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Disentangling Genetic Assimilation from the Baldwin Effect: A Philosophical Perspective

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Abstract

Since the early 1950s, there has been lingering terminological and conceptual confusion in evolutionary biology regarding the definition and mechanism of the Baldwin effect (BE) and genetic assimilation (GA). This paper aims at clearing it up by proposing a distinction of the conceptions of the phenotypic effects of genetic mutations in BE and GA, relying on a classical distinction in metaphysics between two main kinds of properties: “extrinsic” and “intrinsic”. I argue that in its traditional understanding, BE implies that mutations’ effects on the phenotype are dispositional (i.e. intrinsic) properties, whereas GA needs them to be systemic (i.e. extrinsic) properties.

Keywords: genetic assimilation, Baldwin effect, dispositional property, systemic property, Ivan Schmalhausen, Conrad Waddington

Introduction

Since its earliest days, i.e. since 1896-1897 and the publication of Baldwin's, Lloyd Morgan's and Osborn's foundational papers, the history of the Baldwin effect has mainly been a history of controversies about its definition. Many names and almost as many ways to depict this evolutionary mechanism have been proposed: "organic selection" (Baldwin, 1896-1902), "coincident selection" (Russian school), "post-adaptation" (Hovasse, 1941), "stabilizing selection" (Schmalhausen, 1941), "genetic assimilation" (Waddington, 1953a), "Baldwin effect" (Simpson, 1953), etc. The debate is still going on today, as the important book by Mary-Jane West-Eberhard has recently shown (West-Eberhard, 2003). This terminological and conceptual uncertainty has at least a twofold origin. (1) All these evolutionary mechanisms are designed to explain the same phenomenology: the progressive genetic reinforcement of a phenotype that was first elicited by specific and unusual environmental conditions. (2) Major ambiguities between the *description* of the stages of the phenomenon and the *explanation* of its causality have always existed.

This is exactly why Waddington and Schmalhausen opposed the view that their own conceptualization might be understood in the terms of the Baldwin effect (Schmalhausen, 1949, p. 204; Waddington, 1953b; Levit et al., 2006, pp. 101-102). For Waddington especially, genetic assimilation (thereafter GA) was supposed to involve a completely different mode of causality than the Baldwin effect (thereafter BE), which he saw as an almost ineffective process in adaptive evolution (Waddington, 1961, pp. 287-288; Loison, 2019).

Were Waddington and Schmalhausen right? Are there good reasons to draw a substantial distinction between BE on the one side and GA (or "stabilizing selection" as defined by Schmalhausen) on the other? This question is difficult, in particular because some arguments developed during the 1950s and 1960s might no longer seem valid. For instance, one of the main reasons Waddington opposed the identification of BE and GA was that plasticity should be itself conceived as an evolved and hereditary property that is the target of selection, an aspect that was, according to him, ignored in BE (Waddington, 1953b, 1961). Yet, it happens that this issue was already discussed at the very beginning (Baldwin, 1896, p. 551, 1902, p. 157), and, even if it is true that this aspect was absent in some definitions proposed in the mid-1950s (Emerson, 1958, p. 318; Mayr, 1958, p. 354), the genetic basis of plasticity was quickly reintroduced in the standard definition of BE around 1960. For example, one of the most influential definitions of BE was formulated by Ernst Mayr in his seminal book *Animal Species and Evolution* (Mayr, 1963, p. 610, my emphasis):

"Simpson (1953b), who gives an excellent critical discussion of the Baldwin effect, points out that it involves three steps (rephrased by me):

- (1) The *genetically determined* reaction norms of individual organisms permit the development of behavioral, physiological, or structural modifications of the phenotype which are not hereditary as such, but which are advantageous for survival and permit the descendants of the organisms that have them to continue in the given environment;
- (2) Mutations (and gene combinations) occur in this population that produce the favored phenotype obligatory and rigidly rather than as a facultative modification;
- (3) The genetic factors under (2) are favored by natural selection and therefore spread in the population over the course of generations until the facultative character becomes obligatory and fixed."

Thus, it could perfectly be the case that Waddington and Schmalhausen were wrong in their effort to distance their views from BE. The aim of the present paper is to show that they were not. Based on a careful study of the literature published since 1896 until now, I will characterize and emphasize what might be a key difference between these two evolutionary mechanisms. My specific claim is that BE and GA can be distinguished on the basis of their different understandings of the phenotypic effects of genetic mutations. My argument will rely on a classical distinction in metaphysics between two main kinds of properties: "extrinsic" and "intrinsic". I will put forth that, in its traditional (i.e. "Simpsonian") understanding, BE implies mutations' effects on the phenotype to be dispositional (intrinsic) properties of the mutations, whereas GA needs them to be systemic (extrinsic) properties. In the first case, the phenotypic effect is a property of the mutation itself (this is why a selective coefficient could be ascribed to a specific allele). In the second case, the phenotypic effect is the outcome of an interacting process that encompasses the whole genome and the developmental system. This philosophical distinction has

direct implications on both experimental and theoretical levels, some of which will be addressed in the last section of the present article.

