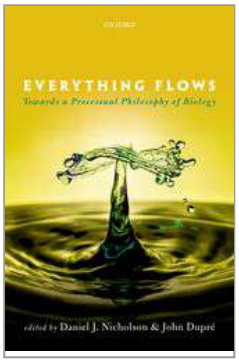


Everything Flows: Towards a Processual Philosophy of Biology
Daniel J. Nicholson and John Dupré

Print publication date: 2018
Print ISBN-13: 9780198779636
Published to Oxford Scholarship Online: July 2018
DOI: 10.1093/oso/9780198779636.001.0001

Waddington’s Processual Epigenetics and the Debate over Cryptic Variability

Flavia Fabris

DOI:10.1093/oso/9780198779636.003.0012

Abstract and Keywords

This chapter reappraises Waddington’s processual theory of epigenetics and examines its implications for contemporary evolutionary biology. It focuses in particular on the ontological difference between two conflicting assumptions that have been conflated in the recent debate over the nature of cryptic variability: a substance view that is consistent with the modern synthesis and construes variability as a preexisting pool of random genetic variation; and a processual view, which derives from Waddington’s conception of developmental canalization and understands variability as an epigenetic process. The chapter also discusses how these opposing interpretations fare in their capacity to explain the genetic assimilation of acquired characters.

Keywords: canalization, cryptic variability, dynamic systems theory, epigenetics, genetic assimilation of acquired characters, homeorhesis, plasticity, process ontology, robustness, Waddington C. H

1. Introduction

From the perspective of the emerging framework of the extended evolutionary synthesis (EES), developmental plasticity appears as an epigenetic process rather than as the predetermined outcome of a program encoded in the genome (Pigliucci and Muller 2010). The EES further suggests that organisms play a central role in evolution, though it rejects the causal primacy of natural selection. It argues that organisms act in conjunction with selection in shaping their particular developmental trajectories. Development is thus viewed as an act of ‘co-construction’ involving the organism and its environment, which

together constitute an integrated causal system (see Oyama et al. 2001; Gilbert and Epel 2015).[1]

Back in the 1940s, Conrad Hal Waddington anticipated various features of the EES framework in his pioneering research into the nature of developmental plasticity. Waddington believed that the study of the phenotype should include an account of how the developing organism is able to change in response to genetic and environmental perturbations. This represented a major point of disagreement with the architects of the modern synthesis. While the latter explained the phenotype straightforwardly as a genotypic product, Waddington suggested that phenotypes are temporally extended epigenetic *trajectories*, as opposed to being entities that occur ‘one gene at a time’ or ‘one trait at a time’ (Wilkins 2008). Moreover, he hypothesized that development plays a directive role in evolution (Waddington 1942).

(p.247) According to Waddington, the process of development takes places concurrently at different levels of organization. At the cellular level, for instance, it takes the form of a complex exchange of information between the nucleus and the cytoplasm that contributes to the construction of the phenotype. This act of construction is directed, in the sense that it constrains the trajectory of development through a series of successive bifurcations that lead to a stable phenotypic state.[2] For Waddington, the stability of the phenotype reflects a dynamic balance between robustness and plasticity. That is to say, the phenotype exhibits a tendency to resist internal and external perturbations, thereby buffering the effects of the variability responsible for evolutionary change.

In agreement with the proponents of the modern synthesis, Waddington maintained that genetic variability accumulates over time and forms an evolutionary substrate, which is ‘hidden’ from the purview of natural selection. This ‘hidden variability’ constitutes an active potential that explains how organisms adapt to their environment when they are subjected to rapid environmental changes. However, in contrast to proponents of the modern synthesis, Waddington argued that this source of evolutionary change should not be understood as a concrete repository filled with neutral genetic information, randomly created and progressively stored. Rather, this substrate should be construed as an *epigenetic process* that builds up variability in response to perturbations. Importantly, Waddington believed that this hidden variability could help account for the ‘inheritance of acquired characters’ in a neo-Darwinian way. In particular, he appealed to it to explain the phenomenon of *genetic assimilation*, whereby environmentally induced phenotypic variation becomes constitutively produced (i.e. it loses dependency for its expression on the original environmental trigger and becomes an inherited trait).

Recently, a lively debate has re-emerged concerning the nature of this hidden variability—or ‘cryptic variability’, to use Waddington’s preferred terminology—and its putative role in explicating the genetic assimilation of acquired characters. According to some authors, acquired characters are manifested when a certain stress threshold is passed; and a buffering mechanism of preexisting genetic variation is invoked to account for how this phenomenon occurs (Rutherford and Lindquist 1998; Rutherford 2000; Masel 2013). Other authors, however, have argued that this model fails to explain how cryptic variability causally accounts for the generation of acquired characters, as these can also be produced by *de novo* (as opposed to preexisting) mutations (Specchia et al. 2010).

The processual perspective that is currently resurfacing in the philosophy of biology (see Dupré 2012 and the rest of the chapters in this volume) provides an ideal tool for shedding light on this ongoing scientific debate. This perspective calls for the adoption of a dynamic understanding of living entities, as opposed to the more conventional one afforded by traditional substance ontology.[3] Substances are **(p.248)** typically conceived of as static entities that exist prior to any forms of change or activity. In contrast, process ontology takes change to be fundamental and regards seemingly static entities as transient stabilities of continuous processes. What I will argue in this chapter is that the contemporary debate over cryptic variability reflects different ontological assumptions about the nature of development, and these assumptions result in conflicting conceptualizations of the relationship between variability and inheritance. By examining the ontological commitments of the participants in this debate, I will show that we are better able to make sense of the different ways in which cryptic variability is currently being construed.

The structure of the chapter is as follows. In section 2 I distinguish between substance-ontological and process-ontological frameworks for biology, paying particular attention to the conflicting presuppositions of the modern synthesis on the one hand, and of Waddington’s epigenetics on the other. In section 3 I discuss Waddington’s epigenetics and its grounding in dynamical systems theory. Then, in section 4, I discuss robustness and plasticity as opposite yet complementary features of development, understood, in Waddingtonian terms, as a homeorhetic (as opposed to a homeostatic) process. After this, in section 5, I discuss the evolutionary implications of Waddington’s view of development as a homeorhetic process. Finally, in section 6, I analyse the two sides of the current debate over cryptic variability by examining their respective models of the phenomenon. As my examination will illustrate, the conflict between the assumptions of a substance view and those of a process view reflects the different capacities of these models to make sense of the inheritance of acquired characters.

