Genetic assimilation and the paradox of blind variation

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Abstract

We confront the neo-Darwinian core tenet of blind variation, or random mutation, with classical and recent models of genetic assimilation. We first argue that all the mechanisms proposed so far rely on blind genetic variation fuelling natural selection. Then, we examine a new hypothetical mechanism of genetic assimilation, relying on non-blind genetic variation. Yet, we show that such a model still relies on blind variation of some sort to explain adaptation. Last, we discuss the very meaning of the tenet of blind variation. We propose a formal characterization of the tenet and argue that it should not be understood solely as an empirical claim, but also as a core explanatory principle.

Keywords: Random mutation, Genetic assimilation, Epigenetics, Modern Synthesis, Neo-Darwinism

In regione caecorum rex est luscus.

Erasmus

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Contents

1. Introduction

A core tenet of neo-Darwinism is that of blind variation, according to which heritable variations that fuels natural selection do not arise because of their adaptive value.[1] Though not always clearly specified in neo-Darwinian writings [Merlin, 2010], such a tenet is central since at least Weismann [1893b], not to mention its importance for Darwin [1859, 209].[2] The tenet is essential in arguing for the sovereign explanatory power of natural selection as regards design. In the extreme case where variation is always maximally adaptive, there is, roughly speaking, no natural selection at all. The question of blind variation is probably the most salient stumbling block of the old and reviving debates between

[1] By 'adaptive value' we mean that which Burian [1983] calls 'engineering fitness': how well a systems behaves in its environment. We purposely use the word 'blind' and not 'random' because, as we develop here, the kind of randomness at stake is not clear. We also preferentially use 'variation' instead of 'mutation' not to give the flavour of restricting heritable variation to genetic mutation. In this chapter we only consider potentially heritable variation; notice we refer to molecular genes, not to mendelian genes [Lu and Bourrat, in press]. Last, we preferentially refer to neo-Darwinism rather than to the Modern Synthesis, which is just one version of it [Mayr and Provine, 1998].

[2] "As modifications of corporeal structure arise from, and are increased by, use or habit, and are diminished or lost by disuse, so I do not doubt it has been with instincts. But I believe that the effects of habit are of quite subordinate importance to the effects of the natural selection of what may be called accidental variations of instincts; – that is of variations produced by the same unknown causes which produce slight deviations of bodily structure." [Darwin, 1859, 209] Darwin's later writings came to emphasize more the inheritance of acquired characteristics, so as to cope with fast adaptation [Hoquet, 2009].

neo-Darwinians and neo-Lamarckians [e.g. Romanes, 1888; Jablonka and Lamb, 1995; 2010].

Genetic assimilation characterizes a situation where some phenotypic variations, which are initially caused by environmental events, eventually get caused by genetic variations.[3] When the phenotypic variations subject to genetic assimilation are adaptive phenotypic responses to environmental challenges, it is tempting to consider that genetic variation is directed, thus contradicting the principle of blind variation. Subsequently, genetic assimilation has given rise to some controversy, especially regarding whether it contradicts, or fits within, neo-Darwinism [Pigliucci et al., 2006].

In this chapter, we wish to clarify several points regarding genetic assimilation and how it connects with the neo-Darwinian tenet of blind variation. First, we briefly sketch the history and current view of genetic assimilation, including recent extensions to this view. We argue that all the mechanisms of genetic assimilation proposed so far rely on blind genetic variation fuelling natural selection. Second, we present a new hypothetical mechanism of genetic assimilation, relying on non-blind genetic variation. This model might be thought of as a highly challenging scenario for neo-Darwinism. Yet, we show that it still relies on blind variation of some sort to explain adaptation. Last, we clarify the tenet of blind variation itself. We argue that, though somehow intuitive, the tenet proves remarkably elusive to formal and empirical characterization. Here, we concentrate on the theoretical novelty of the different models of genetic assimilation and on the way they affect the neo-Darwinian framework. We only evoke or briefly discuss their biological relevance or extent of applicability[4], and predictions.

2. Genetic assimilation

The concept of genetic assimilation can be traced back before the word to the second half of the XIXth century, when authors were looking for a way to accommodate what seemed to be events of fast adaptation in a neo-Darwinian way (Section 2.1). As we show below, this motivation remains intact for the current models of genetic assimilation (Section 2.2).

2.1. The century of genetic assimilation

That organisms may adapt faster than what would seem permissible by natural selection has puzzled biologists ever since Darwin. By the end of the XIXth century, several mechanisms had been proposed to explain fast adaptation, notably involving the inheritance of acquired characteristics (including by Darwin, see Hoquet [2009]). Not all Darwinians were happy with this idea [Romanes, 1888]. The controversies between neo-Lamarckians and neo-Darwinians probably reached a climax with Weismann's famous charge against the inheritance of

[3] 'Cause' means here a difference maker [Waters, 2007].
[4] Sensu Beatty [1997].

acquired characteristics [Weismann, 1893a; Baldwin, 1896, 446; Simpson, 1953a, 110; Depew, 2003].

In this context, several authors independently thought of a way to reconcile neo-Lamarckism and neo-Darwinism [Spalding, 1873, cited by Pigliucci et al., 2006; Morgan, 1896; Baldwin, 1896; Osborn, 1897a;b; Simpson, 1953a, 110; Griffiths, 2003]. They postulated the existence of a biological mechanism that would mimic the inheritance of acquired characteristics, but which would nevertheless rely on natural selection occurring on blind variation. Framed in modern terms, the mechanism postulates a two steps evolutionary process, where organisms, when facing an environmental challenge, can first adapt through adaptive plastic responses, thus letting time for the species to evolve heritable (non-plastic) traits by natural selection [e.g. Baldwin, 1896, 445-7].

This mechanism, later most famously known as 'the Baldwin effect', was "envisioned... as a means of facilitating phenotypic evolution" [Pigliucci et al., 2006, 2362]. Baldwin argued that the mechanism explained what seemed to be occurrences of determinate variation in the fossil record, a fact that otherwise would have seemed in favour of neo-Lamarckism. To Baldwin by contrast, his new mechanism "d[id] away with the need of appealing to the Lamarckian factor" [Baldwin, 1896, 446].

