PHILOSOPHICAL TRANSACTIONS B

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Opinion piece

Cite this article: Helanterä H, Uller T. 2020 Different perspectives on non-genetic inheritance illustrate the versatile utility of the Price equation in evolutionary biology. *Phil. Trans. R. Soc. B* **375**: 20190366.
http://dx.doi.org/10.1098/rstb.2019.0366

Accepted: 14 January 2020

One contribution of 16 to a theme issue 'Fifty years of the Price equation'.

Subject Areas:
evolution, genetics, theoretical biology

Keywords:
George Price, non-genetic inheritance, Price equation, evolutionary theory, development, inheritance

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THE ROYAL SOCIETY PUBLISHING

Different perspectives on non-genetic inheritance illustrate the versatile utility of the Price equation in evolutionary biology

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The diversity of genetic and non-genetic processes that make offspring resemble their parents are increasingly well understood. In addition to genetic inheritance, parent–offspring similarity is affected by epigenetic, behavioural and cultural mechanisms that collectively can be referred to as non-genetic inheritance. Given the generality of the Price equation as a description of evolutionary change, is it not surprising that the Price equation has been adopted to model the evolutionary implications of non-genetic inheritance. In this paper, we briefly introduce the heredity perspectives on which those models rely, discuss the extent to which these perspectives make different assumptions and place different emphases on the roles of heredity and development in evolution, and the types of empirical research programmes they motivate. The existence of multiple perspectives and explanatory aims highlight, on the one hand, the versatility of the Price equation and, on the other hand, the importance of understanding how heredity and development can be conceptualized in evolutionary studies.

This article is part of the theme issue 'Fifty years of the Price equation'.

1. Introduction

Evolutionary biologists commonly wish to explain why, and predict how, the composition of phenotypes in a population changes over time. The Price equation is a general description of the change in the average of a trait from one generation to the next, and it is thus a useful starting point for understanding how different factors contribute to phenotypic evolution. The Price equation can be written as

$$\bar{w}\Delta\bar{z} = \mathrm{Cov}(w, z) + E(w\Delta z). \tag{1.1}$$

This partitions the change in the mean phenotype in a closed population, $\Delta\bar{z}$ (multiplied by $\bar{w}$, average fitness in the population), into two terms. The first term on the right-hand side is the covariance between fitness w, or the number of descendants, and the average phenotype of the parent z, and the second is the fitness weighted expected change in phenotype between the parental and offspring generation (see derivations and explanations in [1,2], [3, p. 166], [4, p. 19], [5, ch. 6], [6]). It is often useful to rearrange the terms into

$$\bar{w}\Delta\bar{z} = \mathrm{Cov}(w, z') + E(\Delta z), \tag{1.2}$$

where the first term on the right-hand side now represents covariation between parental fitness and offspring phenotype z', and the second the expected change between generations, unweighted by fitness. This partition can be interpreted to separate evolutionary change into selection and transmission components. This form can be further partitioned into

$$\Delta\bar{z} = \beta_{z',z}S + \mathrm{Cov}_{wz'.z} + E(\Delta z), \tag{1.3}$$

where the response to selection term now has been split into a selection differential S (representing the within-generation change owing to selection, defined as $\mathrm{Cov}(\omega, z)$, where ω is the relative fitness of the parent) and the slope of the parent–offspring regression $\beta_{z',z}$. Assuming the middle term on the right-hand side (partial covariance of fitness and offspring phenotype, controlling for the effect of parent phenotype on both of these) is zero, and assuming the $E(\Delta z)$ is zero, this gives the breeder's equation that is found in nearly every undergraduate textbook on evolutionary biology.

Regardless of which version is used, it is evident that how the mean phenotype changes from one generation to the next will depend in part on how the phenotypes of offspring are derived from those of its parents. This is not a trivial problem because parents contribute to the development of their offspring in many ways. The offspring DNA is generated using the parents' DNA as a template, and in single-celled organisms the daughter cells will be very similar to the parental cell also in terms of its cellular components and their organization. In multicellular organisms, parents not only produce the egg and ensure that it contains the necessary molecules, including proteins and RNA, but may choose egg-laying sites, feed or interact with their offspring behaviourally, or modify the environment in ways that affect offspring phenotype or fitness. If we refer to the DNA contribution as genetic inheritance, we may wish to collectively refer to the other contributions from parents as non-genetic or extra-genetic inheritance (e.g. [7,8]). Genetic and non-genetic inheritance usually produce a phenotype through a highly complex developmental process that also relies on many features of the world over which the parents have little, if any, control. As a consequence, the relationship between the phenotypes of parents and offspring, the offspring–parent distribution, can take on many forms and vary from one place or time to another.

