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A Symmetrical Approach to Causality in Biology

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Résumé : La description purement génétique de l'embryogenèse a récemment été mise en question. Un intérêt toujours plus ample est accordé aux effets des contraintes mécaniques. Afin de comprendre si ces travaux produisent une authentique intégration de niveaux, cet article propose l'analyse d'une de ces recherches d'un point de vue transcendantal. C'est-à-dire qu'on se posera la question du processus constitutif par lequel on décrit un objet biologique. Cette analyse révèle un processus d'objectivation caractéristique du déterminisme génétique qui ne peut pas représenter une intégration de niveaux. Cela nous conduira à introduire le concept de symétrie épistémologique qui se réfère à une façon équilibrée d'accéder à l'objet biologique. Enfin, on proposera un modèle de symétrie épistémologique explicitement dérivé du concept kantien d'organisme.

Abstract: The purely genetic description of embryogenesis has recently been challenged. Some papers then pay special attention to the causal effects of mechanical constraints. In order to understand if they produce a genuine integration of levels, this paper will analyze one of these researches from a transcendental point of view. That means, we will consider the constitutive process through which a biological object is described. This analysis reveals an objectivation process characteristic of the genetic determinism that cannot represent a genuine integration. That will lead us to introduce a concept of epistemological symmetry that refers to a balanced way of accessing the organism. Finally, we will suggest a model of epistemological symmetry that explicitly comes from the Kantian concept of organism.

Introduction

In this paper we will examine some problems that arise from a standard, deterministic, method of objectivation in our understanding of embryogenesis. Then, we will suggest an alternative procedure of objectivation. In the first section of this paper, entitled “The molecular version of embryogenesis”, we will analyze the purely genetic description of embryogenesis, trying to bring out the non-neutral epistemological framework that underpins it. In fact, this description comes from the idea that a collection of specific developmental genes entirely controls the developmental process of living systems [Nüsslein-Volhard 1997], [Lewis 1997], [Wieschaus 1997]. This theoretical framework has recently been challenged [Neumann-Held & Rehmann-Sutter 2006]. In particular, it makes it difficult to explain the interactions between different levels of organization. Many research papers are now interested in a class of examples, in which extra-genetic factors seem to have a causal role in development. In a reductive account, such as the purely molecular one, the genetic level is established as the primary and fundamental level of organization. Its explanatory power explains why it is given a priority in many accounts of the complex process of embryogenesis. Accordingly, it has to be causally closed, or at least causally sufficient. That means, it has to encapsulate all the conditions of interactions that allow embryogenesis. As a matter of fact, if the genetic level is considered as primary, this forces one to describe other levels as emergent out of it [Bedau 2003]. Then according to him, a causal action going from an emergent level to a basic level gives rise to an interpretation problem. The primary level is taken to be the efficient condition of emergent levels, that are supposed to come later. Thus, it becomes difficult to understand how an emergent level could affect a level that is supposed to underpin it. This apparently produces a causal circularity insofar as the condition seems to be conditioned by its own effect. Such seemingly paradoxical connection between downward causation and causal circularity, in fact, derives from the ontological interpretation of organizational levels. The causal circularity keeps on looking like a sort of contradiction as far as one level of organization preserves its ontological priority. Accordingly, one can easily figure out that this difficulty will be defused in a philosophical framework that challenges the ontological view of organizational levels.

In the field of embryogenesis, some recent research papers [Montell 2008], [Desprat, Supatto, Pouille *et al.* 2008], [Lecuit & Le Goff 2007], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Farge 2009], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010] pay special attention to the causal effects of mechanical constraints of tissues on the genetic level. This kind of research explicitly introduces the requirement of a new theoretical perspective that would be able to capture the complexity of living systems. That is to say a theory, in which the genetic level loses its primary causal role, making room for integration between levels of organization [Farge 2009]. In

