

Avatars of information: towards an inclusive evolutionary synthesis

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Following the discovery that inheritance entails the interaction between genetic and nongenetic processes, biology is undergoing a profound mutation. This paradigm shift implies that the model of heredity that is emerging incorporates genetic and nongenetic processes. A way to integrate all forms of inheritance harmoniously is to consider what unifies genetic and nongenetic heredity. Here, I unify all sources of phenotypic variation within the concept of information and its avatars, discuss a major overlooked methodological problem leading to confounding sources of variation (namely the case of the missing heritability), propose new research avenues, and illustrate how putting concepts of information at the heart of evolutionary approaches will affect the emerging Inclusive Evolutionary Synthesis.

The current call for an 'Inclusive Evolutionary Synthesis'

Biology is undergoing a profound mutation stimulated by discoveries in various fields, including behavioral [1–5] and developmental biology [6–8], as well as epigenetics [9–11] and evolutionary ecology [12–14]. New evidence from these scientific domains led several authors to converge in calling for modernizing the Modern Synthesis of evolution [1,6,8,14–16]. Evolutionary biologists have underlined the importance of formalizing current discoveries in terms of heredity [2,17] to enable the quantitative study of the various sources of phenotypic variation and their consequences in terms of natural selection and evolution [2,5,13,14,17,18]. Today, this weight of evidence implies that the idea that the inheritance of phenotypic variation only rests on genetic variation is no longer tenable [5,14]. Instead, the model of heredity that is emerging incorporates not only genetic, but also nongenetic inheritance into an 'inclusive' [13] evolutionary synthesis [1,5] (equivalent terms used by other authors are 'generalized' [17], 'extended' [8,19], or 'pluralistic' [20] theory of evolution).

In a recent Opinion in *TREE*, Russell Bonduriansky [5] placed this major scientific movement into its historical context, highlighting the controversy between hard and soft inheritance (see **Glossary**) that was at the heart of the building of the Modern Synthesis of evolution during the first half of the 20th century. Bonduriansky discussed how

the evolution of ideas about heredity has been narrowed by the major discoveries of the laws of genetics and the DNA molecule as the material basis of genes. Understandably, we have been so fascinated by the fantastic capacity of genes to encode and transfer information across generations that we became oblivious to evidence of other mechanisms of inheritance. Furthermore, even once it has been recognized that inheritance can encompass the effect of nongenetic mechanisms, the risk of viewing them as parallel and largely independent processes that concur in producing heredity is high. For instance, Günter P. Wagner's claim that 'we know that language, though highly heritable, is entirely nongenetic in its mode of transmission' (<http://news.cell.com/discussions/trends-in-ecology-and-evolution/rethinking-inheritance>) seems to deny the possibility that language inheritance results from interactions between the genetic capacity to learn language and the social environment.

A way to integrate all forms of inheritance harmoniously can be to consider what unifies genetic and nongenetic

Glossary

Culture: part of variation in a trait that is socially transmitted to offspring [21]. Culture thus incorporates all the information that is inherited through social learning, such as song dialects in birds and whales, language in humans, sexual preferences as revealed by mate copying, and so on.

Epistasis: phenomenon where the effects of one gene are modified by one or several other genes; also called 'epistatic interactions'.

Genome-wide association studies (GWAS): analyze the statistical association between the genetic variation observed at very high numbers of genetic markers distributed across the entire genome and phenotypic variation; only account for additive effects.

Hard inheritance: model of heredity based on the transmission from parents to offspring, at conception, of a set of factors whose nature is unaffected by the environment or phenotype of the parents [5].

Heritability: part of variation in a trait that is genetically transmitted to offspring

Inclusive heritability: heredity of differences, whatever the mechanism of transmission.

Information: any factor that can affect the phenotype in ways that may (or may not) influence fitness [21]. Consequently, phenotypic variation results from variation in the information possessed by individual organisms.

Modern Synthesis of evolution: merging of Darwinism with genetics that occurred from the 1930s to the 1950s.

Nongenetic inheritance: part of variation in a trait that is transmitted to offspring through mechanisms other than genetic variation.

Soft inheritance: 'the belief in a gradual change of the genetic material itself, either by use or disuse, or by some internal progressive tendencies, or through the direct effect of the environment' [61]. This original definition implies direct changes to DNA sequences. This term is sometimes used unduly to describe nongenetic inheritance (e.g., [62]).

Transgenerational epigenetic inheritance: part of variation in a trait that is transmitted to offspring through variation in epigenetic marks (DNA methylation and acetylation, histone modifications, genetic imprinting, miRNAs, and prions) [25].