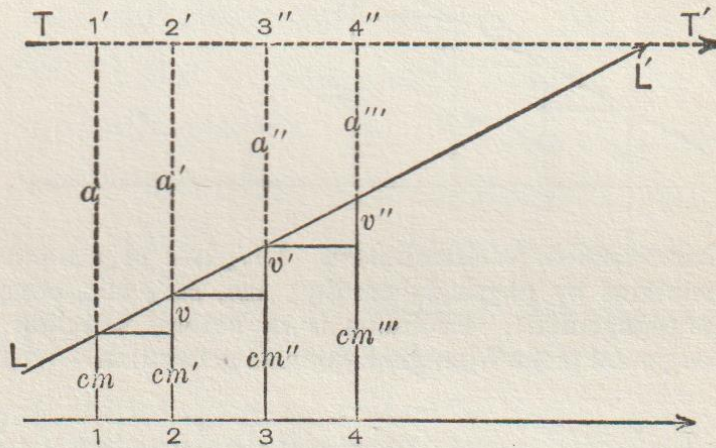
1. Why most existing attempts at distinction are unsatisfactory

Most of the time, BE and GA are understood as more or less synonymous phrases that refer to equivalent concepts (Loison, 2019). Nowadays, it seems that the term “genetic assimilation” is by far the most commonly used, without any necessary reference to the original Waddingtonian conception. Yet, a few biologists are unsatisfied with this terminological vagueness and have recently proposed ways to distinguish between these two mechanisms. In this section, I argue that these existing attempts at demarcation are not conclusive, either because they are misleading (1.a.) or because they remain incomplete (1.b.).

a. The issue of the decrease of plasticity: an unwarranted and inoperative criterion

West-Eberhard and Crispo have been especially eager to disentangle BE and GA. A part of West-Eberhard’s argument in her 800-page book is indeed that BE is a much more interesting mechanism than GA because it does not necessarily imply a decrease of plasticity in the course of adaptive evolution. At the same time, she explicitly opposes the view that GA could be of any interest, because, in her understanding, the concept of canalization deprives the developmental process of any creative significance in evolution (West-Eberhard, 2003, p. 7, p. 8, p. 25). In such a theoretical framework, the distinction between GA and BE is simple and straightforward: “The Baldwin effect (Baldwin, 1896, 1902) is a broader concept (see chapter 6). It includes the possibility of selection for increased condition sensitivity rather than just increased genotypic influence on trait expression” (West-Eberhard, 2003, p. 24; see also p. 151). The exact same distinction is supported in Crispo’s 2007 review (Crispo 2007, p. 2474). This distinction is historically difficult to support, and introduces further confusion in the literature. Additionally and may be more importantly, it remains unsatisfactory because it focuses only on BE and GA’s possible outcomes and not on their causal mechanism.

First, the Baldwin effect, for most scientists from Lloyd Morgan (1896) and Osborn (1896) to Simpson (1953), has been about a *loss* in plasticity, about hereditary fixation. For Baldwin himself, the issue is more problematic and open. On some occasions, when he reflected on human evolution and intelligence, he did consider that “organic selection”, in the end, could preserve or even enhance plasticity (Baldwin, 1902, p. 35; see also p. 117 and p. 207; West-Eberhard refers to those paragraphs precisely (West-Eberhard, 2003, p. 151)). Still in 1909, in *Darwin and The Humanities*, he argued that “in cases where the intelligent or other adjustive factor is on the whole of greater utility, variations toward the disintegration of the instinctive congenital part would be selected” (Baldwin, 1909, p. 21). Yet, such an understanding is missing from the various definitions of organic selection he proposed (see section 2.b.), conceiving it as a more general evolutionary mechanism not restricted to mental evolution in higher vertebrates. For instance, in *Development and Evolution*, he summarized his theory of “orthoplasy”, i.e. the causal process of both organic selection and social heredity, into a diagrammatic representation where the “congenital” variations gradually tend to replace “accommodations” (Baldwin 1902, p. 188):



Theory of Orthoplasy. LL' , line of evolution; 1, 2, etc., successive generations by physical heredity; TT' , line of tradition (social transmission); $cm, cm', etc.$, congenital mean; $a, a', etc.$, accommodations (and modifications) supplementing or screening $cm, etc.$; $v, v', etc.$, (congenital) variations added to $cm, etc.$, by natural selection. The species is kept alive by $a, a', etc.$, and TT' , during the evolution of cm . The line TT' , considered as 'tradition,' is of varying importance according to the character in question and to the grade of the organism in the scale of life; but if it signify any utility for which the accommodations are necessary, it is always present, and may be called the 'line of utility.'

Half a century later, in Simpson's classical account, the decrease of plasticity is unambiguously pictured as the necessary outcome of BE (Simpson, 1953, p. 112, my emphasis):

"(1) Individual organisms interact with the environment in such a way as systematically to produce in them behavioral, physiological, or structural modifications that are not hereditary as such but that are advantageous for survival, i.e., are adaptive for the individuals having them.

(2) There occur in the population genetic factors producing hereditary characteristics similar to the individual modification referred to in (1), or having the same sorts of adaptive advantages.

(3) The genetic factors of (2) are favored by natural selection and tend to spread in the population over the course of generations. The net result is that adaptation originally individual and non-hereditary *becomes hereditary.*"

Moreover, when Mayr entered the debate in the late 1950s and early 1960s, he explicitly opposed BE on the ground that if plasticity is an advantageous character, then natural selection will maintain or even enhance it whereas in BE the new phenotype will in the end be produced "*obligatorily and rigidly* rather than as a facultative modification" (Mayr, 1963, p. 610, my emphasis). In other words, a process of selective maintenance or improvement of phenotypic plasticity, is, according to Mayr, a completely legitimate hypothesis in the framework of the standard Modern Synthesis (Mayr, 1963, pp. 611-612):

"The Baldwin effect makes the tacit assumption that phenotypic rigidity is selectively superior to phenotypic flexibility. This is certainly often not true. [...] It would seem to me that either an epigenetic system such as is found in many plants, in which the phenotype is highly modifiable, or one like that described by Thoday (1953) and Lerner (1954), which achieves great phenotypical stability in spite of great genetic variability, through developmental flexibility, would be selectively superior to the system postulated in the Baldwin effect."