section 2, entitled “The role of mechanical regulation and the hypothesis of mechanosensitive gene”, we will analyze one of these researches—those of the group named *Mechanics and Genetics of Embryonic and Tumoral Development* led by Emmanuel Farge at the Marie Curie Institute in Paris—in order to understand if they indeed manage to allow for an integration of levels in the framework of their interpretation. This kind of result belongs with some other recent researches [Montell 2008], [Desprat, Supatto, Pouille *et al.* 2008], [Lecuit & Le Goff 2007], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Farge 2009], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010] aimed at understanding the impact of mechanical constraints of tissues on the genetic level during the development of the embryo. As we will explain, these results especially show that some mechanical pressures that are produced on the tissues by morphogenetic transformations have a causal role on the genetic expression of the embryo [Pouille & Farge 2008], [Pouille, Ahmadi, Brunet *et al.* 2009]. However, in order to produce an adequate interpretation of level integration, it is insufficient to give a description of embryogenesis in which effects of the context are just added. The main problem consists in considering and explaining in a theoretical framework the mutual interactions between levels [Brenner, Noble, Sejnowski *et al.* 2001], [Noble 2010]. In the research analyzed here extra-genetic levels are recognized as responsible for the regular formation of an organism as well as the genetic one. Even so, as we will show later, the theoretical framework remains implicitly grounded on the idea that the molecular base, especially DNA, has a causal priority. This hybrid approach does not produce a real integration of levels of organization. On the contrary, all instances of integration are reduced to mere additional facts. Furthermore, the problem of *downward causation* connected to causal circularity is not overcome as far as one level of organization preserves its ontological and explanatory priority [Kim 1999], [Bitbol 2012]. This paper specifically relies on these results obtained by biologists because of their strong relevance for the aforesaid philosophical questions. Indeed they have the merit of establishing a causal role of an extra-genetic level on the genetic expression. Nevertheless, their effort to interpret the role of mechanical meets with the theoretical difficulties that have been pointed out above.

In order to understand what is the starting point that allows to build a genuine integration of levels, this paper will develop a reflection from a transcendental point of view in a Kantian sense. In section 3, entitled “The constitution of objectivity”, we will briefly explain what objectivation means. This approach arises from the conviction that thinking and intervening is not a neutral a way of access to a set of pre-given objects. On the contrary, the intellectual and experimental instruments of inquiry are *constitutive* of the biological object. They belong to the wider class of processes of constituting objectivity [Bitbol, Kerszberg & Petitot 2009]. This remark will provide us with some appropriate theoretical tools for analyzing the interpretation of

[Farge 2009], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010]. In particular, we will introduce the distinction between a description by intrinsic properties, and a relational account. In section 4, entitled “Developmental genes and mechanosensitive genes”, we will analyze, by our new tools, the objectivation process of developmental genes. A crucial point to notice is that developmental genes have actually been discovered using the *differential method* of experimental science. As we will show, the differential method is associated with a certain view of the nature of objects which is very close to what we called a *description by intrinsic properties*. This analysis will allow us to look at the hypothesis of mechanosensitive genes from the same perspective. In fact, it will be shown that the interpretation of [Farge 2009], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010] is grounded on the same kind of objectivation process, like the one which is characteristic of genetic determinism. In section 5, entitled “The functional specificity”, this process will be made more explicit by using the concept of functional specificity. We will show that the description of the genetic level is made by way of causal properties [Mumford & Anjum 2011], [Mumford 1998], [Von Wright 1974], recognized as functional specificities. Unfortunately, this kind of description cannot represent an integration of levels. It completely ignores a crucial aspect of objectivation which is the substitution of *description by relations for description by intrinsic properties* [Cassirer 2004].

In section 6, entitled “Access to biological phenomena using an epistemological symmetry”, we will introduce a concept of epistemological symmetry, in order to open up a relational perspective of integration. Epistemological symmetry, as we will explain, means a balanced way of accessing the biological object that does not place its genetic level (ontologically and theoretically) before any other level of organization. This new scheme has to be explicitly built on the notion of relation, in order to allow the construction of a theoretical framework for the integration of levels of organization. Finally, this constructive principle will be derived from the Kantian concept of a living system [Kant 2000], in section 7, entitled “A model of epistemological symmetry for biology: the Kantian notion of living”. By using these new tools we will re-examine the interpretation of [Farge 2009], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010] from a theoretical standpoint, in order to provide an alternative interpretation of levels of organization.

The aim of this paper is to raise a way of access to the living by reflecting explicitly on the process by which a biological object is constituted. This is useful in order to modulate the starting point of any construction of models. That means that this paper does not directly introduce an interpretation of the role of mechanical constraints in embryogenesis. Rather, it has the ambition to go upstream, to the very roots of the elaboration of knowledge, and propose an

adequate framework of interpretation for any relational account of integration. This proposed framework is the principle of epistemological symmetry.