By the mid-XXth century, Simpson [1953a] had dismissed the Baldwin effect as "a relatively minor outcome of the [neo-Darwinian] theory" (p. 115), which had "seldom [been] discussed in detail" (p. 110) since its inception. He also noticed the paradoxical situation that: "everyone who has discussed [the Baldwin effect] at any length has taken the position that... its real importance is in meeting or explaining away the criticisms leveled at natural selection by, especially, the neo-Lamarckians, the Michurinists, and the finalists" [Simpson, 1953a, 115].

At that time, the so-called Baldwin effect nevertheless got a new impulse from the experimental and theoretical works of Waddington [1942; 1952; 1953; 1956, 10] and Schmalhausen [1949]. Fifty years after Baldwin, the question of determinate variation in evolution seemed intact. As Waddington had put it: "it is doubtful ... whether even the most statistically minded geneticists are entirely satisfied that nothing more is involved than the sorting out of random mutations by the natural selective filter." [Waddington, 1942, 563]. Waddington's hypothesis was that by looking at how organisms develop, one could explain some of their seemingly adaptive features. He proposed a mechanism similar to Baldwin's, but framed in a genocentrist way, and with an emphasis put on the importance of canalization in development. A phenotype could be formed as a response to an external stimulus, but during the course of evolution the environmental stimulus could then be superseded by an internal genetical factor [Waddington, 1942, 563-4]. To test this hypothesis, Waddington performed some of his most famous experiments on Drosophila, showing cases of genetic assimilation [Waddington, 1953; 1959]. Using *Drosophila melanogaster*, he showed that certain phenotypes (e.g. crossveinless) can be induced by an environmental stimulus (in this case, a heat stress). He then showed that, after having selected the novel phenotype for relatively few generations (fourteen), the en-

vironmental stimulus was not necessary anymore to induce the new phenotype. Waddington interpreted his results in a neo-Darwinian way as an example of selection acting on pre-existing multi-genic variation (acting on a threshold for environmental induction), explicitly specifying that, in any case, the hypothesis that the treatment had induced new mutations "... could bring little comfort to those who wish to believe that environmental influences tend to produce heritable changes in the direction of adaptation. For there is no reason whatever to suppose that the crossveinless phenotype is adaptive to high temperature" [Waddington, 1953, 124].

In spite of these historical origins, we still find an ambiguity in the status of the Baldwin effect and genetic assimilation today, with both supporters and critics pretending to defend the Modern Synthesis [De Jong, 2005; contra Pigliucci et al., 2006].

2.2. Current models of genetic assimilations

In modern terms, the classical mechanism of genetic assimilation consists in three steps [Pigliucci et al., 2006]:

(1) A population occupies a given environment (Fig. 1, left).
(2) The environment changes, revealing capacity for plasticity within the population. Given the new selective constraints, this plasticity enables the population to persist, initially with no genetic change (Fig. 1, middle).
(3) If natural selection persists, genetic changes can make the phenotype constitutive, that is, flatten the plastic reaction norm (Fig. 1, right). This can occur because of drift (leading to lose a previously selected ability to switch phenotypes) and/or trade-offs on plasticity (e.g. a constitutive phenotype might be less costly than a plastic one).

The model of genetic accommodation of West-Eberhard [2003, 140] generalizes this hypothetical mechanism to cases where the initial phenotypic change can be either induced by environmental changes, as in step (2) above, or by mutation.

This mechanism (including West-Eberhardt's flavour) is thus one of genetic assimilation through plasticity. It relies on the assumption of a redundancy between plastic and non-plastic responses: intragenerational plasticity enables survival at the populational level, allowing time for blind heritable (i.e. non-plastic) variation to occur and take over (Fig. 2a).

Possibly because of its neo-Lamarckian flavor, this model of genetic assimilation has been charged for wrongfully attempting to contradict neo-Darwinism [De Jong, 2005].[5] However, it is clear that the model solely relies on natural

[5] In her paper, De Jong [2005] also argues against slippery uses of the vocable 'genetic assimilation' [esp. by Pigliucci and Murren, 2003], which she thinks do not fit with Waddington's use [Waddington, 1956; De Jong, 2005, 115]. Being less stringent than her on the criterium of family resemblance for the vocable, we follow here the use of Pigliucci and Murren [2003].

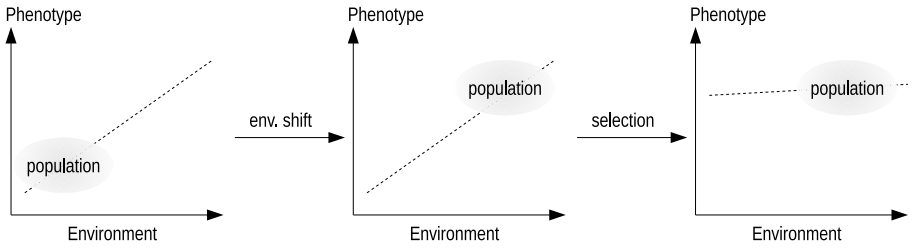

Figure 1: Mechanism of genetic assimilation [after Pigliucci et al., 2006, Fig. 2]. First, a population occupies a given environment; there is an unexpressed capacity for plasticity within the population. The environment then changes; the previously unexpressed capacity for plasticity enables the population to persist, initially with no genetic change. Genetic changes can then take place, flattening the plastic reaction norm (because of drift or trade-offs on plasticity).

selection occurring on blind genetic variation in step (3). The blindness of variation was already central to early ancestors of the model (Section 2.1) and has been repeatedly emphasized since then [Pigliucci et al., 2006].