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heredity. In this article, I (i) unify all sources of phenotypic variations within the concept of information and define an information-driven approach to evolution; (ii) discuss a major overlooked methodological problem leading to confounding sources of variation; and (iii) illustrate how putting concepts of information at the heart of evolutionary approaches will affect the emerging inclusive evolutionary synthesis.

An information-driven approach to ecology and evolution

Information and phenotypic variation

To understand the roots of the current paradigm shift, it is necessary to return to the essence of life, namely the capacity of organisms to reproduce. Reproduction entails the transmission of some information from one generation to the next. Information is a concept that is particularly difficult to grasp in biology. One definition is any ‘factor that can affect the phenotype in ways that may [or may not] influence fitness’ [21]. According to this view, phenotypic variation arises from the fact that different organisms do not have the same information, including variation in not only their genes, but also all aspects of their environment. Thus, decomposing phenotypic variation into its various components is equivalent to studying the various sources of information that organisms have (Figure 1).

Genes, information, and avatars

Genes are often described as sequences of DNA. However, this does not describe their true nature [22]. An equivalent would be to say that the last film of a given director ‘is this

CD’. The CD is not the film, but just one of its avatars (i.e., a material form taken by an abstract entity, here the story conveyed by the film). Films can have various avatars, such as a series of still images on a celluloid film, a magnetic tape, a DVD, or an electronic file that can be downloaded on the web. A film is not one of its avatars, but rather a story with various characters, images, and music. Similarly, the DNA sequence is an avatar of genetic information [23,24] and, accordingly, recent definitions of genes stress their functional aspects [22]. It is the genetic information, not the DNA molecule *per se*, that is the target of natural selection [23].

Distinguishing biological information from its avatars is important because the properties of the avatars determine laws of inheritance. For instance, the properties of genetic inheritance emerge from those of the DNA and the molecular and behavioral machinery that duplicate and transfer genetic information across generations. Similarly, it is the properties of avatars of transgenerational epigenetic information, which include DNA methylation and acetylation, histone modifications, genomic imprinting, miRNAs, and prions [25], that determine laws of epigenetic inheritance. Together, these various patterns can be viewed as an epigenetic code that is transferred across generations.

Interactions between the mechanistic and evolutionary approaches

The laws of genetics were discovered during the first decades of the 20th century, long before the discovery of the genetic avatar (i.e., DNA) in the middle of that same century. This multidecade lag shows that it is possible to study the general laws of an inheritance system in the absence of knowledge about its avatar, which is currently the case for most nongenetic inheritance systems. However, it is only after the discovery of the avatar of genetic information that molecular biology and its amazing implications emerged as a new field of biology. Similarly, the study of epigenetics and epigenetic inheritance really accelerated during the past decade, when new technologies enabled the high-throughput study of one of its avatars, in the form of DNA methylation patterns.

Today, many molecular genetic approaches focus on the mechanisms resulting from the detailed properties of the avatar of genetic information. Contrastingly, in the absence of knowledge about the avatars of most nongenetic information, current nongenetic studies focus on informational dynamics to establish general laws about these systems to understand their impact on evolutionary dynamics.

Potential information becomes realized information during development

Genetic information constitutes potential information (see [21]) that is only realized when confronted by environmental information. More generally, development necessarily entails interactions between the various sources of information possessed by individuals, be they inclusively heritable [13] or not, genetic or nongenetic [14].

Moreover, adopting an information-driven approach to ecology and evolution can foster the long called for reconciliation between developmental and evolutionary sciences [15]. Selection acts on phenotypes that result from the