Given what history tells us, it seems difficult to support the view that a definition of the Baldwin effect should be primarily based on the idea of an increase in plasticity.

Second, and more importantly, to depict GA as a mechanism that will reduce a trait's plasticity is a superficial and incorrect interpretation of Waddington's and Schmalhausen's work. What GA is about cannot be reduced to only the over-simplistic idea of genetic fixation of a plastic trait. The misunderstanding comes from (1) the intrinsic difficulty (and sometimes obscurity) of Waddington's and Schmalhausen's writings; (2) a focus on discrete traits instead of reaction norms; (3) the fact that, usually, canalization and plasticity are understood as strictly opposite properties. As Pigliucci has recently emphasized, this last assumption is inaccurate, given that plasticity could itself be a canalized property (Pigliucci, 2010, pp. 357-358). Such an asymmetric conception of these two properties was already pivotal – yet rarely explicitly – in Waddington's and Schmalhausen's original work. To them, GA was about the transformation of the developmental phase space (the so-called “epigenetic landscape” for Waddington) where some favored pathways will become more canalized, i.e. more resistant to genetic and environmental perturbations, and others less, then significantly altering the reaction norm.

Thus, a much more faithful and enriched characterization of GA should underline the fact that it is a populational transformation of the reaction norm that will result in the canalization of a new one – what Waddington termed the “tuning” of canalization. This more specific definition of GA has an immediate and important consequence: the same canalized reaction norm could be built – precisely because it is canalized – on a wide range of different sets of genetic factors. This aspect will be given special attention in section 3.a.

The fact that GA is about the transformation of a reaction norm and not about a loss of plasticity is especially clear in Schmalhausen's 1949 book *Factors of Evolution, The Theory of Stabilizing Selection*. As he emphasized repeatedly, “modern genetic analysis does not operate with traits but only with the norms of reactions of organisms and their hereditary variations” (Schmalhausen, 1949, p. 139). He distinguished between two types of phenotypic variations causally produced by a change in the environment: “modifications” and “morphoses”. Modifications are plastic and adaptive responses encoded in the genome, the environmental change being only a signal inducing a developmental mechanism that will automatically lead to them. On the other hand, morphoses are the consequences of more drastic environmental changes, pushing embryogenesis beyond the standard canalized reaction norm. GA, as Schmalhausen conceived it,¹ consists in the evolutionary transformation of morphoses into modifications, i.e. in the progressive rebuilding of a new reaction norm (Schmalhausen, 1949, pp. 8-10). Stabilizing selection will reconstruct the developmental basis of the new reaction norm (called “adaptive norm” in the quotation below), one of the most creative aspects of evolution (Schmalhausen, 1949, p. 204, my emphasis):

“The specific results of such reactions are said to be stabilized when a given modification has been acquired by an *entire population* over a number of generations. It is known that the action of stabilizing selection is based upon a selective advantage possessed by the *adaptive norm* (including also new adaptations) over all deviations from it. It operates by the accumulation of *all mutations which do not bring the phenotype beyond the limits of the established norm.*”

From cover to cover, *Factors of Evolution* is a theoretical dissertation devoted to a single topic: how a norm of reaction defined at a populational level could be transformed and stabilized into a new one. At the end of his book, Schmalhausen made sure to emphasize the fact that this ongoing process, driven by stabilizing selection, will not at all lead to a decrease in plasticity, but exactly to the opposite (Schmalhausen, 1949, pp. 242-243):

“In stressing the importance of the stabilization of morphogenesis and the role of stabilizing selection in this process, in order to avoid misunderstanding it must be pointed out that, in the opinion of the author, this stabilization of form does exclude the converse process of labilization. Moreover, there is no implication here of the existence of a tendency towards a decline in individual lability, especially in the adaptivity of forms (nor is there any implication of a diminution of evolutionary plasticity or a “congelation of form” in the sense of Beurlen). On the contrary, attention is called to the increasing plasticity of organic forms, to the growing importance of individual adaptability, and to the organic bond existing between the processes that make for instability and

¹ In *Factors* (1946-1949), Schmalhausen never used the term GA, which was coined only in 1953 by Waddington.

stability of forms. Instability in the general reactions (the acquisition of new norms of general value) is accompanied by stability in particular reactions; namely, by the autonomization of development and the incorporation of new differentiations into the normal organization. Simultaneously with the continuous stabilization of special types of reaction, in particular, of functional differentiations which have attained permanent value in the given conditions of existence, there are also acquired entirely new reactions forms. And the capacity for individual adaptability, including the capacity for adaptive modifications, is based upon these new reaction forms. The capacity for more extensive adaptation is an important acquisition which leads the organism into new paths of progressive evolution.”