Extensions to this model have been proposed. Two of them, which we discuss now, involve non-genetic inheritance [Klironomos et al., 2013; Danchin et al., submitted] .[6]

Klironomos et al. [2013] have proposed a model where the buffering period enabled by plasticity in step (2) above is now ensured by heritable non-genetic materials (Fig. 2b). They consider a population of individuals that can be adapted by presenting either the right profile of epigenetic marks, or the right profile of genetic variations. They consider a full redundancy between genetic and epigenetic materials, the only difference being that epigenetic marks are highly more mutable (to be sure, genetic and epigenetic mutations are blind). Simulations showed that, when experiencing a selective challenge, a population first quickly reaches the adaptive peak thanks to variation and selection on epigenetic marks, while genetic variation evolves neutrally. Then, on-peak genetic variants eventually occur by blind mutation and get fixed (being less mutable, on-peak genetic variants have a slight advantage over on-peak epigenetic variants). At this point the selective pressures bearing on epigenetic variation are released, due to the redundancy between epigenetic and genetic profiles. Epigenetic variation then evolves neutrally, while on-peak genetic variants are retained by selection. In such an evolutionary process, epigenetic and genetic systems seem tailored for adaptation at different evolutionary time-scales. This model represents a mechanism of genetic assimilation through epigenetic inheritance.

Klironomos et al. [2013]'s model surely falls within the frame of neo-Darwinism. The difference with classical genetic assimilation through plasticity is that now intergenerational epigenetic variation, and not intragenerational plasticity, en-

[6] To be precise, Klironomos et al. [2013] do not call their model a case of genetic assimilation.

ables survival at the population level while waiting for blind genetic variations to occur (step 2 above). Again, in Klironomos et al.'s model, everything which is heritable and adaptive (be it epigenetic or genetic) comes from blind variation at the individual level, fuelling natural selection or drift at the populational level.

We and collaborators have pleaded for extending these models of genetic assimilation [Danchin and Pocheville, 2014; Danchin et al., submitted] (Fig. 2c). Like previous authors, we assumed redundancy between non-genetic and genetic materials for the adaptation of the individual. In addition, we pleaded for taking into account the fact that non-genetic variation (heritable or not) can both be induced by the environment and impact genetic materials, for example when adaptive regulatory epigenetic marks favour local hypermutability of the genes they regulate [Wright et al., 1999; Wright, 2000; Gorelick, 2003], a mechanism hypothesized as early as [Davis, 1989]. Interestingly, epigenetically induced local hypermutability of genes had already been proposed by Jablonka and Lamb in the mid-90's as a model of genetic assimilation, under the term 'mutational assimilation' [Jablonka and Lamb, 1995, 167-71]. We modified the model of Klironomos et al. [2013] exposed above to incorporate first an induction of epigenetic marks by the environment (in particular, towards fit), and second a mutagenic effect of epigenetic marks on the corresponding genes. In addition, we assumed that, in some situations, the mutagenicity of epigenetic marks could be context-dependent, that is, that epigenetic marks – or non-genetic materials in general – would be particularly mutagenic only when the individuals would be off-peak. Such context-dependent mutagenicity can occur in situations where a physiological mechanisms up-regulates a gene as long as the desired physiological effect is not reached. Then, if the gene is defective and up-regulation is itself slightly mutagenic [Wright, 2000], up-regulation will continue and have more mutagenic effects until the gene becomes functional (or the individual dies). Notice that in this situation, mutagenicity can be context-dependent as an exaptation of plasticity: the context-dependence of regulation (a capacity for plasticity) provides for free the context-dependence of mutagenicity [Danchin and Pocheville, 2014].

Simulations showed that the two-steps adaptive process of Klironomos et al. [2013] is considerably hastened. The population first quickly finds the peak thanks to epigenetic materials being mutable and inducible, and on-peak genetic variants quickly occur and invade the population, thanks to the context-dependent mutagenicity of on-peak epigenetic marks. We also envisaged the hypothesis that plastic or epigenetic responses are not fully redundant with genetic responses (for instance, because of a cost, delay, or unfaithfulness of plastic responses), reaching similar results as with context-dependent mutagenicity.

In short, this model is one of genetic assimilation through epigenetic mutagenicity.

Again, this model is interpreted within the neo-Darwinian frame. Genetic materials are mutable in a context-dependent way, but for a given gene the very variations produced by mutation are supposed to be blind (see Section 4, Fig. 4). Epigenetic materials are themselves inducible, possibly towards fit, but such a

capacity for induction is supposed to ultimately rely on previous adaptations (or exaptations) provided by blind variation in the past.

3. Genetic memorization

We now argue for the possibility of mechanisms that could hasten the evolutionary process by several orders of magnitude, which would operate at the intragenerational time-scale. Notice that the intragenerational time-scale was somehow blackboxed in the models above, which contrasts with the emphasis classically put on development by authors questioning the neo-Darwinian vision of heritable variation [Jablonka and Lamb, 2005; Pigliucci and Müller, 2010; Loison, 2010, for a historical review].

3.1. Heritable physiological exploration

Our first speculation concerns what could be called 'heritable physiological exploration' at the intragenerational time-scale. Authors having exposed similar views as ours below include [Kirschner and Gerhart, 2005; Braun et al., 2011; Stern et al., 2012; Braun, 2015; Lamm and Jablonka, 2008] although we do not mean to imply that they would agree with our exposition here.

Situations may exist where an organism would be able to explore and stabilize variation at the intragenerational time-scale, and then transmit it to offspring. A putative mechanism of such a pattern would be that when facing an environmental insult, somatic cells in an organism would show (Fig. 2d):

(1) exploration: they would try several regulation profiles and/or genetic rearrangement
(2) stabilization: they would retain those regulation profiles that do the job, e.g. by epigenetic marks
(3) transmission: they would pass them on to the rest of the soma and/or to the germline – something much like Darwin's gemmules [Darwin, 1868, 374].

Hypothesis (1), exploration, is that cells (or living systems in general) are capable of blindly exploring at both the epigenetic and genetic levels, for instance by deregulating gene expression profiles or performing blind genetic rearrangements.[7]

Hypothesis (2), stabilization, is that cells (or living systems) are not totally blind with respect to their own physiological condition. More precisely, the hypothesis is that if living systems are not able to know how to reach a desired physiological condition (particularly when facing an unknown environmental challenge), at least they know when they have reached it, be it a simply viable or unstressed condition. Notice that this hypothesis departs from previous hypothetical mechanisms of non-blind variation where cells where supposed

[7] This step can also plausibly involve, when the environmental challenge is not totally new in the lineage, non-blind reaction at the epigenetic level such as adaptive plastic responses. Here we let aside this possibility that relies on past adaptation.

to select the precise molecular component (protein, RNA, DNA mutation) that would provide a positive fitness effect [Cairns et al., 1988; Cairns and Foster, 1991]. That cells be able to distinguish which molecules provided a fitness effect has been deemed implausible [e.g. Stahl, 1988; Foster and Cairns, 1992]. In our view by contrast, the whole physiological condition is selected by the system, including, possibly, 'superstitious' regulatory features which do not participate in releasing the stress, but happen to do no harm.