1 The molecular version of embryogenesis

The description of living systems always depends on a larger world view and is conditioned by philosophical presuppositions [Gagliasso 2001]. The molecular version of embryogenesis also depends on non-neutral epistemological assumptions. Among many other such assumptions, the notions of program and genetic code are especially relevant because they largely influenced the beginning of molecular biology [Longo 2009], [Longo & Tendero 2007]. In fact, according to a classical molecular interpretation, embryogenesis is described as a process closely controlled by the expression of specific genes called developmental genes. The theory of developmental genes entails that genes are not just involved in the embryogenesis process; they regulate it in a specific way [Nüsslein-Volhard 1997], [Lewis 1997], [Wieschaus 1997]. This ascribes a primary and causal role to the genetic level. Any successive stage of development of embryos is produced by the expression of specific genes. Such a language refers to the idea that a construction program exists in developmental genes present in the oocyte [Farge 2009].

This kind of description is remarkably akin to the theory of preformation, modernized in the fashionable term of *coding*. Indeed, the genetic level here allegedly contains the complete information that allows the entire process of embryogenesis. This approach is grounded on a particularly dominant metaphor in classical molecular biology: the idea that DNA is an instruction program for the organism [Farge 2009], [Keller 2000], [Kupiec & Sonigo 2000], [Paldi 2009], [Pichot 1999], as though it were a virtual copy of phenotype. Such a language refers to the idea that a construction program exists in developmental genes inside the oocyte [Farge 2009].

Now, in recent years, and especially since the complete determination of chemical base pair sequence of human DNA from a physical and functional standpoint [Paldi 2009], the purely genetic conception has been challenged. The hard version of genetic determinism, entailed in classical molecular biology, is insufficient to account for the complexity of living systems. This conception seems to be increasingly corrected through new approaches that include non-genetic mechanisms for explaining changes of phenotype. Accordingly, research in embryogenesis has shown that some elements other than genes are causally involved during the development of the embryo. This means that they are not simply involved in a certain stage of embryogenesis. They play a specific role supposed to regulate the process.

In short, biology is transforming its object into a systematically integrated network. This requires new methods, both material and theoretical. It is

interesting to examine this transition from an epistemological point of view, in order to understand how the integration of the many levels involved in embryogenesis can be achieved.

2 The role of mechanical regulation and the hypothesis of mechanosensitive gene

In this section, we will analyze the biological research mentioned above and especially its fundamental proposition : the hypothesis of mechanosensitive genes. That will allow us to understand what kind of objectivation is used at the level of interpretation implied by this hypothesis.

Gastrulation is an embryonic process that consists in morphogenetic movements. These movements allow the positioning of the germ layer. The researches taken into account here have shown that this kind of movements produce mechanical pressures that have a feedback effect on the biochemical level. This means that the morphogenetic movement impacts genetic expression, and somehow regulates it. This point is very interesting because in any deterministic account, genetic expression is supposed to be sufficient to regulate the morphogenetic movements. In other terms, it is supposed to encapsulate all the conditions of interactions that allow morphogenetic movements. This kind of research show that such framework is no longer acceptable. A double direction of regulation, bottom up and top down, must therefore be taken into account and properly interpreted. We will now try to understand more specifically the special work of [Farge 2009], [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Fernandez-Sanchez, Serman, Ahmadi *et al.* 2010]. Then, we will make the interpretation of their results more explicit, in order to show that, even though this research shows the necessity of a new framework of thought, it only makes a few preliminary steps towards it.