2. Substance versus Process: Two Conflicting Ontologies for Biology

Although organisms are the main targets of biological inquiry, the actual nature of organisms seldom receives any attention. This is because the question ‘What is an organism?’ is often viewed as an insoluble problem, mostly left to philosophers of biology and biologists with philosophical inclinations. The problem can be tackled from different epistemological perspectives. From a synchronic point of view, we can scrutinize organisms by considering their essential morphological structures at a specific timescale: an organ, a tissue, a cell, and so on. The two fundamental questions to answer, in this case, are (1) how organisms are organized into different hierarchical levels; and (2) how these levels relate to one another. Alternatively, we can conceive of organisms as diachronic entities, looking at how they change over time, in order to come to terms with how these structures are modified during development. In this case, the fundamental questions to be answered concern the persistent nature and the directive character of organisms. It is important to realize, however, that we are likely to arrive at different answers to these questions, depending on the ontological assumptions we begin with.

For example, let us assume that we are in the business of studying the developmental trajectory of a cell, from its initial undifferentiated state to its final differentiated adult state. To explain this transition, we need to look at the cell at each **(p.249)** temporal instant. At time t_1 the cell is entirely undifferentiated, at time t_2 it is at a more differentiated stage than at time t_1, and so on, until its process of differentiation ends. According to this picture, an organism’s development—as a multicellular lineage—is the temporal succession of all its stages of differentiation, each one exhibiting a specific structure and characteristic properties. Development, in other words, is the sum of all stages of cellular differentiation, in orderly succession. We can think of this as a *substance* view of development.

It could be argued, however, that thinking about development as a succession of discrete, ordered stages does violence to the very notion of development. Without wanting to dispute the heuristic usefulness of this perspective as a means of modelling change, we might remain unconvinced by a view of development that portrays it as a static order composed of atomic temporal elements (i.e. stages). Rather, we might want to say that what development is corresponds to the whole, temporally extended process—the one that denotes the organism’s entire life cycle. In this view, development is neither localizable nor decomposable. Any particular developmental stage is a mere abstraction, cut off from the integrated spatio-temporal process. We can think of this as a *process* view of development.

Methodologically, if we adopt a substance view, we will start by examining each stage of development independently and explain the dynamicity of the ontogenic process in terms of the temporal succession of these stages. On the other hand,

if we adopt a process view, we will examine the process of development as a temporally extended whole and explain the stability of each stage within the developmental cycle.

The substance and the process views I have just discussed can be said to correspond to two opposing ontologies of the living world (see Dupré 2012). In the biology of the past century, these two ontologies have had a deep impact on the way biologists have conceived of organisms, their development, and their evolution. The modern synthesis seems to have been quite clearly associated with the substance view. The understanding of development shared by most of the architects of the modern synthesis was characterized by a sort of revamped preformationism: the idea that developmental change consists in an ‘unfolding’ or ‘unrolling’ of something that is already present and in some way preformed (Oyama 2000; Lewontin 2000). This neo-preformationist conception legitimated the substance view of development as an ordered succession of stages by emphasizing the role of DNA as the instigator of this process. Development in this picture is a deterministic process executed by a *genetic program*, which stores all the necessary instructions for the construction of the organism.[4] From this perspective, development is not all that different from a domino sequence whose initial trigger is provided by the decryption of the genetic text. Today neo-preformationism is assumed in genomic quantitative analyses that attempt to formalize the hereditary material as a static structure bearing a ‘code script’ (as Schrödinger famously called it) **(p.250)** for the architecture of the organism. The organism, in this view, is reduced to an epiphenomenon of its genes (Gilbert and Sarkar 2000; Nicholson 2014).

Although preformationism was—and arguably, still is—the predominant framework in the explanation of development (see e.g. Eric Davidson’s much publicized work on decoding the regulatory genome of the sea urchin embryo), not too long ago a number of biologists put forward a dynamic view of biology, and of development in particular, grounded in process ontology. Just as the modern synthesis was being forged, a different intellectual movement in biology developed, known as *organicism*, which sought to articulate a non-reductionist and dynamic understanding of organisms inspired by the writings of Alfred North Whitehead. The organicists, who included Waddington, viewed organisms not as organized assemblages of material things but as integrated functional units in which the whole and the parts causally influence each other (see Peterson 2014, Nicholson and Gawne 2015, and chapters 1, 7, 11, and 13 here).

The tacit ontological disagreement between organicists and proponents of the modern synthesis was not confined to the nature of organisms and their development, but also extended to the relation between inheritance and evolution. According to the substance-ontological framework of the modern synthesis, development is construed as a morphological change that has no impact on inheritance or on evolution. The organism is a genetic product; genes

are just code scripts, inert entities waiting to be read and transcribed. In contrast to this picture, the organicists, and Waddington in particular, believed that development exerts a direct influence on both inheritance and evolution. Specifically, Waddington suggested that organisms are capable of shaping their own developmental trajectories, thereby actively contributing to their adaptive persistence. He coined the term ‘epigenetics’ to designate the causal study of molecular processes that sustain organisms through their development. Following his processual inclinations, he articulated a novel account of organisms as dynamical developmental systems, in which genes do not act as scripts but interact with their transcriptional products and their cytoplasmic environment. The genome does not really instruct development (as simplistically assumed by the modern synthesis); it is rather the developmental system as a whole that actively reads and interprets the genome. Having briefly outlined Waddington’s processual view of the organism, let us now examine his epigenetic theory in more detail.