Hypothesis (3), transmission, is that cells are able to communicate aspects of their condition across the organism, and to realise epigenetic and/or genetic transmission of acquired traits (both in the soma and to the germen). Though highly controversial in the past, this hypothesis is now experimentally illustrated, at least regarding epigenetic inheritance. For instance, Devanapally et al. [2015] have shown that, in *C. elegans*, neurons can make double-stranded RNA which can enter the germline and cause transgenerational gene silencing [see also e.g. Szyf, 2015; Sharma, 2015; Rodgers et al., 2015; Bohacek and Mansuy, 2015].

Exploration, stabilization and transmission need not happen in a sequential way. Partially releasing a stress can come with concomitant partial stabilization and transmission. Neither do they need to happen independently in every cell, if cells happen to somehow synchronize their explorations. In some cases, natural selection among cells might also resonate with the exploratory process and amplify the prevalence of successful phenotypes.[8] Our emphasis on regulation resonates with the *cis*-regulatory hypothesis, according to which an important part of evolutionary change corresponds to changes occurring in regulatory regions rather than in coding regions [King and Wilson, 1975; Wray, 2007]. What we argue here is that this change might be initiated and directed by (parts of) the living system at the intragenerational level.

Though we initially thought to propose this model of heritable physiological exploration for theoretical reasons, several recent experimental results suggest that such or similar intragenerational mechanisms are plausible. For instance, Stern et al. [2012] have confronted the development of *Drosophila melanogaster* to an artificial toxic stress. They showed that not only was development modified, but also that the modified development could coincide with increased tolerance to the artificial challenge, and be epigenetically transmitted to the offspring (from 1 to 24 generations). Part of the modification came from the suppression of the Polycomb group genes, which play an important role in stabilizing development [see also Stern et al., 2014] In a similar vein, Braun [2015] has reviewed a set of experiments on *Saccharomyces cerevisiae*, where populations were inflicted an 'unforeseen challenge' by linking an essential gene from one biochemical pathway (HIS3 gene) to the regulatory system of another pathway (GAL promoter). The results gave a picture of adaptation which is highly non-paradigmatic:

(1) adaptation is both fast (10-30 generations) and inherited (though not sta-

[8] On intra-organismal selection see Pocheville and Montévil [2014].

bly inherited at the beginning of the process); adaptation is not due to the selection of rare advantageous phenotypes; many individual cells independently develop the adaptive phenotype as a response to the challenge (50 % on average, and up to 80 %); last, "when mutation arise, they are *induced* late in the process" (p. 11, Braun's emphasis)

(2) adaptation comes with global gene expression responses; these responses are irreproducible between replicate experiments with no dominating molecular mechanism, which indicates the exploratory nature of the adaptive process and the degeneracy of the gene expression-phenotype relation

(3) the population itself is a relevant level in the dynamics, showing slow relaxation towards a stable state far beyond the single generation time-scale (ca. 100 generations); the expression level of the rewired gene also exhibits slow collective modes (10-20 generations) that relax after ca. 100 generations. Interestingly, Braun [2015, 20] provides indirect evidence suggesting that the intercellular environment, not cellular signals, might act as a relay to synchronize cells in the population.

Arguably, these experiments are targeted at challenging the cells at the level of their gene regulatory system, precisely to investigate how cells can respond to such rewiring events when they naturally occur in the course of evolution – that is, not so rarely [Braun, 2015, 5]. The fact that rewiring events are not rare suggests that cells may have physiological responses handling (or taking advantage of) them. This might be why in these experiments genetic mutations seem to play such a minute role. This might also be why adaptation is so fast and frequent in contrast to other experiments with other kinds of severe stresses [e.g. Balaban et al., 2004]. In any case, these experiments open fascinating avenues which might strongly challenge the current view of adaptation.

3.2. Beyond the Central Dogma?

So far, the mechanisms discussed made no mention of non-blind genetic variation. One classical reason to suppose that genetic variation is blind is that it seems implausible that a living system, when facing a new challenge, is able to compute a gene product that would solve the problem and, from this, to reverse-translate the gene product so as to build a corresponding coding sequence. The impossibility of reverse-translation corresponds to the Central Dogma [Crick, 1958].[9] The mechanism, however, seems less implausible when one considers variation at the level of regulatory profiles. This is because regulation both offers unbounded variation[10] (different expression profiles can lead to drastically different phenotypes, such as lung or liver cells), and yet rely on somehow simple and quantitative, finitely describable, variation – to caricature, the change in the constitutive expression level of a gene could for instance be described as an

[9] Some have argued that reverse-translation is possible (Nashimoto, 2001, but see Cook, 1977), but we let this discussion aside here.

[10] Unbounded variation means here a kind of variation which cannot be described in advance in finite terms [Longo et al., 2012].

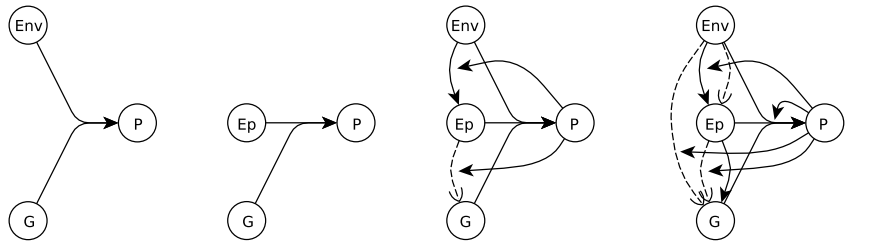

Figure 2: Models of genetic assimilation at the developmental time-scale. G: genetic variation, Env: environment, P: phenotype, Ep: epigenetic variation. Continuous lines: directed effects. Dashed lines: blind effects. (a) Classical model of genetic assimilation tracing back to Baldwin and Waddington [Pigliucci et al., 2006]. (b) Genetic assimilation through epigenetic variation [Klironomos et al., 2013]. (c) Genetic assimilation through context-dependent epigenetic induction and mutagenicity; notice the context-dependence, represented by the feedbacks from P [Danchin et al., submitted]. (d) Genetic memorization, where the phases of exploration (additional blind effects) and stabilization (additional directed effects) are represented. Intraorganismal amplification through intercellular communication and/or somatic selection is not represented.