The process of gastrulation in drosophila embryos starts with two morphogenetic movements: the invagination of mesoderm tissue, followed by germ-band extension. It has been discovered that this mechanical event, activated on the first phase of gastrulation, also becomes a sort of signal that regulates the subsequent post-translational events inducing a specific genetic expression. The mechanical signals trigger the concentration of Myo II (motor protein) in the apical part of the cells. Because of that concentration, cells are compressed and trigger the invagination of mesoderm. In the drosophila embryo, the genetic network involved in mesodermal invagination is activated by the transcription factor Dorsal (maternal factor). Dorsal moves from the nucleus, starting the invagination process and stimulating the expression of Twist (hereafter *twi*) and Snail (hereafter *sna*) genes. Both factors are involved in the genetic control of cell shape movements that cause the compression necessary

for mesoderm invagination. The embryos with a mutation in *twi* do not exhibit the second movement. That happens because the protein Fog, necessary for a stable distribution of Myo II toward the apical part of the cells, is not secreted. The embryos with a mutation in *sna*, also involved in Fog expression, do not exhibit both morphogenetic movements. Accordingly, Snail and Fog seem to be together necessary for triggering the second compression movement. In order to test the hypothesis according to which the distribution of Myo II depends on a mechanical cue, a local deformation was produced in the embryos with a homozygous mutation in *sna* by means of a micro-manipulated needle. The deformation was exerted on the mesodermal tissue exactly two or three minutes after the end of ventral cellularization, which corresponds to the beginning of the first compression movement in the wild-type embryo. Embryos with mutation in *sna*, as previously explained, do not manifest the normal mechanical pressure associated with the first morphogenetic compression phase. The local deformation rescues the mesodermal invagination in 67% of the cases.

The process described above throws light upon the dependence of the Fog signal as well as the redistribution of Myo II and cell compression toward the apical part of the embryo on a mechanical cue. Clearly, the role of mechanical cue is necessary for the correct formation of organs. During gastrulation, the morphogenetic deformation is precisely what induces the successive expression of genes involved in regulation of post-translational phases. In the course of embryogenesis, the constant changes of shape in the embryo frequently create new mechanical compressions that are involved in genetic activation. The hypothesis of mechanosensitive gene is introduced in order to interpret this phenomenon of feedback. Mechanosensitive genes are precisely those genes whose expression is modulated by a mechanical compression on tissues [Pouille, Ahmadi, Brunet *et al.* 2009], [Pouille & Farge 2008], [Farge 2009]. According to this interpretation, such genes are able to interpret morphogenetic deformations as signals. That allows them to understand which stage of its development the embryo has reached, and, in fact, they are activated immediately after the mechanical pressure. This kind of mechanism, a sort of translation from mechanical signal to biochemical signal, is called mechanotransduction. In this way, it seems legitimate to say, in the language of the authors, that mechanical cue constantly reprograms the genetic development during embryogenesis [Farge 2009]. In other words, on one hand there is the DNA, that codes for morphogenesis. On the other hand, there are mechanical deformations of tissue that are interpreted, as the authors say, by DNA as signals of the various developmental stages of the embryo.

This is clearly an attempt to describe embryogenesis by coupling the genetic level with its tissular context through the mechanical issue. Nevertheless, the theoretical framework does not change. The hypothesis remains grounded on a causal priority of the genetic level because even the role of mechanical

deformation is explained by invoking, once again, its possible molecular basis. In fact, the hypothesis ascribes to genes the property of being receptive to mechanical pressures in a specific way. This is in order to explain a specific genetic expression occurring after a morphogenetic movement. Apparently, the problem of circular causality does not arise in this context. Nevertheless, as a matter of fact, the problem is just diverted. The causal role of the action that occurs from tissues to the genetic level is just put aside. In such a way, the feedback causality is reduced to a specific sensitivity of genes.

The effort to connect both the mechanical and the biochemical aspects, in order to account for mutual interactions between levels, falls into a theoretical difficulty. The problem arises in the process of objectivation used to identify and describe the biological object. We introduce now, in a general way, what constitution of objectivity means, in order to render this difficulty more explicit.