It follows, again, if we consider history of science seriously, that GA cannot be defined as a mechanism that will lead to a loss of plasticity. The distinction supported by Crispo and by West-Eberhard is not historically grounded. Moreover, focusing only on BE and GA’s possible end-results means ignoring the causal mechanisms at stake, i.e. the issue’s most central aspect. A conceptually fecund distinction should primarily say something about evolutionary causality.

b. Existing hidden mutations *versus* new mutations

Possibly the most frequently used criterion for the few who have tried to distinguish between GA and BE is the origin of the mutations leading to the genetic reinforcement of the initially plastic and individual response, this time an aspect that is directly related to the causality involved. It is argued that, at least in its original Waddingtonian understanding, GA is an adaptive process that, contrary to BE, does not need new spontaneous mutations to occur. GA builds adaptations only with existing genetic variability (i.e. “hidden” or “cryptic” mutations), an intrinsic polymorphism that previously remained phenotypically unexpressed because of the canalization of development.

For example, Brian K. Hall bases his demarcation between BE and GA mostly on this criterion (from Hall, 2001, p. 220):

Table 1. A summary of the steps in the Baldwin Effect and genetic assimilation to show the major differences between the two processes

Baldwin Effect	Genetic assimilation
1. Interaction with the environment results in phenotypic changes in structure, behaviour, and/or function that are adaptive	Interaction with the environment results in phenotypic changes in structure, behaviour or function that are adaptive
2. Mutations occur that lead to the same adaptive phenotypic changes; existing genetic variability is insufficient	Existing genetic variability is expressed in an assimilated phenotype which appears in the absence of the environmental signal; mutation is not required
3. Selection favors the mutations, which spread through the population; the environmentally induced phenotype is now inherited.	Selection favors the previously unexpressed genetic variability; the number of individuals with the assimilated phenotype increases

This specificity of the Waddingtonian concept of GA has also been recently emphasized by Laura Fanti and her colleagues in their experiments of selection of *de novo* induced mutations in *Drosophila*. In their proposed model, the induced stress increases mutability, which favors the

probability of occurrence of adaptive mutations that will eventually be selected and fixed. They are perfectly aware that on this aspect, their own evolutionary model “recalls the concept of ‘organic selection’, also defined as ‘the Baldwin effect’” (Fanti et al. 2017, p. 2005).

This distinction is without a doubt a historically grounded one: it is true that throughout its history, BE had been conceptualized as requiring the occurrence of adaptive mutations (see section 2.b. for more details) and that GA, as defined by Waddington and Schmalhausen, had been on the contrary based only on existing cryptic mutations (Schmalhausen, 1949, p. 127; Waddington, 1957, 1961). Yet, even if this distinction is historically founded, it remains unsatisfactory unless further developed, because we do not understand why it would matter: what are the reasons why Waddington and Schmalhausen always emphasize this aspect? Could GA involve new mutations instead of existing ones without significant conceptual alterations? Moreover, many theoretical models in population genetics are based on populations of infinite size, which implies that all the genetic variants are present. In such cases, what is left from such a demarcation? As far as I know, these questions are never asked, which makes this distinction only of descriptive and limited value.

The rest of the present article is indeed specifically devoted to the explanation of the theoretical meaning of the distinction between hidden mutations and new mutations. My aim is to show why this distinction was so central to Waddington and Schmalhausen, and why their argument might still be relevant today.

2. Mutations’ effects: Extrinsic or intrinsic properties?

a. What metaphysics tells us

In order to develop the clearest argument possible regarding this pivotal theoretical aspect, I will rely on a series of conceptual distinctions that have a long history in metaphysics. The most fundamental is between two main kinds of properties that can be ascribed to entities, extrinsic *versus* intrinsic. This distinction is usually introduced as follows: intrinsic properties are those that characterize an entity only because of what it is (mass is the textbook example of this) whereas extrinsic properties result from the interactions between this entity and the world (such as weight).

David Lewis’s work in the 1980s was the starting point of several attempts at clarification, which philosophers are currently still working on. Some excerpts from his 1983 article “Extrinsic properties” are of particular interest for my argument. The most helpful might be the following: “The intrinsic properties of something depend only on that thing; whereas the extrinsic properties of something may depend, wholly or partly, on something else. If something has an intrinsic property, then so does any duplicate of that thing; whereas duplicates situated in different surroundings will differ in their extrinsic properties” (Lewis, 1983, p. 197).

This quotation emphasizes two aspects specifically: (1) an entity’s extrinsic property cannot be described without referring to something else than the entity (2) it will differ depending on the environment (“surroundings”). My aim is to show, in the next section, that these two aspects are especially well suited to accounting for the phenotypic effects (the properties) of mutations (the entity or the “thing”) when one compares BE and GA. In BE, phenotypic effects are close to intrinsic properties of genetic mutations, whereas in GA, they are extrinsic properties that “depend, wholly or partly, on something else”, in this case the developmental system.

This classical distinction between extrinsic and intrinsic properties has recently been a core concern in the reappraisal of the stem cell concept. In a series of publications, Lucie Laplane elaborated a more precise typology, distinguishing four forms of properties: categorical, dispositional, relational and systemic (Laplane, 2016; Laplane and Solary, 2019). A categorical property is an intrinsic property that is independent of any interaction with surrounding entities (e.g., the atomic mass of an element). A dispositional property is also an intrinsic feature, but one that only manifests upon interaction with external stimuli (e.g., fragility, which is apparent only on impact). A relational property is an extrinsic property that relies on the interaction between entities (e.g., body weight, which depends on gravity). Lastly, a systemic property is a characteristic that is provided and maintained by the system, i.e. one where the intrinsic properties of the entity considered are almost irrelevant.