increase, decrease, or status quo. Such a simple description of variation suggests that there is no principled reason to suppose that a cell cannot non-blindly modify the genetic sequence in the regulatory regions, for instance under the influence of epigenetic marks which are close to these regions. Notice however that the Central Dogma would remain intact, as it concerns coding regions. Such non-blind mutation might occur in particular during the stabilization phase, in which case it could be called 'genetic memorization'.

3.3. Embedded exploration

In the family of models exposed above, our model of heritable physiological exploration consists in an extension of Jablonka and Lamb [1995]'s and Danchin et al.'s models, now including an explicit intragenerational phase enabling the production of non-blind genetic variation in the offspring (Fig. 2). Notice, however, that genetic (and possibly epigenetic) variation in the exploratory phase by the cells is still blind, letting, in the end, pure chance fuelling the developmental and evolutionary processes with successful variations. (This is the case even in the hypothesis of 'genetic memorization'). Blind variation is selected by the cells (or the organism) themselves through their physiological response. This kind of selection is informed, possibly through previous adaptation or exaptation; that is, cells might know how to select their physiological condition because such an ability could have been selected in the past, or cells might have this ability as an exaptation of already existing physiology. It is also possible that blind variation be selected by natural selection occurring at the intra-organismal level, for instance between cells. Thus, 'selection' (of now two sorts: by the cells and of the cells) of blind variation is still the only explanatory resource accounting

for adaptation (but now at the individual level of phenotypic exploration and accommodation).

The immediate evolutionary consequence of such a mechanism is that the adaptive process is now embedded at the individual level, considerably hastening and widening the evolutionary process. We can draw a comparison with learning: a well known role of learning is to embed the trial-and-error phase at the individual level, enabling adaptation (or accommodation) at the scale of the individual lifetime [Hinton and Nowlan, 1987]. Now, the resulting accommodation can sometimes be transmitted to the offspring. This might lead to a non-trivial multi-scale view of adaptation, with multiple relevant evolutionary processes occurring at different time-scales, in a possibly intricate way. Eventually, our understanding of adaptation in terms of fitness might even be altered, as fitness might vary non-trivially across time-scales [Pocheville, 2010; Braun, 2015].

4. What blindness really is

In the discussion above, we highlighted the central role of blindness in the models of genetic assimilation and heritable physiological exploration. We now wish to give a formal discussion of the concept of blindness to better characterize its epistemic role in evolutionary explanations [see also Huneman, this volume, Section 4]. We will argue that blindness constitutes as much an explanatory principle as an empirical claim.

4.1. Definitions of blindness

Neo-Darwinism did not come up with a definitive concept of blind, or 'random', variation. Authors of the Modern Synthesis, for instance, did not define the words 'random' or 'chance' mutation, and used these terms in a variety of ways, fostering misunderstanding of their theses [Merlin, 2010, 3]. It is worth recalling here what the term 'random mutation' does not mean in the Modern Synthesis [Merlin, 2010; Sober, 1984, 104]. Random mutations are not mutations that are all equally probable, or inherently unpredictable, or even causally independent from the environment [Sniegowski and Lenski, 1995, 572]. Nor does randomness mean that mutations will be equally likely to turn out beneficial, deleterious or neutral. Authors of the Modern Synthesis, and before them, early neo-Darwinians such as Weismann [1893b], generally did not hold such claims. Such claims would have been, in any case, refuted by the (now common) knowledge of the induction of mutation by physical or chemical agents [Benzer and Freese, 1958], the existence of mutation hot-spots [Moxon et al., 1994; 2006], or the common assumption that most mutations are deleterious – an assumption which is, of course, context-dependent [e.g. Simpson, 1944, 55-56, quoted by Merlin, 2010, 20].

To avoid these ambiguities, mutations are sometimes said to be random with respect to their adaptive value: "A central tenet of evolutionary theory is that mutation is random with respect to its adaptive consequences for individual

organisms; that is, the production of variation precedes and does not cause adaptation." [e.g. Sniegowski and Lenski, 1995, 553]. We take this to mean that there is a statistical and/or causal independence between the probability of occurrence of a mutation and its fitness in a given environment. However, as we will see below, such an independence criterion is not yet precise enough to capture the notion of blind variation. Furthermore, because it is not clear what probability space(s) the term "randomness" is supposed to refer to (i.e. the possible variations and their probability distributions), we prefer to avoid the term and use blindness as a default instead.

Merlin [2010] provides a useful review of several concept of blind variation. They can be classified according to whether they emphasize a statistical or a causal independence criterion between mutation and fitness (Table 1). The intuitive idea grounding these criteria is that for variation to be blind, we don't want more beneficial variations to be more probable in a given environment or, if variation shows such a pattern in a given environment, at least we don't want this pattern to be consistently conserved across different environments when the selective challenge changes (Fig. 3).

In formal terms, we can characterize the statistical criterion of blindness as follows. Let's assume that we are given measures for the heritable variation v and the environment e, and a probability function $p(v, e)$ giving the probabilities of the different variations in the different environments. Let's also assume that a fitness function $w(v, e)$ can be defined. Then the statistical criterion of blindness (in Merlin's version, Table 1, with slight modifications) posits that the probability $p(v_i, e_j)$ of occurrence of v_i in e_j is blind to $w(v_i, e_j)$ when at least one of the following criteria is fulfilled:

Statistical criterion 1 The same variation is not relatively more probable in environments where it is more beneficial: $cov^{v=v_i}_{e=e_1,\ldots,e_m}(w(v,e), p(v|e)) = 0$. Here the covariance is computed for a given variation in different environments (environments being equally weighted).[12] For non-blindness to be weak or strong, this criterion would have to be refuted for respectively some or most variations.