3 The constitution of objectivity

The notion of constituting objectivity explicitly comes from Kant's theory of knowledge. This notion arises from the conviction that the objects of science are not already given out there. The objects have to be elaborated out of the phenomena that are perceived by the subject, by means of a categorical framework arising from the understanding of this very same subject [Bitbol 1998, 2000, 2010], [Bitbol, Kerszberg & Petitot 2009]. In other terms, any scientific object is *constituted*, and its configuration depends on the conceptual instruments used to understand it [Bailly & Longo 2006]. More precisely, constituting objectivity means unifying the flow of sensory perceptions, by extracting from it stable regularities and structures that are invariant with respect to a class of transformations [Bitbol 2000, 188]. It is particularly important to insist here on what is typical for this process, namely its relational aspect. As we have just suggested, scientific objects do not already exist in nature, but are constructed by applying concepts to a variety of representations. If this is the case, it is incorrect to consider phenomenal invariants as intrinsic properties of objects, since it is by the location of these very invariants that the scientific object is constructed [Cassirer 2004, 197]. Moreover, a description in terms of intrinsic properties of scientific objects implies a strong ontological commitment: believing in a rigid correspondence between objectivity and reality. This implies a level of realism which is difficult to defend in sciences, especially in quantum physics [Bitbol 1997, 1998]. In fact, it is by finding stable relations between representations that one configures regularities and invariants. Therefore, scientific objects should be described in terms of relations, not of intrinsic properties [Cassirer 2004, 112]. Cassirer explains this relational conceptualization in a particularly clear manner:

We do not isolate any abstract part whatever from the manifold before us, but we create for its members a definite relation by thinking of them as bound together by an inclusive law. [Cassirer 2004, 20]

It is important to notice that the scientific object so constituted, or conceptualized, is entirely free from ontological characteristics, such as having internal and permanent properties. In this context, the relevance of the scientific object is finally defined by notions of order and position rather than by intrinsic features. That means that the object is determined by functional relations throughout [Cassirer 2004].

The principal consequences of the Kantian point of view have been drawn. Now we are ready to analyze the process of constituting objectivity in a molecular version of embryogenesis. That will clarify the reasons why the hypothesis of mechanosensitive genes cannot produce an integration of levels, despite its effort to go beyond a purely genetic vision of embryogenesis.

4 Developmental genes and mechanosensitive genes

From the point of view of genetic determinism, a developmental gene is specific if its activation is directly related to one or several functions necessary for another stage of embryogenesis. From this perspective, it is claimed that certain genes are specific to certain embryogenic functions if the latter are altered after a mutation produced in a DNA segment [Nüsslein-Volhard 1997], [Lewis 1997], [Wieschaus 1997]. Developmental genes have actually been discovered using this method, which is usually called the *differential method*. Now, it is possible to stand back and look at the epistemic process by which the object *developmental gene* is constructed. In this way, it becomes clear that the differential method is associated to a certain view of the nature of objects which is very close to what we called a description by intrinsic properties. Actually, the biological object developmental gene, is defined by way of reducing it to its causal properties. In the case of molecular biology, causal properties correspond to functional specificities. After a mutation of a DNA segment, a change in phenotype such as, say, a lack of morphogenetic movements with respect to the normal formation of the embryo, is observed. These movements are specific because they have a precise role in the global embryogenesis process. For example, after the mutation of a certain set of genes in drosophila embryos, a mutation leg has been observed. Instead of animal feet, a pair of antenna grows. The latter set of genes (that are hox genes) has then been called antennapedia complex ANT-C [Kaufman, Seeger, Olsen *et al.* 1990], [Lewis, Wakimoto, Denell *et al.* 1980]. The specificity of the variation in phenotype is considered as the proper invariant to extract from this observation. This

specificity has been isolated from the entire process by the implicit conceptual act of choice of a reproducible feature. In such a way, the functional specificity is turned into an intrinsic property. As soon as this kind of conceptual act is made explicit, something appears about the epistemological nature of biological levels. We notice that the invariant of *specificity* is extracted from the phenotypic level, while it becomes a property of the genetic level. This happens because the phenotypic level is considered as a process that is continuous in space-time. By contrast, the genetic level is considered as a collection of discrete objects. Intuitively, an intrinsic property cannot be easily attributed to a continuous process such as a movement, but it needs rather a discrete object. This is why the specific functional property is transferred to the genetic level. It is this transfer that generates the constitution of a biological object: the developmental gene. In other terms, the functional specificity of an event is isolated. That makes it discrete and crystallizes a certain number of intrinsic properties that are all linked to its functional specificity. This conceptual act produces the illusion of ontological existence of an objective level that is not described as a level of organization, but as a set of real objects: genes.

We have shown the epistemological process by which developmental genes are constituted. Now it is possible to better discern some theoretical problems. First of all, the standard descriptions of the biological object tend to hide their relational constitution, and to rely on ontological discretization. In other terms, one does not recognize that the object is constituted by the extraction of relational invariant regularities between representations. Instead, one features it in a substantial manner by attributing it intrinsic properties. This description of embryogenesis, although leading to metaphysical realism, does not immediately meet certain technical problems, as long as no one wants to account for interactions between various levels of organization having a feedback effect at the genetic level.