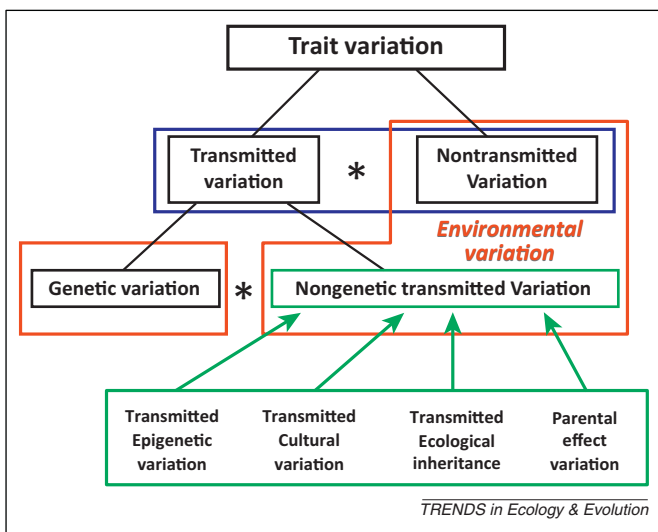


Figure 1. A comprehensive diagram of phenotypic variation accounting for all forms of information inheritance. Evolutionary biologists are particularly interested in estimating the part of phenotypic variation that is transmitted to the next generation because evolution can only affect those traits that are heritable (i.e., whose variation is transmitted to the next generation) [63]. Although genetic information fulfills this important characteristic, it has become clear that this is not the only type of information that is transferred across generations in an inclusively heritable fashion [14]. The bottom green box lists the domains of the biological literature that provide evidence for nongenetic transmitted variation. In red, the current classical partitioning of phenotypic variation, which unavoidably leads to the discarding of some nongenetically transmitted information despite the fact that it is part of evolutionary processes. In blue, the proposed partitioning of phenotypic variance. See [13,14] for definitions of the various nongenetic terms. Stars represent potential interactions among the various components. Adapted from [13,14].

cumulated effects of all the information obtained during previous life of these organisms. Nongenetic heredity further suggests that the inherited information of every organism incorporates genetic and nongenetic information, which condense the history of ancient and recent ancestors (Figures 1 and 2A). Thus, the various types of information in Figure 1 that interact in the building of the phenotype were not only obtained during the lifetime of that organism, but were also cumulated and genetically or nongenetically encoded during the lifetimes of its ancestors.

Distinguishing among the various forms of information inheritance

Thinking about heredity in terms of information inheritance can cast new light on one of the major enigmas of current molecular biology, namely the missing heritability.

So-called genetic traits that prove to be partly nongenetic

As developed above, several elements show that the nongenetic part of inclusive heritability is non-negligible [14]. Increasing numbers of traits that used to be interpreted as mostly, if not purely, inherited genetically are being discovered to be partly inherited nongenetically [13]. Many examples reveal how nongenetic and genetic effects are easily confounded and how nongenetic information can affect adaptation (Box 1). This also illustrates the risk of inferring transmission mechanisms from the sole patterns of resemblance. I expect that more cases will be revealed in which supposedly genetically heritable traits are shown to be inherited nongenetically when researchers study the detailed mechanisms responsible for the inheritance of the study trait.

Overlapping transgenerational pathways of information

All measurements of heritability estimate the statistical link between phenotypic resemblance and kinship. According to the methods, kinship is reduced to the sole parent–offspring relation, as in parent–offspring regressions or, in the best case, encompasses a vast array of kin relations, as in the animal model [26]. The latter method incorporates pedigrees to exploit all the types of kinship existing between pairs of individuals (parent–offspring, siblings, cousins, grandparents, etc.) to extract the part of phenotypic resemblance that is statistically explained by the kinship link.

However, nongenetic information mostly follows the same path as genetic information along lineages (i.e., from parents to offspring). This implies that, in the statistical models, the genetic kinship captures the effect of not only genetic information, but also of the vertically inherited nongenetic information. Thus, models estimate the amount of vertical transmission across generations, an unknown part of which being genetic. Despite this large overlap in the transgenerational pathways of genetic and nongenetic information, the estimated statistical parameter is usually interpreted as revealing gene similarity and, thus, genetic heritability. The only exception is the case of human language inheritance, where we would interpret the statistical parameter estimated from the genealogies of various families from countries speaking different

Box 1. Examples of traits partly inherited nongenetically

A natural ‘mutant’ was described by Linnaeus in the toadflax *Linaria vulgaris* more than 250 years ago [64]. Flowers of the wild type have five petals that are united in a tube ending in four separate lobes with a clear bilateral symmetry. In the peloric form, the five petals are identical and resemble the ventral petal of the wild type and the flower symmetry is purely axial. The peloric mutant was considered to be recessive [64]. However, in 1999, Cubas *et al.* [64] found that there is no mutation; rather, in the peloric form, the *Lcyc* gene known to affect flower symmetry in *Antirrhinum* is highly methylated and transcriptionally silent [64]. The methylation pattern is inclusively heritable and cosegregates with the peloric phenotype [64]. Thus, one of the very first examples of ‘mutations’ affecting morphology happens to be an ‘epimutation’, the heritability of which does not rest on variation in the DNA sequence but rather on the transmission of the methylation pattern.