Statistical criterion 2 A variation is not more probable than other less beneficial variations, in a given environment: $cov^{v=v_1,\ldots,v_n}_{e=e_j}(w(v,e), p(v|e)) = 0$.

[11] Merlin [2010] does provide a statistical criterion but frames her discussion in causal terms: "According to the most influential and persistent meaning in biology, variations are not caused because they can provide adaptation to the individual organisms concerned and their offspring." (p. 20, n4, see also her n11 criticizing Sarkar [1991]'s criterion for being statistical). This slight discrepancy probably comes from the difficulty to frame a causal independence criterion in verbal terms when probabilities come into the dance, hence the proposal made here.

[12] To avoid capturing non-relevant effects such as some environments raising the fitness or probability of all variations, or increasing the variances of the variables w and p without any skew, w and p in a given environment have to be standardized by their mean and standard deviation across all variations in that environment (variations being equally weighted).

Table 1: Criteria of blind variation

Statistical criterion	Causal criterion
"[T]he term 'randomness' as applied to mutation often refers to the lack of correspondence of phenotypic effect with the stimulus and with the actual or the adaptive direction of evolution." [Simpson, 1953b, 86-87] A mutation is directed "if it occurs (or occurs more frequently) in the fitness-enhancing or 'selective' environment", i.e., "in an environment where its associated phenotype has an enhanced fitness." [Sarkar, 1991, quoted by Merlin, 2010, 20, n11] "A mutation is 'directed' if and only if it fulfills the two following conditions: (1) It is more probable in an environment where it is beneficial than in another environment where it is deleterious or neutral (2) It is clearly more probable in an environment where it is beneficial than other deleterious or neutral mutations (in the same environment)." [Merlin, 2010, 7][11]	"The defensible idea in the claim that mutations is random is simply that mutations do not occur because they would be beneficial. (...) It is a little misleading to summarize this result by saying that "mutations occur at random." One might just as well say that the weather occurs at random, since rain doesn't fall because it would be beneficial." [Sober, 1984, 105] "We define as directed a mutation that occurs at a higher rate specifically when (and even because) it is advantageous to the organism, whereas comparable increases in rate do not occur either (i) in the same environment for similar mutations that are not advantageous or (ii) for the same mutation in similar environments where it is not advantageous." [Lenski and Mittler, 1993, 188] "[A] mutation is directed if and only if it is specifically caused by environmental stress in an exclusively adaptive manner" [Millstein, 1997, 151]

Now the covariance is computed for different variations in a given environment (variations being equally weighted). For non-blindness to be weak or strong, this criterion would have to be refuted in respectively some or most environments.

This formalism is purposely simple for illustration and of course comes with the limitations of the covariance formalism. In particular, such criteria do not reflect statistical independence per se, but the less stringent criterion of an absence of direction in the relationship between the variables w and p. In any case, we are confident that other formalisms would not change the rest of the argument.[13]

Arguably, a statistical criterion of blindness is not enough to speak of blindness in causal terms. This is because confounding factors can blur or create any directional relationship between variables. To be able to speak of causation, one has to intervene on the system, so as to break any spurious (non)-directional relationship between variables.[14] A causal equivalent of the formal statistical criterion of blindness can be obtained by intervening on the environment to artificially change the selective pressures at play, while keeping the rest of the system constant. In equations, the fact that the value of the environment is now fixed by an intervention can be written by putting a hat $\widehat{\ }$ on the variable e (this is a common notation). Then, the two criteria above become:

Causal criterion 1 $cov^{v=v_i}_{e=e_1,\ldots,e_m}(w(v,\hat{e}),p(v|\hat{e})) = 0$; the covariance is computed for a given variation in different environments each fixed by an intervention; variables are standardized as above.

Causal criterion 2 $cov^{v=v_1,\ldots,v_n}_{e=e_j}(w(v,\hat{e}),p(v|\hat{e})) = 0$; the covariance is now computed for different variations in a given environment (fixed by an intervention).

These criteria come close to what would be a causal criterion of blindness, that is, a formal criterion translating the idea that an heritable variation does not occur because of its adaptive value.

4.2. Levels of blindness

The criteria (1) and (2) of blindness can be applied at several levels. For instance, we can speak of genetic variation being blind at the level of the genome or at the level of the locus (up to the level of the nucleotide). Imagine a mutator mechanism that changes the probability of several loci to be mutated in different

[13] These criteria will be violated as well in the case of non-blindness for worse, that is when more beneficial variations are less probable.

[14] We embrace here the interventionist view of causation, which we find the most operative for experimental sciences. See Woodward [2003] for a philosophical introduction; Pearl [2000] for a formal introduction; Ay and Polani [2008] for a formal criterion of causal independence; and Griffiths et al. [2015] and [Pocheville, submitted] for formal measures of causation applied to biology.