Now, it must be noticed that the hypothesis of mechanosensitive genes is constructed from the same type of objectivation process as the one which leads to identifying developmental genes. True, here the direction of the differential method is opposite because the alteration is produced at the tissular level instead of the molecular level [Farge 2009]. Nevertheless, in order to account for the modulation of genetic expression by morphogenetic movements, the property of mechanosensitivity is attributed to a well-defined set of genes. Causal properties are once again transferred to the genetic level, and the causal role of the mechanical pressure remains theoretically uncharted.

5 The functional specificity

The perspective that brought about the hypothesis of mechanosensitive genes is grounded on the attribution of a functional specificity to the genetic level.

According to the differential method, a functional specificity is recognized by way of certain characteristics. A visible change is required. The changing factor has to be localized. Once localized, the change has to be predictable [Nüsslein-Volhard 1997]. As documented above, the sensitivity of these developmental genes clearly has a key role in the formation of organs because, when it is inhibited, post-translational movements do not occur. This is indeed a visible change. The change factor can be localized in the relevant genetic expression, because, if this is inhibited, the effect is lost. Once reproduced, the change is a predictable effect. These characteristics allowed one to state that developmental mechanosensitive genes are specific biological objects. These objects were individualized by their reduction to a functional specificity, and then turned into an intrinsic property: mechanosensitivity. But now one must ask what these mechanical pressures are, and what their role is.

The post-translational process preceding good formation of organs does not depend, at this stage of embryogenesis, only on the fact that certain genes are mechanosensitive. Mechanical pressures generated by morphogenetic movements also carry a certain form of specificity. These movements have a functional role because post-translational movements depend on them. Their inhibition has a visible effect: the absence of the predicted genetic expression. The change factor can easily be localized at the precise point where the pressure is realized (or inhibited) and at a precise moment during the embryo's development. This effect can be reproduced and predicted. In spite of this, it seems difficult to consider morphogenetic movements (and the consequential pressures) as specific biological objects because it is impossible to make them discrete. The problem also lies in the fact that, as documented above, a different status is ascribed to these two phenomena. On one hand, the genetic level is considered as a set of biological objects. On the other hand, there is a mechanical context having rather the characteristics of a process. But then, using specificity as a tool of objectivation, there is no reason to identify objects on one side and not on the other side, since both levels involve specificity.

Relating genotypes to phenotypes by the criterion of specificity, which underpins the concept of developmental gene, is quite difficult. In fact, functional specificity becomes a causal property and this fact produced an illusion of priority of level. This illusion interferes with a description of a living system as an integrated network of levels of organization. Nevertheless, even though it is correct to speak about specificity at the genetic level, it must be kept in mind that any other level has a form of specificity.

In order to clarify this point, an analogy with the notion of information in molecular biology can be given. In a classical description of embryogenesis, the notion of digital information is a criterion that allows prioritizing the genetic level in a causal sense. That is because the genome is supposed to contain the complete information of the developmental process. Nonetheless, every measure that allows to speak about information at the genetic level can actually

be found in the egg cell too. The egg cell must contain more information than the genome. This makes the notion of information an inadequate criterion for attributing priority to a given level [Noble 2006, 2008, 2011]. The same happens with the criterion of specificity which raises another concern. When the functional specificity becomes a causal property, this produces not only an illusion of priority of the genetic level, but it also provides discretization of continuous processes into collections of distinct objects.

In the hypotheses of mechanosensitive genes the *sensitivity* to mechanical pressure is presented as an intrinsic property of some developmental genes. Once again, a functional specificity is turned into a causal property in order to maintain the completeness of the genetic level. As shown above, specificity lies in other levels of organization as well, in this case the tissular context. Therefore, the criterion of functional specificity used as a narrow objectifying tool actually does not afford an integration of levels. On the contrary, it maintains a theoretical and arbitrary priority of the genetic level. This priority is founded on the fact that genes supposedly contain all causal intrinsic properties. Nevertheless, causal intrinsic properties come from an implicit conceptual act of choice of invariants (functional specificities) that have been isolated from the entire process. In a nutshell, the concept of specificity used in genetic determinism is ambiguous because it is founded on the hypothesis of the priority of the genetic level, that is actually imposed by it.