Similarly, in two sympatric sister species of the cichlid fishes *Pundamilia pundamilia* and *Pundamilia nyererei*, mate choice experiments in which females were free to choose among two males, one of each species, led to the conclusion that ‘female mating preferences between the sister species are heritable, possibly with high heritabilities, and that few but probably more than one genetic loci contribute to this behavioral trait with no apparent dominance’ [65]. However, the same pattern would be observed if fry were imprinted on their parents during parental care. In a subsequent study, fry were cross-fostered between the two sister species, resulting in the reversal of the preference of each species for its own kind [66]. This finding suggests that the inclusive heritability of female mating preferences is substantially explained by early social imprinting [66] rather than by genes alone. The divergence of these two species thus appears to be at least partially stem from culturally inherited differences [66].

Finally, in *Campanulastrum americanum*, a forest plant dweller that can grow in understory or in open light gaps, experiments showed that seeds that are planted in the same light environment as their mother plant have fitness that is, on average, 3.4 times higher than that of sibling seeds planted in the alternative light environment [67]. Furthermore, the effect of maternal light environment on fitness varied among families, suggesting that there are also other inherited components of fitness. In plants, most seeds disperse at a very short distance from the mother stem, so that seeds usually germinate in the same light environment as their mother. This example shows that there is transgenerational information transfer about light environment and that such nongenetically inherited information can be adaptive.

languages mainly, if not only, in terms of social learning, because we know that languages are mostly inherited socially. However, in most traits, the inheritance system is unknown and, thus, it is impossible to attribute *a priori* heritability estimates to one or another inheritance system. The consequence is that, because of the large overlap in genetic and nongenetic information inheritance pathways, most measures of ‘genetic’ heritability are likely to incorporate the effect of some nongenetic inheritance and, thus, are overestimated.

Missing heritability

This overestimation of genetic heritability can help explain one of the major puzzles of current evolutionary biology, that of ‘missing heritability’ [27,28]. The puzzle comes from genome-wide association studies (GWAS), which analyze how the genetic variation observed at very high numbers of genetic markers (often >500 000) distributed across the entire genome is statistically associated with phenotypic variation. A recurrent and surprising result is that GWAS often explain only a small proportion of the estimated

heritability of these traits (sometimes, amazingly, no more than 5%) [27,28]. Studies concern the inheritance of various morphological traits in plants [29] and animals [30] as well as human disorders, such as Alzheimer's disease [31], psoriasis [32], schizophrenia [33], immune [34] or cardiac [35] dysfunctions, and so on. This discrepancy between total genetic variation associated with a trait and its estimated heritability is all the more puzzling given that most of these studies used vast numbers of genetic markers. Several publications propose explanations to the missing heritability, thus fostering an ongoing controversy [36].

The proportion of heritability explained by GWAS is the ratio of the heritability estimated from GWAS (numerator), to the heritability inferred indirectly from population data (denominator, which is estimated using the methods described in the previous section) [37]. Several mechanisms can explain this discrepancy, including epistasis, gene–environment interactions, the nondetection of genes with very small additive effects [38,39], as well as an insufficient number of genetic markers leading to the absence of markers in some key genomic regions that, together, can lead to the missing of some rare variants [28,38,39]. Whereas most of these explanations focus on potential underestimations of the numerator, the problem might come from an overestimation of the denominator due to genetic interactions [37]. The effects of epistatic interactions are ignored in GWAS, but are included in population estimates of heritability, which, by inflating the denominator diminishes the estimated proportions of heritability explained in GWAS.

Nongenetic information and missing heritability

Another largely overlooked explanation of the missing heritability problem is that population heritability estimates are greatly inflated because of the overlaps between genetic and nongenetic information pathways along lineages [40]. The missing heritability might thus partly result from the inclusion of nongenetic inheritance in population heritability estimates [40,41].

Therefore, whereas nongenetic inheritance has typically been considered to be negligible, the occurrence of missing heritability suggests that it constitutes a significant part of inclusive inheritance. The solution to missing heritability also lies in incorporating nongenetic information into the debate. A first, albeit insufficient, step to do so is to incorporate transgenerational epigenetic inheritance in epigenome-wide association studies (EWAS) that integrate the inheritance of DNA methylation patterns [11,42]. Coupled with GWAS, EWAS would likely estimate the proportion of heritability explained by both genetic and methylation information. GWAS and EWAS were developed because we know the avatars of genetic and some epigenetic information. Unfortunately, the fact that, at this stage, we do not know the avatars of other forms of nongenetically inherited information constrains us from generalizing this approach to incorporate all forms of inherited information into a sort of 'informome-wide association study'.