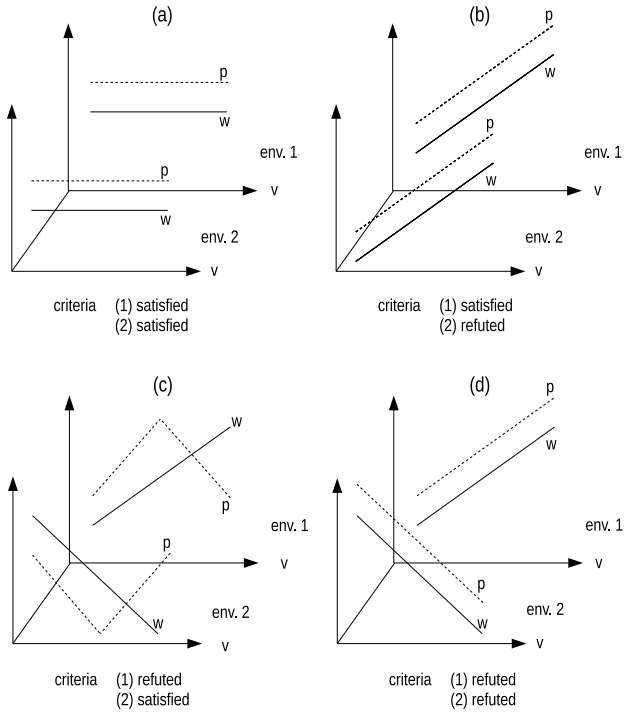

Figure 3: Four situations illustrating the criteria of non-blind variation. v: variations; p, w: probability of appearance and fitness of each variation in a given environment; env: environment. (a), (b), (c) illustrate blind variation, (d) illustrates non-blind variation. (a) The probabilities and fitnesses of the variations are not context-dependent (both criteria are satisfied). (b) In a given environment beneficial variations are more probable (criterion 2 refuted), but for a given variation its probability of occurrence does not depend on its fitness across environments in which the living system can live, thus the system cannot be said to non-blindly respond to these environments (criterion 1 satisfied). (c) For a given variation, the probability of occurrence does depend on its fitness across environments (criterion 1 refuted), however in a given environment more beneficial variations are not more probable than other variations (criterion 2 satisfied). (d) In a given environment more beneficial variations are more probable (criterion 2 refuted) and for a given variation, its probability of occurrence is higher in environments where it is more beneficial (criterion 1 refuted). This last situation illustrates non-blind variation.

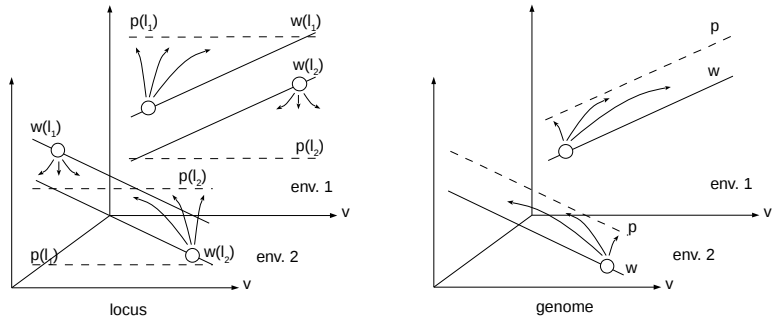

Figure 4: Blind variation at the locus level leading to non-blind variation at the genomic level. A living system is put in environment 1, where its current variation at locus 1 does worse than average, while its current variation at locus 2 does better than average. By increasing the mutation rate preferentially at locus 1, the living system would increase its chances of doing better while avoiding the cost of mutating locus 2, even when mutation is blind at locus 1. The situation would be similar in environment 2, if the variation at locus 2 were now the one which did worse than average.

environments in an adaptive way (as we proposed above), but which lets the relative probability distribution of mutations unchanged for each locus. Such a mechanism would be non-blind at the level of the genome, but still blind at the level of the locus (Fig. 4). This kind of blindness can be formally expressed by conditioning on the locus of study: we would simply replace $p(v_i|\hat{e}_j)$ by $p(v_i|\hat{e}_j, \hat{l}_k)$ in the criteria above, where l_k is the locus producing variation v_i, and we would restrict the formula to the variation produced at that given locus. From a mechanistic point of view, such a conditioning enables to show how, for instance, non-blind variation at the level of the genome can be obtained without refuting the Central Dogma at the level of the gene (as far as coding regions are concerned). From an evolutionary point of view however, the fact that variation is non-blind at a given level remains significant.

4.3. Epistemological status of blindness

There is an epistemological difficulty in the causal criteria of blindness given above which is worth spelling out. Usually, when we say that a putative cause has no effect on a putative effect, we mean that there is no relation between any intervention on the cause and the value obtained for the effect (this would for instance result in a null covariance between the manipulated cause and the effect).

Now, when we say that variations do not occur because of their fitness, the putative cause in question is, supposedly, fitness, the putative effect being the probability of occurrence of variations. However, the putative cause bearing a hat in our formula above is the environment, not fitness. That is, both terms in the covariance (fitness and probability of occurrence) are now effects of a putative intervention on the environment. Ideally, we might have desired to

contrast a term reflecting the cause only, bearing a hat, (i.e. fitness) and a term being the effect only, with no hat (i.e. the probability distribution of variations).

However, since fitness is a function of the variation and the environment, it is impossible to manipulate the fitness of a given variation independently from the environment, and thus without potentially affecting at the same time the probability of occurrence of that variation in that environment.[15] In formal terms, the fitness is not 'modular' with respect to the variation and the environment.[16] Thus, we cannot check whether fitness is a cause increasing the probability of occurrence. This means one cannot distinguish the direct effects of the environment [Darwin, 1859, 11] on the probability distribution of variations, from the effects of an adaptive system which would sense the environment and produce variations according to their fitnesses in that environment.[17] Thus, we cannot distinguish fitness from the environment as a cause of non-blind variation. Statements such as mutations not occurring "because they would be beneficial" [Sober, 1984, 105], or "advantageous to the organism" [Lenski and Mittler, 1993, 188] are, taken literally, causal claims where the cause is not open to manipulation. They are useful as catchphrases, but they are empirically empty.[18]

By contrast, the causal criteria of blindness given above constitute an empirically testable claim: variations can surely occur because of the environment, but any directional association (if any) between the fitness and the probability of variations should not be consistently conserved when drastically changing the adaptive challenge.

There is, however, more to the tenet of blind variation than a mere empirical claim. It is also an explanatory principle. Namely, we do not need to suppose that adaptive variations have a special reason to be produced, that is to say we do not need to suppose any other explanation of design than natural selection, because natural selection is enough. This is, for instance, how Sniegowski and Lenski [1995, 556] read (in part) the wide acceptance of the hypothesis of random mutations among geneticists and evolutionary biologists in the 1930's, before direct experimental evidence. The virtue of such an explanatory principle is that it provides a kind of teleological void from which teleological explanations can be derived. This principle is an explanatory choice, that is, it consists in segregating out of the theory other (compatible) explanatory schemes. It is

[15] Paul Griffiths, whom I warmly thank, pointed to my attention that Waddington precisely seems to be able to manipulate the fitness independently of the environment. Indeed, Waddington arbitrarily selects the crossveinless phenotype, which he supposes is not adaptive to high temperatures [Waddington, 1953, 124]. The contradiction dances on an ambiguity in the term fitness. Waddington, say, is external to his experimental set-up. What he does, then, is not to modify the adaptive value (engineering fitness) of the crossveinless phenotype, but the realized reproductive success. The latter is only a proxy for the former – and there is no mystery a proxy can be manipulated independently of its target.