These new distinctions prove to be fruitful in the reconsideration of different kinds, ontologically speaking, of stem cells (Laplaine, 2016). In sections 2.b. and 2.c., I will support the view that two of these four categories are tailor-made to account for how the effects of genetic mutations have been considered in GE on the one hand and by Schmalhausen and Waddington on the other. Throughout the history of BE, mutations' effects have been thought as dispositional properties, which could be expressed or not depending on various conditions, but remain nevertheless intrinsic features of the mutations themselves. This understanding is far broader than the one at work in BE, and is also at the basis of the Modern Synthesis (MS). This is why selective coefficients, in standard population genetic models, could be directly ascribed to alleles. On the contrary, for Waddington and Schmalhausen, as I will argue, mutations' effects are best defined as systemic properties, because their consequences on the phenotype are in the main provided by the developmental system as a whole.

b. BE: phenotypic effects as dispositional properties of mutations

At the root of the MS is the idea that mutations are random variations regarding adaptation: there is a causal independence between the probability that a mutation will occur and its fitness in a given environment. This axiomatic proposition implies that the effect of a mutation is an intrinsic property in the sense defined in the previous section: the causal relationship between a genotype and a phenotype is robust enough that it means something to say that mutations *are* random. It would be complete nonsense to base an explanatory framework on the randomness of genetic mutations if their phenotypic effects were not the consequences of what they are essentially.

The effect of a single mutation could of course be altered by various features such as the presence of other alleles (genetic background) or the “environment”. Yet, it remains that genes have phenotypic effects that are specific enough – i.e., the genotype-phenotype map is close to linear – that it is reasonable to ascribe selective coefficients to genotypes if not to single alleles, even if the competitive interactions arise in the main at the organism's level. This is the very basis of the mechanistic models of standard population genetics.

From the start, i.e. from the late 1890s, and until nowadays, this view has also been universally expressed in the numerous definitions proposed for BE. In BE, the plastic response is important first because it allows time for adaptive mutations to occur. Adaptive mutations are the ones that parallel plastic accommodations. The property of being adaptive – or maladaptive – is an intrinsic feature of the mutation. The table below presents a representative sample of BE definitions elaborated over more than a century (note that before 1900 and the rediscovery of Mendel's laws, “variations” or “congenital variations” was the term used for what is now called mutations).

Author	Date	Definition
J.M. Baldwin	1896	“The variations which were utilized for ontogenetic adaptation in the earlier generation, being thus kept in existence, are utilized more widely in the subsequent generation. Congenital variations, on the one hand, are kept alive and made effective by their use for adaptations in the life of the individual; and, on the other hand, adaptations become congenital by further progress and refinement of <i>variation in the same lines of function</i> as those which their acquisition by the individual called into play.”
C.L. Morgan	1896	“It is here suggested that persistent modification through many generations, though not transmitted to the germ, nevertheless affords the opportunity for the occurrence of <i>germinal variation of like nature</i> .”
H.F. Osborn	1897	“Thus all the individuals of a race are similarly modified over such long periods of time that, very gradually, <i>congenital variations which happen to coincide</i> with the ontogenic adaptive modifications are collected and become phylogenetic.”

J.M. Baldwin	1902	“The imitative function, by using muscular coordinations, supplements them, secures accommodations, keeps the creature alive, prevents the incidence of natural selection, and so gives the species all the time necessary to get the <i>variations required</i> for the full instinctive performance of the function.”
S. Kirpichnikov	1947	“If individual adaptive modifications happen to be present, those among the numerous divers <i>congenital variations will be favoured that are coincident</i> with a given useful modification. Such variations will gradually accumulate. If the conditions that called forth the given plastic modification are continued for a considerable period, the accumulation of <i>coincident variations</i> will progress slowly, but inevitably.”
G.F. Gause	1947	“Baldwin (1896, 1902), Osborn (1897) and Lloyd Morgan (1900) suggested about half a century ago that modifications repeated for a number of generations may serve as the first step in evolutionary change, not by becoming impressed upon the germ-plasm, but by holding the strain in an environment where <i>mutations tending in the same direction</i> will be selected and incorporated into the constitution.”
R. Hovasse (my translation from French)	1950	“Thanks to these non-inherited phenotypes [<i>accommodats</i>], however, the organism finds itself in harmony with its environment: it is temporarily adjusted, and, in a sense, able to wait... For the arrival, one day or the other, among the germinal variations found in each organism, of <i>mutations corresponding to adaptive non-inherited phenotypes</i> , and that are vis-à-vis the latter “ <i>coincident</i> ”; they will find themselves automatically retained by the selective sieve, already oriented “as appropriate”. Thus the ontogenetic modification will be able to become congenital; in other words, the summation, the non-inherited phenotype, will become mutations, or more accurately, will be replaced by corresponding mutations.”
J. Huxley	1963	“We have here a beautiful case of the principle of organic selection (p. 523), as enunciated by Baldwin (1896, 1902) and Lloyd Morgan (1900), according to which modifications repeated for a number of generations may serve as the first step in evolutionary change, not by becoming impressed upon the germ-plasm, but by holding the strain in an environment where <i>mutations tending in the same direction</i> will be selected and incorporated into the constitution. The process simulates Lamarckism but actually consists in the replacement of modifications by mutations (see also Osborn, 1897).”
B.K. Hall	2003	“The essential elements of organic selection therefore are: - animals choose a new habitat or life style and adapt to it; - <i>mutations occur that favor the changes</i> ; and - selection favors those individuals best adapted to that new habitat or life style, and the adaptation spreads through the population”
P. Godfrey-Smith	2003	“Here is my understanding of the original ‘effect.’ Suppose a population encounters a new environmental condition, in which its old behavioral strategies are inappropriate. If some members of the population are plastic with respect to their behavioral program, and can acquire in the course of their lifetime new behavioral skills that fit their new surroundings, these plastic individuals will survive and reproduce at the expense of less flexible individuals. The population will then have the chance to produce <i>mutations that cause organisms to exhibit the new optimal behavioral profile</i> without the