6 Access to biological phenomena using an epistemological symmetry

As shown above, the method of locating a biological object through its intrinsic properties raises a set of interconnected problems. First of all, this method is derived from the concept of functional specificity that is ambiguous because it imposes its own condition of possibility (the priority of the genetic level), and grounds it. This involves a metaphysical commitment to an ontological priority of a certain level: the genetic level. In addition, by using this kind of conceptual method in order to localize a biological object, it is impossible to account for any causal role of another level of organization, in this case the tissular level. This is why the hypothesis of mechanosensitive genes, based on this kind of process of objectivation, actually denies any theoretical causal role other than the role of genes. All these difficulties are linked to a more general confusion that arises from considering causality as a property [Mumford & Anjum 2011], [Mumford 1998], [Von Wright 1974] existing inside the biological object, and not as a possible relation between levels of organization. This leads to legitimate the assumption of causal completeness of the genetic level, and to ascribe thereby a sort of ontological priority to it, whereas it is precisely because of this confusion that the genetic level keeps its causal priority.

In order to overcome these difficulties, one must construct descriptions of living systems as integrated networks of levels of organization. Accordingly, it can be useful to find a mode of access to phenomena that does *not* consider a level as being ontologically privileged with respect to any other. This balanced mode of access can be called *epistemologically symmetrical*. It allows us to look at embryogenesis, and more generally at living systems, from a more neutral perspective. A perspective that does not impose directions of dependence to levels of organization. Most importantly, a perspective where levels of organization, understood as levels of dynamic relations, do not depend on a privileged level. A level made of quantifiable and localizable discrete objects. In doing so, a theoretical equivalence of value can be established between levels of organization. It is only from this symmetry that we can then determine a biological object by the relations of order and of position that constitute it. This corresponds to the Cassirerian substitution of a description by relation for a description by intrinsic properties [Cassirer 2004].

7 A model of epistemological symmetry for biology: the Kantian notion of living

According to Kant, "... a thing exists as a natural end *if it is cause and effect of itself*" [Kant 2000, 243]. A living organism perfectly fits this condition for three reasons.

1. The living organism is cause and effect of itself, because it preserves itself as a species by generating another organism of the same species: the cause of maintaining the species is then this species itself, which is its own effect.
2. The living organism grows, but it is not a growth by mechanical laws; rather it is a process involving self-production. Each organism is then cause of itself because it develops, but it is also its own effect because it develops by using a substance that is its own product.
3. Finally, the conservation of an organism depends on the conservation of its parts, which depends in turn on the conservation of the whole. Parts are functional in regard to the whole, and the whole has parts.
[Kant 2000, 242–243]

As soon as the logical structure of the teleological judgment has been extracted, it appears as a remarkable model of an *epistemological symmetry* of access to living phenomena. Indeed, it is possible to find in teleological judgment a relevant tool for constituting objectivity that is both balanced and specific to the living object. Teleological judgment is an epistemic process requiring access to the object through its unity (this object being cause and effect of itself), before giving a discrete description of its parts. This means

that an identifiable property is not merely a characteristic of a part of an organism. Instead, any part of the organism considered as a local object only arises from relational properties. These relational properties are generated continuously from the global functioning of the system organism which is cause and effect of itself (in so far as it is self-generative). This approach allows one to rebuild a mode of access to the living from the very relations of order and position that constitute it. Therefore, this approach allows one to substitute a description by relation to a description by intrinsic properties.