Because of these complexities, formal theory represents development in a highly idealized manner. One common idealization is to assume that only genes are inherited, and that there is a simple relationship between genotype and phenotype. This genetic representation of heredity forms the basis for most evolutionary theory. The literature on the evolutionary implications of non-genetic inheritance recognizes that this representation has limitations. There are several different ways to include some element of non-genetic inheritance in evolutionary theory, however. While the choice of approach can be justified on pragmatic grounds, such as the problem agenda and the tools available for modelling, it may also reflect assumptions or conceptual commitments that are not always well recognized.

We have previously suggested that it can be useful to recognize four heredity concepts that are commonly used by evolutionary biologists [9]. The first is to conceptualize inheritance as the transmission of some 'developmentally privileged' [10] material from parents to offspring. From this perspective, it may seem as if heredity can be understood without knowledge about how the transmitted variants come to have phenotypic effects. A different perspective rejects this separation of heredity and development, and consider heredity to be about the similarity in the entire developmental process. One consequence of this view is that whatever may be transmitted is not developmentally privileged and hence cannot stand in for heredity [11]. A third perspective that appears to avoid this distinction altogether is to consider heredity as a statistical relation between parents and offspring, or the phenotypic covariance. Finally, heredity could be seen as a form of communication, whereby information is transferred from parents to offspring. These four perspectives are not mutually exclusive. For example, while the genetic representation considers heredity a matter of transmission of developmentally privileged material (i.e. genes), it is compatible with treating heredity as phenotypic covariance and to consider the alleles or additive genetic variance that is transmitted to carry information. Nevertheless, how heredity is understood influences what aspects of biology that seem important to evolution [9,12,13].

Here, we discuss and exemplify how three of these perspectives are reflected in the use of the Price equation to extend evolutionary theory to include non-genetic inheritance. We explain why different perspectives can influence what role non-genetic inheritance is assigned in evolution and suggest that they motivate distinct but overlapping empirical research programmes. We do not aim to provide new mathematical analyses or a systematic review of all theoretical work on non-genetic inheritance. Rather, the aim is to illustrate the versatile utility of the Price equation and provide some insight into the internal structure of what is a large and rather unwieldly body of research on non-genetic inheritance and evolution.

2. Heredity as transmission

For more than 100 years, biological inheritance has been represented by the transmission of genes from parents to offspring [14]. Thinking of inheritance as transmission makes it natural to represent non-genetic inheritance as the transmission of non-genetic variants through one or several non-genetic channels of inheritance. This is indeed how early models of non-genetic inheritance were construed, including the cultural evolution and gene–culture coevolution framework pioneered by Feldman & Cavalli-Sforza [15] and Boyd & Richerson [16] among others. More recently, the growing interest in epigenetic inheritance has motivated several analogous models that study how the environmental lability and transmissibility of epigenetic variants affect phenotypic and genetic evolution (e.g. [17–19]). The use of the Price equation to understand the evolutionary dynamics of cultural evolution is covered elsewhere in this issue [20] and we therefore simply note that the Price equation has been applied to culturally inherited traits by several authors (e.g. [21–24]), and that the similarities between cultural transmission and other forms of non-genetic inheritance are discussed elsewhere [25].