		need for learning. Selection will favor these mutants, and in time the behaviors which once had to be learned will be innate.”
Sznajder et al.	2012	“The prediction from theory on the Baldwin effect is that if <i>genetic variation in the direction of the learned traits</i> exists (or it subsequently occurs through mutation) then there is potential for learning to guide the evolution of the genetic basis for these traits (provided that they are indeed positively associated with fitness).”

I hope these instances unambiguously demonstrate that from the start and throughout this complex history phenotypic effects have been conceived as something close to intrinsic properties of mutations. Essentially, BE is about allowing time for “good mutations” to spontaneously occur and be selected. This aspect is especially apparent in the term “coincident” variations/mutations, initially coined by Lloyd Morgan in the late 1890s and then very quickly used by other biologists, including Baldwin himself (Baldwin, 1902, p. 142). To label a mutation “coincident” clearly underlines that its phenotypic effect is a consequence that can be traced back to the mutation itself: some have the property to mimic the plastic response, others have not.

In BE, the issue of the preexistence of these “good” mutations is indeed irrelevant. Whether they were there before or not does not change the fact that they are coincident because of what they are essentially, i.e. intrinsically. Statistically speaking, the most probable is that most of them are not already present in a population, but this remains an empirical question for existing populations.

All being considered, such an understanding is nothing more than what is already at stake within the standard MS. This is why, for instance, Mayr always claimed that BE was not a threat. It is only chance mutations and natural selection.

c. GA: phenotypic effects as systemic properties of the developmental system

Things are completely different when one carefully looks at Schmalhausen’s and Waddington’s writings.

In *Factors of Evolution*’s second part, Schmalhausen gradually develops a conception of mutations’ effects as systemic properties of the developmental system. He starts by criticizing standard population genetics on several grounds. One of them, the most interesting for my argument, is that “even an individual mutation does not necessarily have a constant effect” (Schmalhausen, 1949, pp. 141-142). According to him, this is an over-simplistic view because mutations’ effects “are influenced by individual characteristics of each genotype, so that their phenotypic expressions and their physiologic effects may vary considerably” (Schmalhausen, 1949, p. 144). The more an organism is complex, the more epistasis and pleiotropy are the rule, until a point where it becomes almost impossible to individualize a specific gene effect on the phenotype. What drives embryogenesis and the phenotype production is no longer a sum of discrete genes, but a much more complicated system that cannot be described in terms of additive gene action. Schmalhausen repeatedly emphasizes this crucial theoretical stance in the final third of his book, and especially on pages 218 and 219 (Schmalhausen, 1949, p. 219):

“As the systems of correlations become more complex, they lose their genetic character; in other words, the effects on individual genes can no longer be distinguished (more precisely their disruption by mutations has lethal consequences). Morphophysiologic interrelationships and their systems may be regarded as entities that are not capable of analysis in genetic terms. These correlation systems consist fundamentally of the mutually related vital functions of the organism, which are responsible for the harmonious course of the general physiologic processes.”

Thus, for Schmalhausen, there is no sense, at least for complex organisms that produce their phenotype through an elaborated developmental process, in ascribing discrete phenotypic effects to specific mutations. Phenotypic effect is a systemic property.

The same exact position can be found in Waddington’s later writings, from the early 1950s until his death. As emphasized by Paul Griffiths, “in Waddington’s vision, phenotypes are global expressions

of genomes, but it does not follow that particular parts of the phenotype express particular parts of that genome” (Griffiths, 2006, p. 97). Already in 1953, as Waddington tried to avoid any conflation between GA and BE, he emphasized that “by speaking of mutations as ‘random’, which is true enough at the level of the gene as a protein-DNA complex, we obscure the fact that *the effect* of a mutation, as far as natural selection is concerned, is conditioned by the way it modifies the reaction with the environment of a genotype which has already been selected on the basis of its response to that environment” (Waddington, 1953b, p. 386, my emphasis). He makes this point much explicit and clearer in his 1957 magnum opus, *The Strategy of the Genes* (Waddington, 1957, p. 188, my emphasis):

“We have been led to conclude that natural selection for the ability to develop adaptively in relation to the environment will build up an epigenetic landscape which in its turn *guides the phenotypic effects of the mutations available*. In the light of this, the conventional statement that the raw materials of evolution are provided by random mutation appears hollow. The changes which occur in the nucleoproteins of the chromosomes may well be indeterminate, but the phenotypic effects of the alleles which have not yet been utilized in evolution cannot adequately be characterized as ‘random’: *they are conditioned by the modelling of the epigenetic landscape into a form which favours those paths of development which lead to end-states adapted to the environment.*”

Such a conception, at odds with the standard view of the MS, can be found in many articles and books after 1957 and should not be seen as a speculative and secondary proposition. It was at the core of Waddington’s thinking (see for example Waddington, 1959, p. 56; 1961, p. 288; 1968, pp. 184-185).