3. Waddington’s Epigenetics in the Context of Dynamical Systems Theory

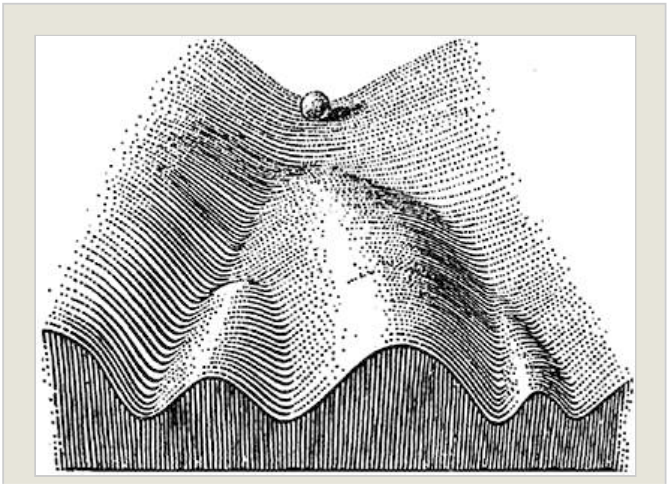
Waddington sought to provide a firm scientific grounding for his process-ontological views. He found such a foundation in the theoretical framework known as dynamical systems theory (DyST).[5] Contemporary proponents of DyST describe changes in **(p.251)** a system as transitions between stages (e.g. Slack 2002; Fagan 2012; Ferrel 2012; Huang 2012; Jaeger and Monk 2014). The dynamism of the system resides in the succession of one stage after another and, as the system develops, this succession describes the progression of the system through time. Applied to embryogenesis, DyST enables the system’s development to be analysed in terms of a succession of stages. A change in the system is conceptualized as the shift from one stage, with its particular embryological features, to another. We should not be tempted, however, to understand development as something *composed* of these stages, as stages are not ontological constituents of the developmental process. Instead, the stages described by DyST are mere abstractions: mathematical representations of stable sections of the whole process. In general, a system that undergoes such changes is referred to as a ‘coupled dynamical system’. This is how Waddington thought of organisms.

From the perspective of DyST, a dynamical system can be described with a set of independent variables that represent numerically the properties that the concrete system manifests. The value of all variables at any given time is referred to as the ‘state’ of the system (see Van Gelder 1998). Coupled dynamical systems are those whose variables vary in relation to the external parameters that lead the system to shift from one state to another. Parameters, in turn, often depend on the state of the system. For instance, a particular environment modifies and is modified by the particular organism that inhabits it. For this reason, the variables of the dynamical system and the parameters with which it is coupled can be thought to constitute a larger causal system (provided

that both jointly account for the changes it undergoes). This larger system as a whole, Waddington claimed, is stabilized by a flux of activities, which flow in and out of it (Waddington 1959).

During development, nucleus and cytoplasm interact by means of feedback loops to selectively stimulate different networks of genes. These networks do not always act in the same sort of way. Rather, they exhibit dynamic behaviours only in specific embryological stages, in which they can be switched (see Waddington 1956, 1961). Waddington called the switching of these networks ‘competence’. Each competence is a stage at which the organism may change its developmental path. However, the more the organism develops, the faster it loses its competence to differentiate further. Thus, the developmental space progressively restricts or constrains the possible developmental outcomes—and thereby the possible phenotypes—that the organism might exhibit through time. Waddington called this phenomenon of progressive restriction of competences ‘canalization’.

In order to better convey his idea of canalized development, in *The Strategy of the Genes* Waddington (1957) represented the progressive restriction of competences as a multidimensional developmental surface of the egg cell, the famous ‘epigenetic landscape’ model (see Figure 12.1). The landscape depicts the development of the cell from its undifferentiated, regionalized state to its final stage. The surface is composed of ‘chreods’, which are formed under the action of selective pressures (see ibid., 29). Chreods, which in the landscape resemble a system of valleys and pits, act as possible developmental pathways, connecting early undifferentiated cytoplasmic states—which in Waddington’s picture are represented at the top of the hill—with alternative **(p.252)** discrete end states.[6] As the ball rolls down the hill, it exhibits a tendency to restrict its developmental potentialities—its competence—over time (Waddington 1940, 1956, 1957, 1961, 1968a; see also Gilbert 2000; Slack 2002; Fagan 2012; Griffiths and Stotz 2013; Fusco et al. 2014).



As we have just noted, the general developmental potentialities of the organism during embryogenesis become restricted over time, leading to stable end states or *steady states*.[7] These resulting states correspond to the final stage of the landscape, when the cell comes to be fully differentiated. It is important to note, however, that competences are also steady states. All of these stages are phases of dynamic equilibria or stable

metabolic regimes. Accordingly, phenotypes are best construed not as fixed end products, but as transient (and therefore partial) stabilities of a continuous process (Waddington 1968a).

Figure 12.1 Pictorial representation of (a part) of an epigenetic landscape. From Waddington 1957.

To illustrate how transient stability underlies a processual view of the phenotype, consider the life cycle of *Drosophila melanogaster*. At an early developmental stage, the drosophila is just a larva. It exhibits certain stable features and characteristics particular to this stage. Later on, a subsequent form of partial stability emerges when the drosophila becomes a pupa. The pupa and the larva differ substantially in their properties and abilities. Nevertheless, both are temporal stages of the same developmental entity (i.e. the drosophila). Thus, the phenotype of the drosophila is not just its end state, that is, the adult stage it reaches in the latter phase of its life cycle. Rather, the phenotype comprises each dynamically stable regime that the organism manifests in the course of its developmental trajectory. If we want to consider the larva and the **(p.253)** pupa as being one and the same organism, they have to be understood as stable phases of a plastic, temporally extended developmental entity; that is, as stages at which the developmental entity, though adaptively plastic, manifests specific as stable equilibria. It is by virtue of these equilibria that the organism possesses different competences over time. Let us now see how this dynamic stability is achieved.

4. Development as the Homeorhetic Balance between Robustness and Plasticity

I have already mentioned that, even though developmental competences degrade over time, the organism’s ability to maintain itself in a dynamic equilibrium and to interact adaptively with its environment remains invariant. While its adaptive capacities diminish as development unfolds, the organism’s compensatory ability seems to be ‘hardwired’ (i.e. it does not deteriorate). In his experimental work Waddington identified a global characteristic—an independent parameter of the system as a whole—that enables it to resist perturbations (be they genetic or environmental), while at the same time allowing developmental resources to be used in different ways during embryogenesis. The phenotype, understood by Waddington in processual terms, manifests two specific (though seemingly contradictory) properties: *robustness* and *plasticity*. Robustness is the ability to display stability in the face of perturbations, and it accounts for how an organism that develops (and is thus subjected to internal and external changes) maintains certain configurations constant for prolonged periods of time. Plasticity, on the other hand, is the capacity to alter these same configurations over time, in other words, to produce different yet coherent somatic states in response to internal and external stimuli.