Day & Bonduriansky [26] generalized the Price equation in a way that illustrates the kind of models one may look to under the transmission view of heredity. They considered inheritance via two or more separate channels, where at least one of them is genetic. The transmitted variants can be more or less anything, including alleles, epialleles, quantitative phenotypes including cultural features, breeding values or their non-genetic analogues such as maternal resources that contribute to a trait. The variants may also represent dummy variables that indicate the presence or absence of a particular variant. Allowing for overlapping generations and within-generation change, Day & Bonduriansky ([26], eqns 1a, 1b, p. E21) derived a version of the Price equation

that describes the change in the population mean values of genetic ($\bar{g}$) and non-genetic ($\bar{h}$) components

$$\bar{w}\Delta\bar{g} = \mathrm{Cov}(w, g) + E(b\Delta g^b) + E(p\Delta g^p) \quad (2.1a)$$

and

$$\bar{w}\Delta\bar{h} = \mathrm{Cov}(w, h) + E(b\Delta h^b) + E(p\Delta h^p). \quad (2.1b)$$

The first terms on the right-hand side represent the covariance between the number of descendants and the genetic (g) and non-genetic (h) value of the parent, respectively. The second terms represent the expected change that occurs during transmission from one generation to the next (g^b and h^b, weighted by fecundity b) and the third, the change that occurs within an individual's lifetime (g^p and h^p, weighted by survival p). This formalism allows analysing complex cases where each inheritance channel exhibits its own selection and transmission rules. It also allows the genetic and non-genetic variants to affect evolution through their interaction. Such interactions are perhaps easiest to understand by recognizing that individual fitness can be a function of both the genetic and non-genetic components, and that it is possible that the genetic and non-genetic values of an individual are not independent. In these cases, selection on both the genetic and non-genetic components can be considered to have two components and change from one generation to the next ([26], eqns 2a, 2b, p.21):

$$\Delta\bar{g} = \sigma_{g,g}\beta_g(\bar{g},\bar{h}) + \sigma_{g,h}\beta_h(\bar{g},\bar{h}) + \frac{1}{\bar{W}}E(b\Delta g^b)\ \frac{1}{\bar{W}}E(p\Delta g^p) \quad (2.2a)$$

and

$$\Delta\bar{h} = \sigma_{g,h}\beta_g(\bar{g},\bar{h}) + \sigma_{h,h}\beta_h(\bar{g},\bar{h}) + \frac{1}{\bar{W}}E(b\Delta g^h)\ \frac{1}{\bar{W}}E(p\Delta g^p). \quad (2.2b)$$

The first term on the right-hand side of equation (2.2*a*) is the selective change that results from the variance in the genetic value ($\sigma_{g,g}$) and the selection gradient (β_g) on the genetic value, given the population mean values ($\bar{g},\bar{h}$), and the second is owing to the covariance between the genetic and non-genetic ($\sigma_{g,h}$) value and the selection gradient (β_h) on the non-genetic value (and vice versa for equation (2.2*b*)). In other words, selection may act on the non-genetic value both directly or indirectly.

Day & Bonduriansky derived a number of specific models to demonstrate that this covariance can arise for several different inheritance mechanisms and that it will influence evolutionary trajectories and existence and stability of equilibria. Furthermore, they expanded the models to allow for conditional fitness effects such that the variants in the two channels affect each other's fitness effects, akin to epistatic interactions in genetic models. For example, the fitness effect of a genetic allele can depend on whether or not it is methylated, while the phenotypic or fitness effects of a methylation mark can depend on which of several alleles is present at the genetic locus that is methylated. In this case, the rate of loss or gain of methylation determines whether or not the population ends up with a genetic or epigenetic polymorphism ([26], example presented in their fig. 2). The genetic and non-genetic components can also interact through the other two terms of the Price equations. The epigenetic marks can vary in how strongly they are determined by the underlying genetic variation [27], epigenetic packaging of DNA can influence mutation rates, some DNA sequences can be more likely to become epigenetically regulated than others, and so on. Other models have been developed to explore such more complex scenarios (e.g. [28–30]).

As expected from a general modelling framework, these transmission genetic-plus-non-genetic models were found to recover evolutionary consequences of non-genetic inheritance on evolution that had previously been demonstrated by quantitative genetic models of maternal effects and more specific population epigenetic and gene–culture coevolution models. For example, when a maternally transmitted component affects the trait value, the response to selection will show a time-lag [31]. More importantly, Day & Bonduriansky also model new scenarios, such as transmission of small RNAs, evolution under indirect genetic effects and how non-genetic inheritance influences evolutionary divergence. These examples illustrate the breadth of non-genetic inheritance mechanisms that have evolutionary consequences.