This explains why it matters, for both Schmalhausen and Waddington, that GA works on existing mutations (and does not need to wait for “coincident” ones). GA needs hidden genetic diversity in order to rebuild developmental pathways, but GA, in opposition to BE, does not need specific mutations precisely because phenotypic effects are close to systemic properties. Thus, this philosophical distinction between GA and BE explains why the criterion to distinguish between existing mutations and new mutations is relevant, i.e. why it makes sense in Schmalhausen’s and Waddington’s theoretical framework.

3. Theoretical and experimental implications: a quick overview

If this distinction between GA and BE is well-founded, it implies a series of consequences on both experimental and theoretical levels for the mechanism of GA. As I cannot address them all in detail in this section, I will only offer a brief survey.

a. GA: multiple realizability of the same reaction norm by different sets of genes

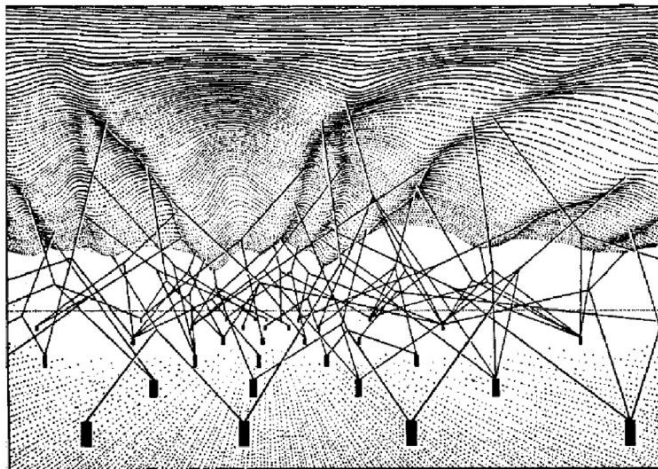
What might be the most immediate implication of such a systemic understanding of mutations’ effects concerns the final genetic reinforcement of the new reaction norm. It is not a single “coincident” mutation or even a few genes that accommodate and hereditarily stabilize phenotypic change, but “a new system of genic connections” (Schmalhausen, 1949, p. 155). In 1953, Waddington already emphasized this aspect too when he wrote that “the same phenotypic effect might be produced with quite a different genetic basis” (Waddington, 1953a, p. 124).

In the late 1950s and 1960s, he tirelessly restated its centrality for GA, especially in comparison to BE. In his detailed 1961 review, he concluded that GA involves the genome as a whole (Waddington, 1961, p. 264 and p. 267), exactly as Schmalhausen did in 1949 (Schmalhausen, 1949, p. 219 and p. 229).

A contextual difference between Waddington and Schmalhausen is that Schmalhausen was greatly affected by Lysenkoism in USSR, to such an extent that he was unable to conduct any experimental researches on evolution in the early 1950s (Levit et al., 2006). During those crucial years, Waddington, in the much more peaceful and conducive environment of the University of Edinburgh, was able to devise several key experiments for testing some aspects of GA. In the late 1950s, in close collaboration with his student K.G. Bateman, he designed experiments to test the possibility that a single phenotype could be stabilized upon different genetic bases (1956-1959). Using several stocks of *Drosophila*, the goal was to observe whether or not different strains might evolve, through GA, towards

the same adaptive phenotype despite their initial genetic differences. Bateman repeated and extended the original experiments on the selection of the four venation phenocopies (namely *pcvl*, *acvl*, *fpcv* and *smcv*). Waddington and Bateman eventually came to disagree about the results and their interpretation. For Bateman, if these series of experiments unambiguously shows the reality of GA, it remains that “assimilated characters are not controlled merely by an indefinite number of genes of individually small effect, i.e. are not ‘polygenic’” (Bateman, 1959, p. 461). On the contrary, for Waddington, GA “have involved changes at many loci throughout the whole genotype” (Waddington, 1961, p. 267).

This direct implication for GA of the fact that mutations effects are systemic properties is also explicit in Waddington’s numerous diagrammatic representations, and especially in one of the more meaningful figures published in *The Strategy of the Genes*. In Figure 5 (p. 36), he aimed at picturing “the complex system of interactions underlying the epigenetic landscape”. Each peg represents a gene and each string its contribution to the network that causally produces the epigenetic landscape.



The more present-day genetics learns about genes’ products and their causal roles in development, the more these are viewed as included in a complex system of interactions, namely an interactor, where it becomes difficult to individualize the effect of a specific gene. To put it briefly, thinking of the genome in terms of Genetic Regulatory Networks (GRNs) where the topology of the network is more relevant than the genes involved gives scientific substance to some of Schmalhausen’s and Waddington’s core speculations (A. Wagner, 2005, Chapter 13; Wilkins, 2007).

b. Two types of mutations, two forms of selection

If mutations’ effects are close to systemic properties of the developmental system, then it also implies that natural selection is, at least in some cases, not so much about the cumulative addition of alleles with specific phenotypic expressions but rather about the stabilization/canalization of developmental paths.

