogenetic field of the dorsal lip, dictating to other territories their fate, triggered a frantic race in order to isolate the Inducing Substance [27,28], which cannot be isolated, since it is a network of signal transduction pathways. The signal transduction pathways may also underlie Waddington's creode (chreode, necessary path). The morphogenetic field, an essential notion in embryology, will disappear faced with the triumph of the gene and molecular biology only to be rediscovered in the form of compartment and its syntagmata in 1973 [2,29].

2.2. The paradox of differentiation

At the end of the 19th century, Hans Driesch isolated one of the two blastomeres of a two-cell-stage sea urchin embryo and he obtained the development of a complete, half-sized individual, concluding that each cell is totipotent, although only part of the embryo [30]. By this experience carried out at the age of 25, Hans Driesch contradicted Wilhelm Roux, who killed one blastomere of the two cell stage frog embryo with a hot needle obtaining a hemi embryo, and he contradicted August Weismann (1892), who proposed a progressive splitting up of the hereditary substance during development by unequal mitoses parcelling out specific determinants, in order to explain differentiation [31]. Therefore, the part is as large as the whole. Paul Foulquié in his schoolbook *Metaphysics* [32] for secondary schools ending with a theodicy of nearly a hundred pages, used this paradox as an argument in favour of vitalism, hence of a catholic, apostolic and Roman God. Hans Driesch, who wrote a book

on the construction of the organism [33,34] was so disturbed by the paradox of differentiation that he gave up biology and henceforth dedicated himself to philosophy and vitalism and therefore became discredited [35]. He died in 1941 without knowing the solution.

The solution came from Jacques Monod, André Lwoff and François Jacob and the lactose operon a few years later: all the information is in every cell, but not all the genes are expressed in every cell. Jacques Monod who stayed together with Boris Ephrussi in Thomas Hunt Morgan's laboratory, came back to France and, after some experiments carried out with Boris Ephrussi on *Drosophila*, investigated the growth curves of *E. coli*, especially the diauxic phenomenon and so turned to the adaptive enzymes, a Lamarckian phenomenon that was to be solved by Lamarckian fellow-countrymen. As early as 1947, he perceived the close links between genetics and cell differentiation [36] and in 1953 the adaptive enzymes were renamed inducible enzymes, thus pulled out from the Darwinian domain of evolution and connected to the domain of embryology, where induction plays a fundamental role [37–40]. The article was signed by Melvin Cohn, Jacques Monod, M.R. Pollock, Sol Spiegelman and R.Y. Stanier [41]. The operon model proposes that the substrates (e.g., lactose) induce the enzymes (e.g., β -galactosidase) required for their catabolism and, hence, the enzymes are regulated by the metabolites of the biochemical pathways they control (a loop, a feedback system). The environment can modify the phenotype. The operon includes several genes involved in the same biochemical pathway, and in this way is somehow like the syntagma. In 1961, Jacques Monod and François Jacob wrote the conclusions of the Cold Spring Harbor Symposia of Quantitative Biology and the very first word of the title is: Teleonomic [42] – Jacques Monod did not use the term of teleology, which can be considered as equivalent – and according to this article, “the transitions of state in such systems should very closely mimic true transmissible alterations of the genetic material itself”. This phenomenon as well as functional modifications of the heat-shock molecules [43] shed a new light on the heredity of acquired characters. So far for the two concepts of teleology and differentiation.

3. Modern times

After Buffon and Lamarck, the classifier of invertebrates and founder of transformism, i.e., evolution of species [44], after Étienne Geoffroy Saint-Hilaire and the baron Cuvier and their academic debate on the unity of plan – still on the agenda –, which had a tremendous impact on Goethe, Balzac and on the whole of Europe [45–48], came natural selection in order to explain transformism (1859, [49]). The natural selection of Darwin–Wallace is a selection of variants by external constraints: survives who survives. Nothing is said on the internal constraints, i.e., on the mechanisms of how to construct an organism and therefore on the production of variants. That is exactly the problem Aristotle attacked and biology attacks today. It is an irony of history that the French society, who stubbornly resisted triumphant Darwinism would now appear to accept it (a chair of Historical Biology and Evolutionism was founded at the ‘Collège de France’ recently), at the moment when biology leaves it to its own intricacies and turns resolutely to the analysis of the mechanisms of how to construct an organism (ontogenesis). Hans Driesch and Oskar Hertwig both rejected Darwin's principle of natural selection: “It is the curiosity of our century” [31].