Waddington proposed to take robustness and plasticity as mutually complementary properties resulting from a single compensatory process, which he referred to as ‘homeorhesis’. In analyses of development, it is crucial to distinguish homeorhesis from homeostasis. Waddington appealed to cybernetics to make sense of this distinction. Within a cybernetic framework, homeostasis refers to the tendency of a system to revert to its original configuration and thereby to restore the stability of its internal environment. It thus denotes the persistence through time of a specific static configuration. There are many physiological examples of homeostatic responses. The way in which the human body reacts to sudden changes in temperature is one of them. Despite wide variations in the external temperature, the body constantly maintains its internal temperature within a relatively narrow interval; if the boundaries of this interval are violated, the body faces dramatic consequences that may, in some cases, lead to death. The body’s internal temperature, in other words, does not vary as a consequence of changes in the temperature of the external environment. Assuming initial parity, if the latter drops to 12° C, the former does not experience the same decrease. The body here exhibits a homeostatic response: it actively maintains its internal temperature following changes in the external temperature so as to ensure that it does not fall outside a narrowly defined physiological range.

Homeorhesis, like homeostasis, also refers to the regulatory ability of a system to reach a dynamic form of stability by compensating against perturbations within a specific **(p.254)** range of responses. The difference is that, while a homeostatic response concerns the maintenance of a single, fixed steady state, a homeorhetic response refers to the *stability of the temporally extended trajectory of the system* (Waddington 1957, 1968b). In the context of development, homeorhesis is what enables the embryo to undergo differentiation in a robust yet plastic way, guaranteeing the normal operation of the physiological processes in the system that otherwise would be disrupted. Homeorhesis is, in a sense, a more general biological property than homeostasis, as it maintains the organism in a stable state over the course of its development by means of a range of specific homeostatic responses.

Having explained how homeorhesis differs from homeostasis, we can now consider its bearing on the epigenetic landscape (Figure 12.1). As noted above, the chreods in this model correspond to the slopes along the valley. Waddington referred to this as the ‘chreodic profile’: the branching system of temporal trajectories through which an egg cell is robustly canalized. The stability of the entire developmental pathway is explained by the robustness of chreods, which preserves the system in ‘continual change along a certain pathway’ (Waddington 1977: 105). At the same time, robustness also secures the system’s plasticity, that is, its ability to produce different somatic states in response to stimuli. From both a mathematical and a cybernetic point of view, the concept of homeorhesis is intimately related to the concept of chreod. Influenced by his friend, the

French topologist René Thom, Waddington came to understand chreods in mathematical terms. Within the framework of DyST, a chreod can be described ‘as a multidimensional domain that contains a vector field converging on a time extended attractor’ (Waddington 1968a: 526). This move allowed Waddington to offer a more precise description of the contrast between homeostasis and homeorhesis. In Waddington’s own words,

> the fact that the vector fields converge on to the attractors gives rise to a process of homeorhesis, which can be contrasted with the more conventional idea of homeostasis in which the vector fields converge on to a *static point* which is not time-extended.
>
> (Waddington 1968a: 526; emphasis added)

To summarize, then, Waddington introduced the concept of homeorhesis in order to resolve the apparent contradiction between the robustness of development and the plasticity of phenotypes as developmental products. Homeorhetic processes differ from homeostatic ones, even though both lead to stability. So far, I have discussed homeorhesis in the context of development. Since Waddington’s primary intellectual enterprise was to bridge the gap between embryology, genetics, and evolution, I will now discuss how the compensatory behaviour described by homeorhesis is crucial for understanding the inheritance of acquired characters.

5. Evolutionary Implications: The Genetic Assimilation of Acquired Characters

In the previous section I have discussed inflexibility (i.e. robustness) and flexibility (i.e. plasticity) as the characteristic features of development. The developmental system is inflexible in the sense that it is canalized in a robust way despite environmental or genetic **(p.255)** perturbations. And it is flexible in the sense that its ontogenetic path can be modified through different steady states. The homeorhetic regulatory capacity of ontogeny connects developmental products—the phenotypes—with the underlying epigenetic network. Together, they guarantee robustness in a highly plastic developmental path.

Waddington believed that the genome is continuously modified by the behaviour of the developmental system, that is, by the way in which the system acts and reacts to inducing signals. However, these signals cannot influence the genome directly; in other words, they cannot induce any heritable modification (i.e. variability) by simply exerting a selective pressure. Local inducing signals are ‘absorbed’ by the system and may result in internal genetic changes, but these local changes do not affect the global epigenetic network; they remain underneath the chreodic profile (Waddington 1957). Although they are causally active, they are prevented from affecting the global ontogenetic path. The regulatory behaviour of the whole epigenetic network guarantees the invariance

of the phenotypes, thereby explaining why the phenotype is not constantly reshaped by external stimuli. According to Waddington, this regulatory behaviour is what grounds the evolutionary capacity for the genetic assimilation of acquired characters (Waddington 1953, 1956, 1975).

Waddington’s understanding of development and of its regulatory capacities marked an important departure from the modern synthesis, as it provided an alternative explanation of variability and its evolutionary role. The architects of the modern synthesis were deeply suspicious about the possibility of acquiring variation by means of simple interactions with the environment. Recognizing the possibility of this acquisition seemed to imply collapsing the canonical Weissmanian distinction between germ plasm and soma. Inheritance and evolution were considered to be relevant only to the former. Conflating the two lines was tantamount to dismissing the causal priority of the DNA over all other cytoplasmatic elements. And, in the context of molecular biology, it also meant violating the so-called central dogma (see Jablonka and Lamb 2005).

The modern synthesis, as a framework that combines Darwinism and Mendelism, links phenotypic variability to genetic variability, which exists independently of the environmental context. The ability of lineages to undergo evolutionary change is taken to derive from their tendency to produce and preserve genetic variability. In this view, what matters for evolution is the heredity of a static, genetic substratum. This substratum resides in the nuclear chromosomes and is not significantly affected by its surroundings.

The idea of hidden genetic variability dates back to the forging of the modern synthesis, when population geneticists provided explanations of the evolution of organisms in terms of changes in the distribution of genetic alleles in populations. Theodosius Dobzhansky, in particular, postulated the existence of a pool of allelic variants capable of bringing about beneficial effects to phenotypes in unusual circumstances. More specifically, he claimed that the adaptive plasticity of organisms should be explained by an underlying store of concealed genetic variability, which underlies the organism’s capacity to adapt to rapid environmental changes. The causal effects of random hidden mutations, he argued, fuels evolution by producing beneficial phenotypes under new circumstances (see Paaby and Rockman 2014; Ledon-Retting et al. 2014).