This was explicitly addressed by Schmalhausen in section 2.D. of *Factors of Evolution*, where he contrasts two forms of selection, dynamic selection and stabilizing selection. What he calls the “dynamic role” of natural selection is the standard understanding of it: when selective pressures are changing, natural selection alters the reaction norm in order to adapt the phenotype to the new environmental conditions. “Stabilizing selection” is a different form of selection, and a creative one in its own way (Schmalhausen, 1949, pp. 92-94), because it transforms the developmental path that leads to the new phenotype. For Schmalhausen, “stabilizing selection” is close to what Waddington later termed “canalizing selection” (Waddington, 1957, p. 73), and it eventually leads to the reorganization of the interactions between the genome and the developmental system in order to optimize the reliability of the new reaction norm, which becomes resistant to genetic and environmental perturbations.

Canalizing selection produces developmental canalization and canalization, in return, guides the phenotypic effects of genetic mutations.

Therefore, as soon as the genome works as an integrated system, the process is self-reinforcing: canalization diminishes the impact of mutations, which favors the efficiency of stabilizing/canalizing selection and thus enhances canalization. In the course of evolution, as more complex organizations are produced, stabilizing selection tends to become more important and more creative than standard “dynamic” selection (Schmalhausen, 1949, pp. 238-245).

For both Waddington and Schmalhausen, canalizing/stabilizing selection was a much more powerful and complex mode of natural selection than in our modern understanding. In the standard framework of present-day evolutionary theory, stabilizing selection is often reduced to normalizing selection, i.e. cases where an intermediate phenotype for a variable trait (such as size) is the fittest (see for example Futuyma, 1998, p. 366 or Barton et al., 2007, p. 476). Normalizing selection, understood as selection against phenotypes that deviate in either direction from an optimal value of a character, has no necessary impact on canalization. Whether this was well-founded or not, Schmalhausen and Waddington attributed major consequences to stabilizing/canalizing selection, described as capable of generating canalization because of its complete restructuring of the developmental pathway leading to the adapted phenotype. Ascertaining the extent to which canalizing selection is able to produce a significant degree of canalization remains tricky to this day. This issue has been tackled anew by Günter Wagner and his colleagues since the late 1990s: on what conditions could canalization evolve (Wagner et al., 1997)? It must be emphasized that Wagner, exactly like Waddington, makes a clear-cut distinction between what he calls “stabilizing selection” (normalizing selection) and the much more interesting process of canalizing selection, which “refers to the *different* process by means of which the genetic architecture of the trait evolves so that it is less likely to produce extreme individuals (Gibson and Wagner, 2000, p. 374, my emphasis).

c. Genome as follower

In the wake of West-Eberhard, Pigliucci and others, the “genes-as-followers” label has gained momentum over the past twenty years or so. The positive reappraisal of the possible evolutionary role of plasticity is usually connected to the idea that the first step in a micro-evolutionary process is not the spontaneous occurrence of chance mutations but the plastic and adaptive accommodation of phenotypes to new environmental challenges (West-Eberhard, 2003). This primary phase of the physiological response is “buying time” (Pennisi, 2018) for genetic evolution to catch up: the phenotype takes the lead, genes are only followers.

This is consistent with the logic of BE, where phenotypic effects are intrinsic properties of mutations. It is quite easy, indeed, to find instances in the history of BE of phrases very close in their formulation to our contemporary “genes-as-followers”. For example, Baldwin himself put it as follows: “The line of acquired modification takes the lead, variations [i.e. mutations] follow.” (Baldwin, 1902, p. 180). Yet, this BE concept of genes-as-followers is a weak one as long as phenotypic effects are intrinsic properties of mutations. If the genetic basis of an adaptation is too specific, selection of adaptive mutations remains the decisive step in the evolutionary building of adaptations, which is of course fully compatible within the internal logic of the MS. Ultimately, what is selected are the adaptive alleles, and the plastic response is reduced to only a transient phase that will necessarily lead to their fixation. This is also the main reason why BE is difficult to experimentally ascertain: in the end, establishing whether the good set of alleles has been directly or only indirectly selected remains difficult.

Whereas if (3.a.) the genome as a whole accommodated the building of the new reaction norms and if (3.b.) stabilizing/canalizing selection is a creative process, things would be significantly different. Selecting for an appropriate developmental system, in such a framework, is not tantamount to indirectly selecting for a specific set of alleles. The genome, as a system, follows developmental reorganizations. This distinct understanding, not focused on specific point mutations, might give the phenotype-as-a-leader a much more creative role in the causal process of evolutionary adaptation.

Conclusion

The philosophical distinction between GA and BE proposed in the present article is founded on two opposite conceptions of the phenotypic effects of genetic mutations. Based on an almost comprehensive survey of the literature published since 1896, I put forth that BE requires phenotypic effects to be dispositional properties of mutations whereas GA, in its original and still neglected understanding, conceives them as systemic properties of the whole developmental system. The proposed distinction is purely theoretical in the sense that it does not need to be confronted to empirical knowledge to be well-founded. It could perfectly be the case that, in experimental and natural populations, there is a continuous line between cases where phenotypic variants are mostly the consequences of specific mutations and cases where such a bijective relationship is impossible to establish. As always in biology, this is an issue of relative frequencies between different theoretical possibilities and the clear-cut metaphysical distinction between “extrinsic” and “intrinsic” is unlikely to be directly applicable in our complex empirical world.

Yet, unlike in the twentieth century, nowadays, genomics and systems biology are giving more and more momentum to the idea that the genome is a highly integrated system and that new entities, the interactome and the GRNs, has to be considered between the genotype and the phenotype. This new holistic perspective is much more congruent with Schmalhausen’s and Waddington’s unorthodox conceptions than with the mechanistic models of standard population genetics (Wilkins, 2008).

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