Implications and applications of an information-driven approach to evolution

Adopting an information-driven approach to evolution changes the way in which we envisage ecological and

evolutionary processes. It even led to the redefinition of evolution as 'the process by which the frequencies of variants in a population change over time' [13,14,43], the term 'variant' replacing the word 'gene' to incorporate all forms of inherited information, be it genetic or nongenetic. Note that, according to this definition of biological information that equates variation in information with phenotypic variation [21], the term 'variant' could be replaced by the word 'information' (as defined in [21] as well as in this article).

Unifying transmitted and nontransmitted forms of information

Putting concepts of information at the center of an inclusive modern synthesis of evolution unifies all components of phenotypic variation into a single framework (Figure 2). This can be achieved by identifying the selective pressures that potentially favor the encoding of such, or such environmental characteristics, in a way that matches the type of environmental variation (Figure 2B) with the advantages and disadvantages of the information encoding systems (Figure 2A).

This approach predicts the existence of some association between the type of inheritance system and the type of environmental variation. For instance, for information that varies too rapidly relative to generation time (right side of Figure 2), there is no selection for any transmission to the next generation. This can explain most nontransmitted phenotypic variation (Figure 2A). At the other extreme, some environmental characteristics are so stable (left side of Figure 2) that selection favors their encoding in a similarly rigid and mostly irreversible system to that of genetics. For factors that vary with intermediate rates of predictability, selection probably does not favor genetic encoding, but rather their transmission through reversible systems as this would enable the tracking of environmental change, a possibility that genetic encoding would hardly allow. Cultural inheritance, for instance, may enable the inheritance of information that is stable over several generations, but in a way that is sufficiently plastic to allow culturally inherited information potentially to track environmental changes. There is thus no selection for encoding such information more rigidly. Finally, transgenerational epigenetic inheritance (examples in Box 1) may encode even more stable, but still not totally stable, environmental information in a way that may be more rigid than culture, but that is still reversible.

The conclusion is that the various inheritance systems can transmit different types of environmental characteristic. Although purely verbal, these 'at equilibrium' theoretical predictions about the type of encoding of specific environmental characteristics need to be tested theoretically and empirically. It may well be that, in nature, because of the resilience of the system, the encoding of environmental information is not as optimal as that.

Avatars and hard to soft inheritance

The contrast between genetic versus nongenetic inheritance differs from that between hard versus soft inheritance (Figure 2A) because soft inheritance implies changes in