(p.256) From a modern synthesis perspective, the phenotypic manifestation of hidden variability is explained by the crossing of a threshold in a polygenic system. Since polygenic inheritance is related to the small additive effect of many alleles, the effect of each individual allele is too small to be noticed by natural selection (Mather 1941, 1943). This variation accumulates over time without being manifested; as long as it stays under a certain threshold, it remains phenotypically hidden. However, when organisms are in unusual or stressful environmental circumstances, this concealed variation can be

phenotypically manifested, and therefore selected. In this view, the capacity to inherit phenotypic plasticity resides in a static, preexisting, adaptive substratum.

Waddington’s proposal is fundamentally different. The proponents of the modern synthesis, in order to explain adaptive plasticity, postulated what present-day scholars refer to as an ‘evolutionary substratum’ (Paaby and Rockman 2014). Waddington, by contrast, claimed that this so-called ‘substrate’ is rather something that is actively maintained and modified by the developmental system as a whole. Following Dobzanhsky (1951), he agreed that hidden variability explains how organisms adapt to their environment when subjected to rapid environmental changes. But, in contrast to Dobzhansky, he stressed that the crypticity of these mutations must be understood in terms of the canalization of development, and hence in terms of the *epigenotype* (i.e. the whole dynamic developmental network that connects the genotype to the phenotype; see Waddington 1942).[8] What this implies is that this hidden variability is an effect of the controlled action of the organism on its own development. The more the organism is able to organize and shape such variability, the more it is able to develop selectable adaptive capacities. In this way, hidden variability should be understood, according to Waddington, by appealing to the homeorhetic dynamics of the canalization of development, instead of by resorting to the progressive accumulation of discrete genetic variation.

Genetic assimilation, as we have already noted, is the process by which particular phenotypic answers to environmental stimuli can be incorporated into the genotype through a process of selection. Waddington called these phenotypes ‘heritable acquired characters’, because they can be manifested again in the offspring even in the absence of the original environmental stimulus (Waddington 1975). He found evidence of genetic assimilation in drosophila in experiments he conducted in the 1950s. By using a heat-shock treatment to induce the *crossveinless* phenocopy and, in another experiment, by using ether to induce *bithorax*, Waddington showed how somatic mutations could become heritable.[9] He demonstrated that these characters, if selected for a certain number of generations in the presence of the same stress, could be assimilated in the germline. Interpreting these results in Darwinian (as opposed to Lamarckian) terms, Waddington appealed to the modern synthesis notion of hidden variability. However, he referred to it as *cryptic* variability, as it **(p.257)** seemed to be concealed beneath the robustness of the developmental paths. Waddington’s idea was that, when developmental trajectories diverge from their ordinary path, processes that buffer variability act so as to guarantee the control of their alterations (Waddington 1977). However, if an environmental stress is strong enough to overcome this robustness, an alternative adaptive path can become available through the expression of genetic variants. These variants can then be selected and become heritable through the process of genetic assimilation.

Overall, by applying the concept of homeorhesis in the context of evolution, Waddington was able to offer a novel Darwinian interpretation of the old Lamarckian problem of the inheritance of acquired characters. In the next section, I shall discuss how Waddington’s hypothesis is being interpreted by contemporary authors.

6. Assessing Two Contemporary Models of the Canalization of Development

In current discussions, authors seldom distinguish between the concept of *hidden* variability, postulated by the architects of the modern synthesis, and Waddington’s own preferred notion of *cryptic* variability. This is the case in spite of the fact that most of them ostensibly lean towards an interpretation of adaptive plasticity along Waddingtonian lines. Despite decades of empirical research, the nature of this variability is still hotly debated (see e.g. Rutherford and Lindquist 1998; Queitsch et al. 2002; Specchia et al. 2010). As Waddington’s original model involved a buffering mechanism that conceals variability, several contemporary authors have attempted to investigate its molecular makeup. In this final section, I will examine the two predominant models for the buffering process of the canalization of development originally hypothesized by Waddington. Ultimately, I will argue that only one of the two is consistent with Waddington’s homeorhetic processual view, which conceives of variability as an epigenetic phenomenon.

6.1. How the two models differ in their interpretation of cryptic variability

In contemporary genetics and molecular biology, there are two major models of canalization, both involving the function of the chaperone heat-shock protein Hsp90—a protein that responds naturally to environmental changes. Although these models are able to account for the same experimental data regarding the genetic assimilation of acquired characters, they differ radically in their respective assumptions concerning variability. While one conceives the phenotypic variation as the manifestation of preexisting hidden genetic information (Rutherford and Lindquist 1998), the other explains acquired characters in terms of *de novo* mutations (Specchia et al. 2010). Let us now examine both models and compare their respective ontological assumptions regarding the nature of variability and its putative role in the inheritance of acquired characters.

In 1998 the geneticists Rutherford and Lindquist observed that, in flies and plants, a reduced activity of Hsp90 was correlated with the induction of a wide spectrum of phenotypic variants (Rutherford and Lindquist 1998). These variants play an **(p.258)** evolutionary role: under selection they can be assimilated and passed to subsequent generations, even after the function of Hsp90 is restored. This experimental finding provided the impetus for new investigations of Waddington’s theory of genetic assimilation, taking Hsp90 as the molecular buffering mechanism responsible for the phenomenon. In both flies and plants, when the activity of Hsp90 is reduced via silencing from mutations or treatment

with inhibitors, a wide spectrum of phenotypic variants is induced (Rutherford and Lindquist 1998; Queitsch et al. 2002). It was thus suggested that Hsp90 acts as a sort of ‘capacitor’ of morphological evolution, that is, as an on/off switching mechanism that affects ‘the visibility of a particular set of conditionally neutral variants’ (Masel 2013: 1). Hsp90 buffers preexisting accumulated genetic variation and, when it is inhibited, it induces the release of this variation.