[16] On modularity see Woodward [2003, 329], Pearl [2000, 42], [Pocheville and Montévil, submitted].

[17] We thank Philippe Huneman for this formulation.

[18] This consideration, of course, holds only insofar as we adopt an interventionist stance on causal claims.

not an empirical claim, but it is not independent from empirical results either. For, of course, if we were to find consistent non-blind variation (as defined above) across various circumstances, we would have to seek for alternative or complementary explanatory schemes for this fact.

4.4. Implausibility of non-blindness

It has been claimed that finding consistent non-blind heritable variation in the living is implausible, particularly as regards genetic variation.

A first reason is the implausibility that a physiological mechanism producing non-blind variation be generated in evolutionary history. The problem of finding (in advance) which variation will be beneficial seems an uncomputable problem for a living system [Merlin, 2010, 15]. Rephrased in our own terms, the objection is that living systems seem to be complex systems in somehow critical situations, where small changes can have drastic effects, immersed in spatially and temporally heterogeneous (and similarly unpredictable) environments. However, strictly speaking our theories of biological functioning are too scarce yet to decide what is or is not computable for living systems. At least, it seems that the recruitment of similar mechanisms for plasticity and adaptive processes may provide exaptative pathways to mechanisms of non-blind variation, in particular as regards the regulatory patterns [Jablonka, 2013; Danchin and Pocheville, 2014].

A second reason to dismiss the possibility of non-blind variation is that it might not be evolutionarily advantageous. A mechanism linking heritable variation to the state of the environment could jeopardize the heritable materials. For instance, the sequestration of heritable materials from external influences provides protection against noisy environments [Piraveenan et al., 2007]. This sequestration hypothesis, however, does not preclude the possibility of a beneficial directed influence from the environment in stressful situations. Actually, we would argue that non-blindness should constitute a large evolutionary attractor: mechanisms of heritable non-blind variation, once come into existence (for instance as an exaptation of plasticity), should tend to be selected because of their positive effects, which may also result in a virtuous circle if these mechanisms happened to favour the improvement of non-blindness itself. Non-blindness may thus be advantageous at the level of first order (non-blind variation) and second order (non-blind evolvability) evolutionary processes. We are not going to defend such an optimistic view here; suffice it to remark that the sequestration of heritable materials (if any sequestration) may also be discriminatory in a beneficial manner, and that non-blindness may indeed be evolutionarily advantageous. This line of reasoning, when pushed to the limit, could as well lead to interpreting any occurrence of non-blind variation as the result of past selective processes (on blind variation of variation-producing mechanisms).

Yet another argument against non-blind variation is one of epistemological implausibility. There are indeed good reasons to consider that assessing which variations are possible in advance, as well as their respective adaptive (or physiological) value, is an uncomputable problem for us (though not necessarily for the living system) in the current state of science [Longo et al., 2012]. If listing

possible and beneficial variations is uncomputable for us, a handy hypothesis to model evolution is that of blind variation. We think this is why, to our knowledge, all models of heritable non-blind variation in fine rely on blind variation of some sort.

5. Conclusion

In this contribution, we emphasized the compatibility of most models of genetic assimilation with the most orthodox neo-Darwinism. We also proposed slightly more challenging views.

Historically, the Baldwin effect and genetic assimilation have been designed as a defence of neo-Darwinism, even if neo-Lamarckians and others may have intended to use it as an argument for their own views. These mechanisms indeed rely on selection of heritable blind variation to produce heritable adaptive change. In the current view, genetic assimilation relies on a hypothetical redundancy between the plastic response and the genetic variation, which enables classical selection (or drift) to take place on the reaction norm [Pigliucci et al., 2006]. In Klironomos et al. [2013]'s model, heritable epigenetic variation now plays the role previously played by intragenerational plasticity, but the role of natural selection acting on blind variation (epigenetic or genetic) is intact. In Jablonka and Lamb [1995]'s and Danchin et al.'s models, the case is more subtle. Due to the inducibility of epigenetic variation which leads to targeted mutagenicity at the locus level, genetic variation is now non-blind at the genomic level. As we have seen, genetic variation is still blind at the locus level, however, and the Central Dogma is left unaffected.

We proposed a more stringent model of genetic assimilation where genetic variation is not necessarily blind, thanks to exploration and encoding at the individual level. This model relies on a central role of regulation in evolution and development, postulating that regulation enables unbounded variation to emerge from somehow bounded variation. Yet, the role of blind variation remains central: it is selection of blind variation (at the individual level) which explains how physiological exploration can be successful.

This permanence of blind variation in adaptive explanations is not fortuitous. It comes from the fact that blindness is epistemically economical, enabling to explain adaptations that literally come from nowhere, in that blindness is precisely that which does not seem to require an explanation. This is probably where the core of the neo-Darwinian paradigm lies.

In general, we are confident that the empirical implausibility of non-blindness will be refuted by biology – there might well be some patterns of non-blind variation in some specific, or not so specific, situations. But understanding these patterns with mechanisms that do not rely in fine on blind variation will require to get out of our current theoretical conceptions of the living.

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Étienne Danchin is Director of research at the French CNRS, formerly leading the laboratory Évolution & Diversité Biologique (EDB) in Toulouse regrouping 50 researchers and university teachers (from the Université Paul Sabatier), plus about 50 PhD students and postdocs. He also co-lead a Laboratoire d'Excellence 'TULIP' that regroups five laboratories totalling 400 staff members. He is an expert in behavioural ecology for which he wrote a textbook published by Oxford University Press. His fields of interest range from social information use in habitat and mate choices to the evolution of coloniality in birds, as well as cultural evolution and information flows as determinants of ecological and evolutionary dynamics. He advocates the necessity to generalize the Modern Synthesis of evolution into an inclusive evolutionary synthesis by incorporating all the dimensions of non-genetic inheritance. He also studies costs of multiple mating in birds through sperm ageing and sperm-mediated bacterial transmission.

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