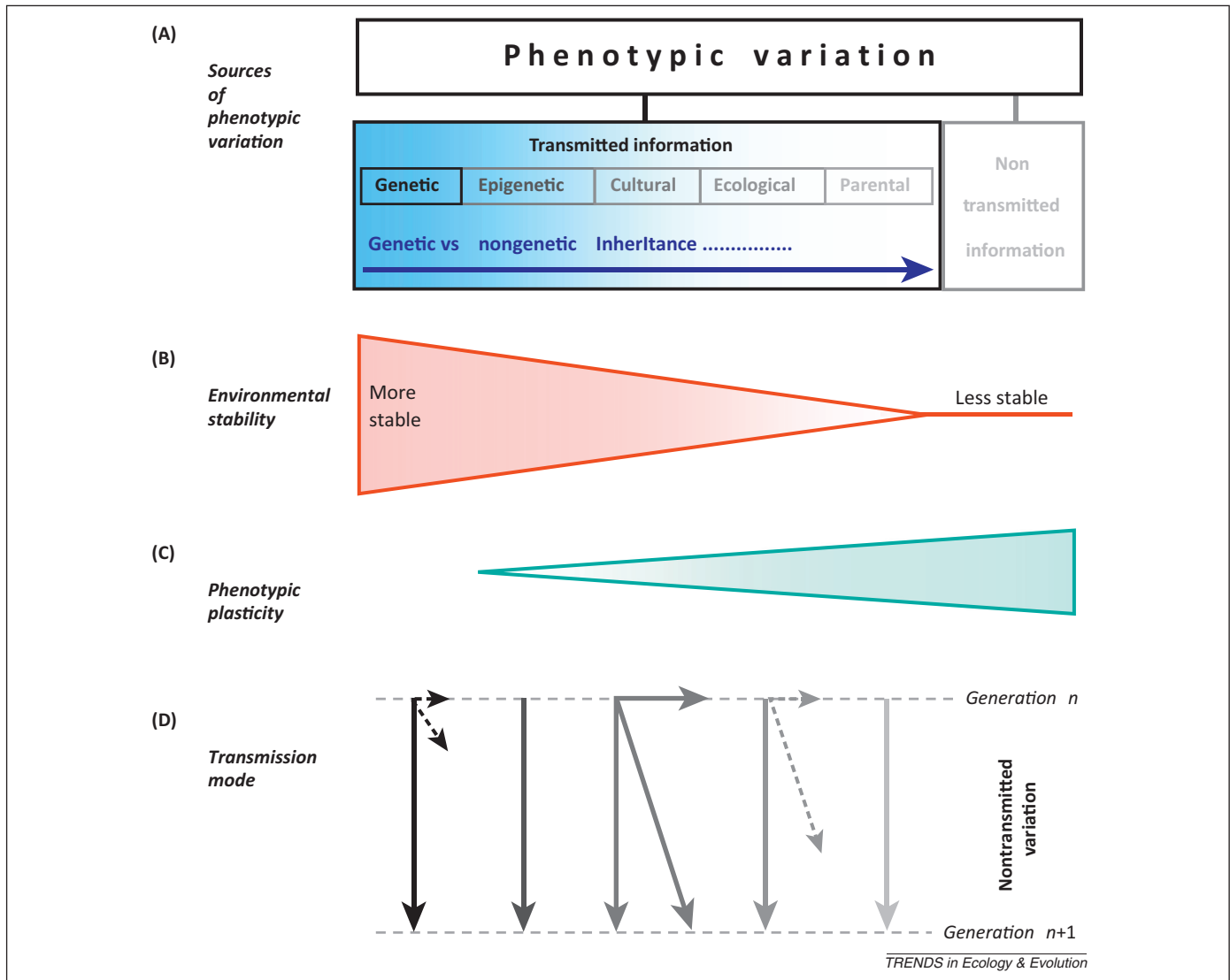


Figure 2. An information-driven approach to phenotypic variation. The figure reads from top to bottom and from left to right. **(A)** Sources of phenotypic variation in Figure 1 (main text) can be arranged along a gradient from genetic to nongenetic inheritance from left to right. **(B)** This gradient parallels a gradient of the underlying environmental characteristics from more stable (left) to less stable characteristics of the environment (right). Only the transmission of environmental characteristics that last for more than one generation can be adaptive. Thus, when the rate of change is too high, no inheritance is expected (right component), which explains the existence of nontransmitted information. At the other extreme (left), environmental characteristics that remain stable across generations create selective pressures favoring their encoding into one of the inheritance systems because they lead to the transmission of the adapted phenotype across generations. **(C)** All variation to the right of genetic variation is part of phenotypic plasticity. **(D)** Transmission modes sharply differ, as sketched in the transmission block, which highlights some of the major differences among transmission systems in terms of the way in which they can be transmitted. Unbroken versus broken arrows: taxonomically widespread versus rare processes. Arrow length represents the relative importance of each transmission modes. These differences should affect the equilibria reached by populations along evolutionary times. See [13,14] for definitions of the various nongenetic terms.

the DNA sequence. The gradient in Figure 2A may reflect a gradient in the capacity of avatars to encode, transmit, and memorize information. Coming back to the metaphor of the film and its avatars, properties of the avatars can affect transmission. The clumsiness of the celluloid avatar limits diffusion. The CD avatar greatly favors transmission, and the electronic file can be downloaded from the web by millions in a single day. Similarly, the paper and electronic avatars of a book can affect information durability and transmission; electronic books are transmitted rapidly but are more likely to disappear, except if it is printed (i.e., encode it in a more resistant type of avatar).

The properties of avatars of biological information also affect information dynamics. On one side, genetic information is encoded digitally in the DNA sequence. The

epigenetic code is less explicit, partly because it has several avatars. Even when considering only methylation patterns, it seems that it is not the actual position of every methyl radical on the DNA molecule but rather the rate of methylation of a given part of a gene that regulates its expression. For the other nongenetic inheritance systems, at present there is no clear indication of the existence of a specific avatar. Cultural information is probably stored in the brain, ecological information resides in the properties of the environment itself, and some parental effects involve hormones or antibodies, but it is more difficult to consider these as real codes. We can only talk of a code when there is an avatar. It may well be that some non-genetically inherited information does not involve a real avatar.

An interacting set of processes

Researchers who dismiss nongenetic inheritance often claim (as underlined by Kevin N. Laland in <http://news.cell.com/discussions/trends-in-ecology-and-evolution/rethinking-inheritance>) that, in the end, only genes persist over the long term, implying that nongenetic inheritance is unimportant. However, in the same way as it is not possible to explain all physics by the sole properties of quarks (i.e., the most fundamental known components of matter), it is not possible to explain every property of organisms by the sole properties of their genes.