The second model, formulated by Specchia and colleagues, suggests a totally different understanding of the canalization of development (Specchia et al. 2010). According to these researchers, the buffering, storage, and release of preexisting genetic variation does not represent a general evolutionary mechanism for the genetic assimilation of acquired characters. Instead, they hypothesize that Hsp90 regulates silencing mechanisms mediated by Piwi-interacting RNAs (piRNAs); a class of germline-specific small interfering RNAs (siRNAs) known to play a role in maintaining repetitive sequences and transposons in a repressed state (Piacentini et al. 2014). When Hsp90 is altered and the respective products are absent, transposable elements move into the germline. Consequently, a wide range of phenotypic variants can potentially be induced (Piacentini et al. 2014). Heritable phenotypes are thus explained by *de novo* mutations correlated with the insertion of transposons (Elgart et al. 2015; Paaby and Rockman 2014; Sato and Siomi 2010). This model results in a rather different interpretation of Waddington’s theory. The phenomenon of genetic assimilation is not explained by an actualization of a hidden inner genetic variability, but as a co-selection process between transposable elements and the germline (Piacentini et al. 2014).

Specchia and colleagues are not alone in advocating this novel conception of variation and its role in adaptive plasticity. Decades earlier, Barbara McClintock argued that genomes are dynamic entities that do not react in a programmed fashion, but rather constantly reorganize their resources (McClintock 1984). She suggested that the activation of transposons by stress reshapes the genome, leading to the formation of new species through the creation of new adaptive resources. Specchia and colleagues have confirmed this evolutionary role, and have suggested that genomes exhibit an adaptive plasticity that enables organisms to reshape their developmental paths. According to this view, when an organism is subjected to an environmental stress, processes of silencing transposons—which usually keep them in a repressed state—can be disrupted, inducing the mobilization of transposons that become active. This process is thus deemed to be responsible for the creation of new variability, which can serve as a potential source of adaptive evolution (see Piacentini et al. 2014 for a more detailed discussion of these models).

Overall, according to the first model, proposed by Rutherford and Lindquist, cryptic variability is grounded in the progressive accumulation of genetic information. **(p.259)** The buffering mechanism contributes to create a storage

of nucleotidic information that is gradually accumulated during the organism’s development. According to the second model, proposed by Specchia and colleagues, cryptic variability is a *process* that leads to modifications at the level of the whole epigenotype. Development is construed here as the interplay between the flexibility and the inflexibility of the genome and of its products. While in the first model the focus is on how genetic variability is maintained and conserved, in the second it is more on how it is actually produced. By resisting the assumption of a preexisting repository of genetic mutations as the main source of variability, the second model provides a more accurate interpretation of Waddington’s conception of cryptic variability. Indeed, for Waddington, crypticity is a property of the developing organism *as a whole*, rather than one localized in specific preexisting genetic mutations.

6.2. Do both models capture the homeorhetic nature of canalization?

In evolutionary biology, plasticity is often described as a ‘conservative or *homeostatic* factor in evolution that prevents, rather than promotes, change’ (West-Eberhard 2003: 8, emphasis added). More generally, evolutionary biologists have tended to construe evolution in terms of a frequency-dependent equilibrium theory and to describe evolutionary causes (such as mutation, selection, and drift) as departures from this equilibrium. This is exemplified by the Hardy-Weinberg law of equilibrium, which was traditionally adopted by population geneticists to explain the evolutionary tendency of populations to resist modification ‘unless perturbed by definite force or chance events’ (ibid.). This orthodox viewpoint contrasts with Waddington’s homeorhetic conception of developmental stability, which he regarded as the active, dynamic process that buffers modifications despite constant environmental and genetic perturbations. The concept of cryptic variability is, for Waddington, an expression of this developmental capacity. In the remainder of this section, I shall assess whether the contemporary models we have just discussed conform to the requirements of Waddington’s concept of canalization: more specifically, whether they capture its homeorhetic (rather than homeostatic) nature.

Let us start with the first model. According to Rutherford and Lindquist, Hsp90 is responsible for the buffering of canalization in development. In normal conditions, Hsp90 conceals hidden genetic mutations and buffers the system against internal and external perturbations. However, when its function is compromised, these variants become manifested, leading to a wide range of abnormal phenotypes in both flies and plants (Rutherford and Lindquist 1998; Queitsch et al. 2002). The data from this model are represented as a spike threshold (see Sato and Siomi 2010: 2). In these graphs, variations accumulate quantitatively in peaks or spikes. These spikes represent genetic variations that tend to accumulate over time during the organism’s development. According to this model, once the spike is high enough to pass the threshold, the information accumulated is manifested. When the organism is highly stressed, these thresholds become lowered and the variation depicted in the spikes begins to be

uncovered. As a consequence, preexisting variations become manifested in the system. The manifestation of variants is thus a responsive phenomenon, represented by a threshold that moves up and down in response to environmental **(p.260)** stimuli. There is therefore no room in this model for any compensatory process of the system as a whole vis-à-vis its own variability. Canalization is just an equilibrium between a pool of stored variants and the environmental stimuli. As a result, this model fails to capture Waddington’s homeorhetic conception of canalization.

In the second model, the buffering is not performed by any particular molecular component. Here the threshold is not described in homeostatic terms, with respect to a specific parameter (as in the postulated buffering role of Hsp90 in the first model). Instead, it is represented by a bundle of different parameters that contribute to describe the phenomenon. Consequently, there is no need to postulate a specific threshold responsible for the manifestation of hidden variants, as variability itself does not derive from a storage of preexisting genetic information. In this model there is no causal priority of the genetic variants with respect to the manifestation of acquired characters. Consequently, this model can be said to capture Waddington’s homeorhetic conception of canalization.

7. Conclusions

In this chapter I have examined Waddington’s epigenetics and his processual account of cryptic variability, which is based on his notion of homeorhetic stability. I have shown that Waddington offered an account of development that represented a novel alternative to more traditional preformationist interpretations, which in many ways have prevailed to the present day. I have discussed how Waddington’s epigenetics, cashed out in terms of DyST, brought together his process-ontological inclinations (deriving from his adoption of Whitehead’s antireductionist metaphysics) and his cybernetic understanding of development. His proposal, homeorhetic stability, represents an important and, as it turns out, still valuable way of understanding (a) phenotypes as developmental products, and (b) development itself as a dynamic balance between robustness and plasticity. Moreover, Waddington’s concept of homeorhesis is able to account for the phenomenon of genetic assimilation, and thus enables us to bridge the gap between evolutionary and developmental explanations. Today, Waddington’s epigenetics is the standard theoretical reference point for the molecular explanation of developmental canalization. I have argued, however, that not all contemporary models satisfy the requirements that the dynamic nature of homeorhesis imposes on the explanation of the genetic assimilation of acquired characters. More generally, I submit that whether any such model ultimately succeeds in contributing to the emerging conceptual framework of the EES will depend on its capacity to capture the original insights of Waddington’s processual theory of epigenetics.