Under this transmission perspective on inheritance, the evolutionary consequences of any form of inheritance depend on only three parameters: (i) how the transmissible variants affect fitness; (ii) rules governing the transmission from parents to offspring, and (iii) rules governing changes in individual phenotypes over individual lifetimes [26]. These parameters probably differ between biological mechanism of inheritance, but it is important to recognize that mechanisms which are strikingly different can behave in similar ways. For example, the transgenerational stability of some epigenetic states may fall within the same range as the stability of behaviours that are learnt from parents. This suggests that it is not always necessary to understand the mechanistic underpinnings of the non-genetic inheritance mechanisms to understand how they affect evolution, and that different mechanisms may have surprisingly similar implications on evolutionary change [25,26].

What are the implications of these models for empirical research? For the empiricist, the three parameters that determine the evolutionary consequences of non-genetic inheritance in these models become the main variables of interest to measure. Accordingly, two main tasks are to establish the rules that affect the stability of heritable variants and how particular variants affect fitness. That these variables are possible to study is perhaps most readily seen for epigenetic mechanisms that resemble genetic inheritance. For example, it is possible to identify and track the DNA methylation status of a particular DNA sequence from one generation to the next and calculate its covariance with fitness. Indeed, quantifying the environmental sensitivity and transgenerational stability of epigenetic variation has emerged as a major research focus over the past decade (see [32–35]). In particular, plants appear to have interesting combinations of environmental lability and transgenerational stability of epigenetic variation, but detailed studies in model organisms like *Caenorhabditis elegans* have revealed that animals too have mechanisms of epigenetic inheritance that fulfil the requirements for being evolutionarily consequential (e.g. [36]). It is less obvious how to empirically identify the stability and selection of 'variants' that are composed of behavioural interactions between parents and offspring. Nevertheless, the transmission-based perspective has influenced empiricists to quantify the stability and fitness effects of behavioural and cultural inheritance (see [37,38]).

In summary, the transmission perspective on non-genetic inheritance has generated an active and progressive research

programme on the evolutionary implications of non-genetic inheritance. Nevertheless, many biologists and researchers in the human sciences may find it difficult to come to terms with a representation of heredity that is typically used to analyse variants transmitted from parents to offspring, rather than focusing on the phenotype. As a result, they may look for alternative representations of heredity where transmission becomes less important; approaches that require less attention to the variants that are inherited and pay more attention to the phenotype.

3. Heredity as phenotypic covariance

The transmission-based approach to non-genetic inheritance comes naturally to many biologists because it treats non-genetic inheritance as if it was analogous to genetic inheritance. Under this perspective, non-genetic inheritance affects evolutionary predictions because the transmissibility or selective advantage of non-genetic variants is different from that of genetic variants. The transmission view of heredity thus has close conceptual links to the assumptions that underlie theoretical population genetics (indeed, inheritance of more than one genetic locus can be represented as separate inheritance channels, just like the addition of non-genetic inheritance above), and the terminology such as mutation rates and epistatic effects of variants easily translates across inheritance channels (e.g. the effects of an allele depends on its methylation status). Population genetic equations become cumbersome when there are more than a few loci, however. Animal breeders interested in quantitative traits therefore developed a statistical approach known as quantitative genetics, which has also become the favoured tool for many evolutionary biologists [5]. Under this perspective, it is no longer necessary to keep track of the transmission of individual variants, but rather to assess how much of the covariance between the phenotypes of offspring and parents that can be attributed to shared genes with additive effects. That is, heredity is phenotypic covariance caused by genetic inheritance, and instead of transmission and stability of variants, the focus is on statistically partitioning phenotypic variation into heritable and non-heritable components.