The example of deadly mushrooms illustrates how nongenetic inheritance can impact the course of evolution. We all learnt, sometimes through active punishment by our parents, not to touch certain types of mushroom. It is easy to understand how the capacity to transmit that information was selected for. However, the fate of a population is strongly affected by that capacity. In its absence, populations are exposed to the toxins and will soon develop resistance and those mushrooms might become a potential resource. By contrast, in populations able to transmit information culturally about mushroom toxicity, resistance to the corresponding toxin will never evolve and that potential resource will never be exploited. Thus, nongenetic heredity can strongly affect the end product of evolution.

Referring to another domain of biology, claiming that inheritance boils down to genes is equivalent to saying that human behavior and thoughts can be explained by neuron-centered approaches alone. However, in the same way as neurosciences can provide major insights into psychological disorders, genetics is undoubtedly central to understanding inheritance. Nonetheless, genetics cannot explain all heredity, which is produced by the various information inheritance systems, be they genetic or nongenetic.

Similarly, the recurrent claim that nongenetic inheritance can have only short-term consequences for evolution constitutes an *a priori* that needs to be tested and that is contradicted by the evolution of humanity, because many aspects of the human genome have been shaped by gene-culture interactions [4,44].

Gene flow versus information flow

Focusing on information also leads to generalizing the concept of gene flow that has proved to be so useful in evolutionary ecology. Ecological feedbacks, speciation, and evolutionary dynamics not only result from gene flows, but also more generally from 'information flows' among demes. Dispersers, for instance, bring not only their genes into their new population, but also their phenotype, which brings key information on the conditions that prevail outside of the population [45]. They also bring their cultural habits (e.g., dialects), so that high immigration rates can lead to cultural meltdown in a single generation [46], which is equivalent to the loss of a genetic structuring. Such cultural meltdown should affect the inclusive heritability of a local population and, thus, its evolutionary dynamics [45]. Similarly, female preferences have usually been considered as being essentially genetically heritable, females with different

mating preferences being supposed to have different alleles on certain unidentified loci [47]. The consequence is that high gene flow can prevent the onset of reproductive isolation. However, the cichlid example (Box 1) as well as mate choice-copying studies in an increasing number of other animal taxa strongly suggest that a great deal of the inheritance of mating preferences is cultural [48]. This implies that, in the cichlid system, as well as in cases where reproductive isolation results from precopulatory processes, the onset of reproductive isolation can be strongly affected by cultural information flow. Generalizing the concept of gene flow into that of information flow should enable us to incorporate the richness of inclusive inheritance into the study of information evolutionary dynamics.

What next?

New concepts should help in gathering new facts (Günter P. Wagner in <http://news.cell.com/discussions/trends-in-ecology-and-evolution/rethinking-inheritance>). In the case of nongenetic inheritance, facts are accruing (reviewed in [1,2,14,18,49]). Two complementary approaches, empirical data and theoretical models, can be used. Concerning empirical approaches, at this stage, it is necessary to quantify genetic and nongenetic components of inclusive inheritance within natural and experimental populations and to study how they interact. Methods are being proposed [18–20,50–54] that should be applied to a wide variety of systems. For instance, methods based on genetic diversity data can be used to detect transmission via cultural or genetic inheritance of, for instance, fertility [55]. Two other methods build on the Price equation to estimate the various components of heredity [19,52]. Furthermore, variance due to epigenetic inheritance can be

Box 2. Practical implications of nongenetic inheritance

Recognizing the importance of nongenetic inheritance in evolution has major potential implications and applications. In medicine, for instance, the missing heritability of some so-called 'genetic disorders' suggests that they are inherited through a combination of genetic and nongenetic factors, implying that therapeutic research should go beyond purely genetic approaches. For instance, at some stage, it might become pointless to increase the number of genetic markers in GWAS in the hope of detecting more of the genes affecting the trait if the remaining unexplained part of inheritance is of a very different nature. Including epigenetic as well as all other potential components of inclusive heritability would probably constitute a more promising avenue of research in the design of new therapies. Several lines of research in neuroscience have already adopted this kind of approach by considering, for instance, that at least some adult neurological disorders can have originated during early development [68,69].