Acknowledgements

I would like to thank Dan Nicholson and John Dupré for the opportunity to participate in this project. I’m also grateful for the comments and advice I received from two anonymous referees, Dan Nicholson, Eva Jablonka, Marion Lamb, Paul Griffiths, Jan Baedke, Alan Love, Staffan Muller-Wille, Rani Lill Anjum, Stephen Mumford, Andrea Raimondi, Davide Serpico, Anne Sophie Meincke, and the Exeter ProBio Group.

(p.261) References

Bibliography references:

Bertalanffy, L. von. (1968). *General System Theory: Foundations, Development, Applications.* New York: George Braziller.

Dobzhansky, T. (1951). *Genetics and the Origin of Species*. New York: Columbia University Press.

Dupré, J. (2012). *Processes of Life: Essays in the Philosophy of Biology*. Oxford: Oxford University Press.

Elgart, M., Snir, O., and Soen, Y. (2015). Stress-Mediated Tuning of Developmental Robustness and Plasticity in Flies. *Biochimica et Biophysica Acta* 1849 (4): 462–6.

Fagan, M. B. (2012). Waddington Redux: Models and Explanation in Stem Cell and Systems Biology. *Biology & Philosophy* 27 (2): 179–213.

Ferrell, J. E. Jr. (2012). Bistability, Bifurcations, and Waddington’s Epigenetic Landscape. *Current Biology* 22 (11): R458–R466.

Fusco, G., Carrer, R., and Serrelli, E. (2014). The Landscape Metaphor in Development. In A. Minelli and T. Pradeu (eds), *Toward a Theory of Development* (pp. 114–28). Oxford: Oxford University Press.

Gilbert, S. F. (2000). Diachronic Biology Meets Evo-Devo: C. H. Waddington’s Approach to Evolutionary Developmental Biology. *American Zoologist* 40: 729–37.

Gilbert, S. F. (2012). Commentary: ‘The Epigenotype’ by C. H. Waddington. *International Journal of Epidemiology* 41 (1): 20–3.

Gilbert, S. F. and Epel, D. (2015). *Ecological Developmental Biology: The Environmental Regulation of Development, Health, and Evolution*. Sunderland: Sinauer Associates.

Gilbert, S. F. and Sarkar, S. (2000). Embracing Complexity: Organicism for the 21st Century. *Developmental Dynamics* 219 (1): 1–9.

Goldschmidt, R. (1935). Gen und Ausseneigenschaft: I. Zeitschrift für induktive Abstammungs- und Vererbungslehre 69: 38–69.

Griffiths, P. and Stotz, K. (2013). *Genetics and Philosophy: An Introduction*. Cambridge: Cambridge University Press.

Huang, S. (2012). The Molecular and Mathematical Basis of Waddington’s Epigenetic Landscape: A Framework for Post-Darwinian Biology? *BioEssays* 34 (2): 149–57.

Jablonka, E. and Ehud Lamm, M. J. (2012). Commentary: The epigenotype—A Dynamic Network View of Development. *International Journal of Epidemiology* 41 (1): 16–20.

Jablonka, E. and Lamb, M. J. (2005). *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*. Cambridge, MA: MIT Press.

Jaeger, J. and Monk, N. (2014). Bioattractors: Dynamical Systems Theory and the Evolution of Regulatory Processes. *Journal of Physiology* 592: 2267–81.

Ledon-Rettig, C. C., Pfennig, D. V., Chunco A. J., and Dworkin, I. (2014). Cryptic Genetic Variation in Natural Populations: A Predictive Framework. *Integrative and Comparative Biology* 54 (5): 783–93.

Lewontin, R. C. (1983). Gene, Organism, and Environment. In D. S. Bendall (eds), *Evolution from Molecules to Men* (pp. 273–85). Cambridge: Cambridge University Press.

Lewontin, R. C. (1996). Biology as Engineering. In J. Collado-Vides, B. Magasanik, and T. F. Smith (eds), *Integrative Approaches to Molecular Biology* (pp. 1–10). Cambridge, MA: MIT Press.

Lewontin, R. C. (2000). *The Triple Helix: Organism, Environment, and Evolution*. Cambridge, MA: Harvard University Press.

Masel, J. (2013). Q and A: Evolutionary Capacitance. *BMC Biology* 11: 103.

Mather, K. (1941). Variation and Selection in Polygenic Characters. *Journal of Genetics* 41: 159–93.

(p.262) Mather, K. (1943). Polygenic Balance in the Canalization of Development. *Nature* 151: 68–71.

McClintock, B. (1984). The Significance of Responses of the Genome to Challenge. *Science* 226: 792–801.

Nicholson, D. J. (2014). The Machine Conception of the Organism in Development and Evolution: A Critical Analysis. *Studies in History and Philosophy of Biology and Biomedical Sciences* 48: 162–74.

Nicholson, D. J. and Gawne, R. (2015). Neither Logical Empiricism nor Vitalism, but Organicism: What the Philosophy of Biology Was. *History and Philosophy of the Life Sciences* 37 (4): 345–81.

Odling-Smee, F. J., Laland, K. N., and Feldman, M. W. (2003). *Niche Construction: The Neglected Process in Evolution*. Princeton: Princeton University Press.

Oyama, S. (2000). *The Ontogeny of Information. Developmental Systems and Evolution.* Durham, NC: Duke University Press.

Oyama, S., Griffiths, P. E., and Gray, R. D. (2001). *Cycles of Contingency: Developmental Systems and Evolution*. Cambridge, MA: MIT Press.

Paaby, A. B. and Rockman, M. V. (2014). Cryptic Genetic Variation, Evolution’s Hidden Substrate. *Nature Reviews Genetics* 15: 247–58.