Present times (1924–1994) have been marked by the divorce between the genetics of Thomas Hunt Morgan and the embryology of Hans Spemann and the union of both is very recent going back to the time when it became possible to explain the phenomenon of Spemann in terms of gene interaction and signal transduction pathways [50,51]. The gene, a central concept in genetics, had competed out the morphogenetic field, a central concept in embryology, so much that the latter vanished from the scene in spite of the attempts of several authors to link genetics to embryology, notably Richard Goldschmidt (hopeful monsters [52, 53]), Conrad Hal Waddington (studying wing mutants in *Drosophila* [54]), Boris Ephrussi (investigating eye pigment in *Drosophila* with George Beadle, 1935–1937) and above all Ed Lewis, from whom all started off again [55]. During this period of 70 years biology did what could be done technically (reductionist biology) ignoring the embryological problems (holist biology): isolate the DNA [56], resolve the structure of double helix [57], isolate the mRNA, elucidate the genetic code, work out cloning [58–60]. Molecular bi-

ology ruled over biology and henceforth everything was thought to be understood, whereas actually the problems were ahead: how does a linear filament of genomic DNA develop into an organism? Precisely DNA is not linear, it is not just naked DNA in nothing, proteins are wrapped around it in a cell, with a nucleus, a cytoplasm and signal transduction pathways, all of it being organized according to a very precise architecture indispensable for the egg to develop into an organism. Knowledge of the nucleotidic sequence alone does not help very much, as long as you ignore the transformation code, i.e., how the signalling machinery mediates physiology of the cell and embryology of the organism. *E. coli* is one organism in one cell, the mouse is one organism of 10^{13} cells functioning in an integrated manner and the range of problems to be solved is of a different scale. What are the rules organizing such a huge amount of cells leading always to the same architecture? In order to resolve this problem Thomas Hunt Morgan, a former embryologist [61] having published with Hans Driesch, turned to the fly to discover the secrets of embryological mechanisms, which the fly consented to reveal at last through the investigation of the *bithorax* mutants (1978 [55, 62]), of the wing (the compartment, 1973 [29]) and of mutants from a saturation mutagenesis (1980, [63]). Within a few years the foundations of molecular and cellular embryology were laid down. Discussing a paper of Ed Lewis in 1951 Ernst Hadorn pointed out that the *bithorax* and the *bithoraxoid* mutants affect the anterior half and the posterior half of the adult segment [64]. In 1973 Antonio Garcia-Bellido et al. published a paper of two and a half pages describing the compartment, a concept derived from the experimental analysis of cell growth of the *Drosophila* wing imaginal disc [29]. He develops since this concept: there are two compartments, one anterior, one posterior, separated by a boundary not crossed by cells (lineage restriction). These compartments are organized by selector genes and realizator genes linked by syntagmata (i.e., coordinated sets of signal transduction pathways) which may be reminiscent of Étienne Geoffroy Saint-Hilaire's principle of the connections of the parts. The long sought link between genes and morphogenesis was at last found, regulating the coordinated behaviour of the cells and the expressed genes. These results prompted a reaction from Francis Crick and Peter Lawrence in 1975: "For the first time there

is a real prospect of understanding the logic behind gene deployment in pattern formation" [65]. The logic of construction of the organism would appear to be modular. Since this Ariadne's thread has been found, the compartment has become the paradigm, i.e., the example for explaining the development of an organism, and one looks for it everywhere, especially in vertebrates in the form of compartment (rhombomere, neuromere, [66]), in the form of an inducing boundary of the Spemann–Mangold type (isthmus in the brain), or in the form of homologies of syntagmata, i.e., of signal transduction pathways: the mirror image duplications of chick wing generated by grafting the zone of polarizing activity (or by SHH bead implantation) are homologous to the mirror image duplications of the *Drosophila* wing by mutation from which the gene can be isolated. The interpretation of homology is dependent on the level considered (organ, genes, signal transduction pathways). Following up this line the similarity of resegmentation in invertebrates (parasegments, segments in *Drosophila* recently described) and in vertebrates (somites, vertebrae described in the 19th century) is striking. The morphogenetic field that had vanished is coming back with an increased strength in the form of the compartment and its signal transduction pathways, hence the all-important role of these pathways and therefore of the cytoplasm (embryology) compared to the nucleus (genetics).

How far can the syntagmata be traced back? To the Precambrian? How did they appear? Lewis Wolpert says that the cell is more complex than the organism: "Once you have the cell, it is all the way down." Coming years will be dedicated to deciphering signalling pathways and networks, the combination of which might be useful in defining a semiotype that would define an organism and therefore a species. This would appear to be the true criterion to be used in order to construct phylogenetic trees. The union of genetics and embryology paves the way for a rational and functional investigation unthinkable only ten years ago, including palaeontology, inducing an institutional reorganisation of laboratory practices: the same signal transduction pathway is explored in *Drosophila*, mouse, chicken, zebrafish and *C. elegans* side by side. For the moment, the interpretation of the experiments is usually on the level of gene interaction and not yet on the level of signal transduction pathways: this will be the work of this century. With the help of the con-

cepts of compartment, of gradient and of positional information [67,68], of molecular clock linked to segmentation (with René Thom's interpretation in the framework of the catastrophe theory, 1972 [69], taken up by E.C. Zeeman and Jonathan Cooke, 1998 [70], and demonstrated by Isabelle Palmeirim and Olivier Pourquié [71–73]), of cell lineages [74] and of the Hox gene work [75], the mechanism of construction of an organism considered as a teleological system is now being cracked [76–79]. Remaining problems are regeneration (stem cells), brain and self-consciousness [80] above all we may tackle morphogenesis in a different way [2,69].

Does the universe correspond to a pre-established harmony, to an order, to a rational world, i.e., to a living organism with a beginning and an end and therefore with an internal teleology [81]? The answer is unknown, but as we say in French: “les théories passent, la grenouille reste”.

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