Similarly, some domesticated plants do not differ from the wild type by mutations but rather by inherited 'epimutations'. This could be the case of the cultivated sunflower (*Helianthus annuus* L.), where some selected decorative forms have been shown to differ from the wild type by epigenetic marks only [70], implying that one can make hard money with 'soft' inheritance.

More generally, I expect that increasing numbers of examples will be found, similar to those described in Box 1, where supposedly genetically inherited traits will be discovered to be at least partly inherited nongenetically, when we study the detailed mechanisms that underline the estimated statistical association between resemblance and kinship.

estimated by including the number of times that epigenetic marks may be reset between generations [51]. Colleagues and I also proposed the Double pedigree approach that mixes classic cross-foster experiments to uncouple the genetic from the cultural pedigree with an extension of the animal model [53]. Studies may also focus on the various components of nongenetic inheritance. Concerning culture, for instance, it is now crucial to demonstrate fully the existence of cultural transmission in a wide array of animals and traits (methods reviewed in [13,14,53]). Similarly, the quest for a solution to missing heritability should incorporate the possibility of the existence of nongenetic inheritance (Box 2). Major discoveries are expected to emerge from the study of how these various systems interact (Box 3).

Concerning theoretical approaches, it is necessary to build models incorporating the properties of the various nongenetic inheritance systems to understand their impact on evolutionary dynamics. This approach was adopted by several authors (e.g., [19,52]) and produced theoretical evidence that populations with nongenetic inheritance mechanisms evolve differently to populations without such mechanisms (reviewed in [14]). A common output of these models is that ‘nongenetic inheritance can take populations to equilibria that they would not otherwise reach, and that these influence the evolutionary process in a myriad of other ways’ (Kevin N. Laland in <http://news.cell.com/discussions/trends-in-ecology-and-evolution/rethinking-inheritance>). This is particularly the case of culture where the first theoretical approaches were published almost four decades ago [56–59]. It is now vital to amplify these theoretical and empirical approaches to establish the general laws of nongenetic inheritance in interaction with those of genetics to build the inclusive theory of evolution. Finally, it is essential to recognize that nongenetic inheritance has major potential implications and applications, some of which are detailed in Box 2.

Box 3. Outstanding questions

Mechanisms of nongenetic inheritance

- Describe the detailed processes underlying nongenetic heredity
- Quantify the contribution of nongenetic inheritance to patterns of heredity of various morphological and behavioral traits
- Understand how genetic and nongenetic inheritance interact to produce heredity

Evolutionary consequences of nongenetic inheritance

- Model the impact of the various forms of nongenetic inheritance on evolutionary dynamics
- How to build the inclusive theory of evolution?

Applications

- To what extent can nongenetic heritability account for the missing heritability?
- To what extent has nongenetic heredity been used by humans in the domestication of plants and animals?
- Accounting for nongenetic inheritance will enable us to design new therapies for human disorders that were previously only envisaged from the genetic point of view
- Accounting for nongenetic inheritance will enable us to design new approaches to study adaptation with some direct implications for conservation biology

Concluding remarks

Following the discovery that genetic inheritance cannot explain all aspects of heredity, biology is undergoing a major paradigm shift that future biologists might consider to be as important as the Modern Synthesis of the first half of the 20th century. Here, I have underlined how the various processes of inheritance interact in producing heredity. I have also developed how the concepts of information and its avatars can unify genetic and nongenetic inheritance into an Inclusive Evolutionary Synthesis. Such an ‘information-centric’ vision of heredity and evolution is currently opening new avenues of research that should profoundly impact evolutionary biology during the next decades (Box 3).

More generally, nongenetic inheritance probably does not affect the overall structure of the evolutionary equation, but it certainly affects the structure and, thus, the value of each of its three main components; heredity, variation, and selection. First, it is now becoming accepted that heredity incorporates nongenetic information [1–5,8,9,13–15,17–19]. Second, previous studies have shown that mutation frequency can be greatly increased in methylated genes (e.g., [60]), suggesting that nongenetic inheritance also strongly affects variation (see also the mushroom example above). Finally, it is clear that accounting for nongenetic inheritance can profoundly change selective pressures [44,55] (reviewed in [4] and see the mushroom example above). One way by which culture can, for instance, affect the course of evolution is by generating a cultural niche, which can profoundly change selective pressures [13]. Thus, the importance of the ongoing mutation of biology can be compared with that of astrophysics during the early 20th century. In the same way that Einstein did not refute Newton’s theory but generalized it, the long-sought Inclusive Evolutionary Synthesis does not invalidate the Modern Synthesis, but generalizes it by incorporating all dimensions of evolutionary processes.

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