Peterson, E. L. (2014). The Conquest of Vitalism or the Eclipse of Organicism? The 1930s Cambridge Organizer Project and the Social Network of Mid-Twentieth-Century Biology. *British Journal for the History of Science* 47 (2): 281–304.

Piacentini, L., Fanti, L., Specchia, V., Bozzetti, M. P., Berloco, M., Palumbo. G., and Pimpinelli, S. (2014). Transposons, Environmental Changes, and Heritable Induced Phenotypic Variability. *Chromosoma* 123: 345–54.

Pigliucci, M. and Muller, G. B. (2010). *Evolution: The Extended Synthesis*. Cambridge, MA: MIT Press.

Queitsch, C., Sangster, T. A., and Lindquist, S. (2002). Hsp90 as a Capacitor of Phenotypic Variation. *Nature* 417: 618–24.

Rutherford, S. L. (2000). From Genotype to Phenotype: Buffering Mechanisms and the Storage of Genetic Information. *BioEssays* 22: 1095–5.

Rutherford, S. L. and Lindquist, S. (1998). Hsp90 as a Capacitor for Morphological Evolution. *Nature* 396: 336–42.

Sato, K. and Siomi, H. (2010). Is Canalization More Than Just a Beautiful Idea? *Genome Biology* 11 (3): 109.

Slack, J. M. W. (2002). Conrad Hal Waddington: The Last Renaissance Biologist? *Nature Reviews Genetics* 3: 889–95.

Specchia, V., Piacentini, L., Tritto, P., Fanti, L., D’Alessandro, R., Palumbo, G., Pimpinelli, S., and Bozzetti, M. P. (2010). Hsp90 Prevents Phenotypic Variation by Suppressing the Mutagenic Activity of Transposons. *Nature* 463: 662–5.

Van Gelder, T. (1998). The Dynamical Hypothesis in Cognitive Science. *Behavioral and Brain Sciences* 21 (5): 615–28.

Waddington, C. H. (1940). *Organisers and Genes*. Cambridge: Cambridge University Press.

Waddington, C. H. (1942). The Epigenotype. *International Journal Epidemiology* 41: 10–13.

Waddington, C. H. (1953). Genetic Assimilation of an Acquired Character. *Evolution* 7: 118–26.

Waddington, C. H. (1956). *Principles of Embryology*. London: George Allen & Unwin.

Waddington, C. H. (1957). *The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology*. London: George Allen & Unwin.

Waddington, C. H. (1959). *Biological Organization: Cellular and Sub-Cellular*. London: Pergamon Press.

Waddington, C. H. (1961). *The Nature of Life*. London: The Scientific Book Club.

(p.263) Waddington, C. H. (1968a). Towards a Theoretical Biology. *Nature* 218: 525–7.

Waddington, C. H. (1968b). *Towards a Theoretical Biology*, vol. 1: *Prolegomena*. Edinburgh: Edinburgh University Press.

Waddington, C. H. (1975). *The Evolution of an Evolutionist*. Ithaca, NY: Cornell University Press.

Waddington, C. H. (1977). *Tools for Thought*. St Albans: Paladin.

West-Eberhard, D. M. J. (2003). *Developmental Plasticity and Evolution*. Oxford: Oxford University Press.

Wilkins, A. S. (2008). Waddington’s Unfinished Critique of Neo-Darwinian Genetics: Then and Now. *Biological Theory* 3 (3): 224–32.

Notes:

([1]) The idea of conceptualizing the relation between organism and environment as a ‘co-construction process’ is often associated with Richard Lewontin, who famously stressed that ‘organisms fit the world so well because they have constructed it’ (Lewontin 1996: 10; see also Lewontin 1983, 2000). An organism, according to this view, is an active agent that is capable of constructing an environment suited to its own ends. The importance of this perspective for evolutionary biology has been recently highlighted by the theory of niche construction (Odling-Smee et al. 2003), which maintains that environments are shaped by the niche-constructing activities of organisms. In this view, the environment is not only deemed to be involved in the selection of genetic variation (as conceived by the modern synthesis), but is also considered to be instrumental in the developmental construction of the organism’s phenotype.

([2]) By ‘bifurcations’ I mean sudden qualitative changes in the developmental trajectory.

([3]) I am aware that ‘substance ontology’ is a rather broad term for a wide range of positions within metaphysics, and my usage of it is not intended to do justice to all of them. Here I am using it primarily for the purposes of contrasting this position with the processual one I describe in the next section.

([4]) One of the major implications of a substance ontology in biology is *essentialism*, the thesis that ‘essential properties’ are necessary and sufficient conditions for the existence of things. Within a substance-ontological framework, essential properties are offered as a causal explanation of why a thing persists despite the changes it undergoes (see chapter 1 for a more detailed exposition of this point). The metaphor of the genetic program is a clear example of essentialism, in which DNA sequences are conceived of as the essential properties that determine the developmental outcome of organisms.

([5]) For the purposes of this chapter, I will use the abbreviation DyST to distinguish dynamical systems theory from developmental systems theory (which is often referred to in the philosophy of biology by its acronym, DST). On the relation between DyST and DST, see chapter 11.

([6]) Waddington coined the term ‘chreod’ to refer to a canalized trajectory. A modern compound based on the combination of two ancient Greek words, namely the verb χρῆ (‘is necessary, must’) and the noun ὁδός (‘way, road’), this term should be understood as meaning ‘obliged pathway’ (< *chrē-hodos*; see Waddington 1961, 1968b). In Waddington’s own words, it indicates ‘a path of change which is determined by the initial conditions of a system and once entered upon cannot be abandoned’ (Waddington 1961: 64).

([7]) The notion of steady state refers to ‘a time-independent state where the system remains constant as a whole and in its (macroscopic) phases, though there is a continuous flow of component materials’ (Bertalanffy 1968: 125). The thermodynamic basis of the steady state concept and its relevance to a processual biology are examined in chapter 7.

([8]) On the concept of the ‘epigenotype’, see Gilbert 2012 and Jablonka and Lamm 2012.

([9]) The term ‘phenocopy’ refers to ‘the appearance of a phenotype which mimics that produced by some recognized mutant allele’ (Goldschmidt 1935, quoted in Waddington 1975: 77). Waddington adopted this term in his experiments on the genetic assimilation of acquired characters (see Waddington 1953) to describe the mutation that results in broken posterior *crossveins* in the wings of drosophila.