It is now possible to come back to the case of mechanosensitivity examined above. If we use the theoretical instruments of Kant's *Critique of judgment*, it seems legitimate to access embryogenesis directly by its unity. One then considers a global process of mutual constraints, where no signal communication is assumed and interpreted by intrinsic properties. Rather, the process becomes a relation of self-constitution that makes it possible to talk about levels without granting privilege to any one of them. Indeed, in this case, levels are not pre-given but define themselves by displaying discrete, local and partial effects in the continuous process of embryogenesis. In particular, it is possible to recognize the genetic level only by the effect it has on the tissular level and morphogenetic movements. In other words, by way of this epistemological symmetry it is possible to individualize organization levels without compromising their reciprocity. This is so because this instrument of access takes into account the practical procedures that have been used as part of the process of objectivation. In this way, we understand that the alleged flux of causation from the biochemical level to morphogenetic movements arises from the fact that we act experimentally in this direction. This being granted, a reciprocal action is also possible, and that is proved by the kind of research analyzed above. Such fundamental results derive from the fact that we do not need pre-existing properties regulating other properties in the strongest sense (e.g., when the regulator is considered as primary and cannot therefore be regulated in turn by its emergent level). On the contrary, we make explicit that we are constructing a set of characteristics that allow us to interpret the possibility of interaction between levels. Developmental genes have been brought out by acting on a certain level of organization. Mechanosensitive genes have been discovered in the same way, but by acting on another level of organization. Interpreting these findings by the usual pictures of intrinsic properties forces one to reduce all these properties to the biochemical level, even if the specificity, as shown above, arises from the tissular level. By assuming epistemological symmetry, we no longer need to posit intrinsic properties and we interpret the double regulation as a totally legitimate possibility depending on our twofold way of access.

As it was shown above, the theoretical framework of genetic determinism in embryogenesis implies that the genetic level has a causal priority over the organism. Of course, it comes up against several circularity problems as soon

as feedback from emergent levels occurs. In the hypothesis of mechanosensitive genes, the problem was overcome by attributing the property of *sensitivity* to the relevant developmental genes. That fitted with prior causality at the genetic level without contradiction. The genetic expression, in fact, was considered as caused by the property to react to morphogenetic movements and not by mechanical pressures. Nevertheless, this way of approaching the regulation of embryogenesis remains incomplete in regard to the role of organismic context and, moreover, it comes against the problem of specificity and description by intrinsic properties. By contrast, tackling the regulation of embryogenesis by the method of relational objectivation allows one to overcome causal circularity, because the notion of level is interpreted in a non-dualistic framework. Indeed, levels no longer exhibit a substantial distinction nor a prior distinction between properties and structures. Instead, properties and structures are identifiable as an outcome of the access to the biological object as an interacting system. Causality is no longer taken as a property; it becomes a constitutive relation of the level under consideration and the problem of circularity is thereby overcome. In other words, teleological judgment implies a top-down and bottom-up dependency. That means, the level considered as an effect can also be characterized as a cause of what it is the effect of. This is possible by shifting the constitutive relation. If we take the second part of Kant's definition: "Each organism is then cause of itself because it develops, but is also its own effect because it develops through a substance that is its own product", we realize that it is exactly this aspect that is missing in molecular interpretation of embryogenesis. Genetic level being described as a set of real discrete objects full of causal property, it can never become an effect. In fact, it cannot have causes, and this imposes an epistemological asymmetry unsuitable to the relational circularities in life phenomena.

Conclusion

The requirement to overcome genetic determinism in embryogenesis produced a considerable amount of research papers. The aim of this paper is to include non-purely genetic determinants in the process of the embryo's development. This paper closely studied research about the effect of tissular mechanical constraints on the genetic control of development. This was done in order to understand how an integration of levels was produced. The problem was set in a transcendental framework, asking questions about the nature of the objectivation process implied in the concept of genetic determinism. A critical observation has enlightened difficulties linked to a description of the living object by intrinsic properties (notably a metaphysical commitment of existence of a privileged level), as well as an ambiguity of the functional specificity criterion, and a problem of causal circularity. In such a way it was shown that alternative hypotheses remain often linked to deep presuppositions about the

way an object should be construed. That happens, despite the fact they try to overcome the causal hegemony attributed to the genetic level by genetic determinism. In this paper, we suggested accessing the organism by way of an epistemologically symmetrical approach of biological objects, an approach based on a theoretical equality of epistemological value of any level of organization. We then found a model of this epistemological symmetry in Kant's notion of the living. This allowed us to identify a mode of constitution of objectivity in which the definition of levels, as well as of causal directions, is subordinate to the practical procedures that have been used. The problem of causal circularity was thus approached in a completely non-dualistic way, without any ontological commitment in favour of the priority of a level of organization on another. By introducing the principle of *epistemological symmetry*, this paper proposed a new interpretation of relational accounts of inter-level integration.

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