To make the statistical analyses tractable, quantitative geneticists commonly assume that traits are influenced by many loci, each with a small additive effect on the phenotype, and that the joint distribution of parent and offspring phenotypes are multivariate normal (see [3] for an excellent treatise of many of the points covered below). It is also commonly assumed that the mean phenotype does not change from one generation to the next unless there is selection or drift. As a result of these assumptions, one can derive a modified version of the Price equation (see equation (1.3)):

$$\Delta\bar{z} = \beta_{z',z} S\,, \tag{3.1}$$

where $\Delta\bar{z}$ is the change in the mean phenotype in the population from one generation to the next, $\beta_{z',z}$ is the linear regression of offspring phenotype on parent phenotype, and S, the selection differential, is equal to the covariance between phenotype and fitness. This is the famous breeder's equation which states that the response to selection is a function of heritability multiplied by the selection differential. How evolution proceeds thus depends on the phenotypic covariance between offspring and parents. If this covariance is low relative to the trait variance, heritability is low and selection becomes inefficient at changing the trait average in the population.

It is common to see heritability defined not as a regression coefficient, but in terms of the ratio of additive genetic variance to the total phenotypic variance. The additive effect measures the amount of phenotypic variance that would be accounted for by fitting an additive model to the data ([3], ch. 7). Why would the additive genetic variance be interesting if one simply can calculate heritability by regressing the offspring phenotype on the parental phenotype? This is because quantitative genetics were born from multi-locus population genetics, where changes in genes are the currency of evolution. However, inherited genes are not the only thing that influence the slope of the regression; for example, it will also be affected by shared environmental effects. Thus, the slope of the regression of offspring phenotype on parental phenotype was considered an estimate of the heritable effects of genes or the additive genetic variance, with the latter being the real value of interest (see [3,39]). Because the discrepancy between the two heritability estimates increase with increasing deviation from assumptions of additive and uncorrelated effects of genotypes and environment on phenotype, it is often considered desirable to estimate the additive genetic variance rather than using parent–offspring regression.

Not all genetic sources of phenotypic variance are additive because alleles at single loci can show dominance and alleles at different loci can interact (epistasis). There are also various sources of phenotypic variance that are not owing to inherited factors (environment). The total phenotypic variance, assuming independence of the sources of variance, is the sum of all these variances:

$$V_p = V_a + V_d + V_i + V_e, \tag{3.2}$$

where V_p is the total phenotypic variance, V_a the additive genetic variance, V_d the dominance and V_i the epistatic variance and V_e the environmental variance.

Where does the phenotypic variance caused by non-genetic inheritance fit under this perspective? In quantitative genetics, the non-genetic effect of the parental phenotype is typically treated as a component of the non-heritable variance and referred to as a maternal effect. However, because the maternal effect is caused by the phenotype of the parent, it may also have a genetic component and evolve. As a result, maternal effect quantitative genetic models generate interesting evolutionary dynamics (reviewed in [40,41]).

The recognition that it is possible to consider the effects of parents on the phenotype of their offspring as inheritance makes those maternal effects shift from being an environmental source of variation to be treated as putative sources of both additive and non-additive non-genetic variance. That is, one may decompose the phenotypic variance into additive genetic, additive epigenetic, additive behavioural variance, additive environmental variance and so on, which together with various sources of non-additive and environmental sources of variance sum up to the total phenotypic variance in a population [42,43]:

$$V_p = V_g + V_{\mathrm{tng}} + V_{\mathrm{nt}}, \tag{3.3}$$

where $V_g = V_a + V_d + V_i$, and V_{tng} stands for transmitted non-genetic variation, and V_{nt} for non-transmitted variation. V_{tng} can be further split so that $V_{\mathrm{tng}} = V_{\mathrm{tepi}} + V_{\mathrm{pnge}} + V_{\mathrm{tecol}} + V_{\mathrm{tsoc}}$ so that it comprises transmitted epigenetic, transmitted

parental non-genetic, transmitted ecological and transmitted social components, respectively [43].

Several models demonstrate theoretically that it is possible to distinguish the different sources of additive variance and to estimate their contribution to the total or 'inclusive' heritability. This approach is based on the idea that genetic and epigenetic factors contribute in different ways to similarity of relatives [44]. For example, Tal *et al*. [45] modelled how the transmissibility of an epigenetic mark influences the inclusive heritability by calculating how transmissibility influences the phenotypic variances and covariances between relatives. Note that this makes use of a transmission perspective to generate expectations that can be handled by quantitative models.

Like the extended transmission-based approach described in the previous section, these extended quantitative genetic models can be used to study how non-genetic inheritance affects the ability of populations to track environmental change, the rate and direction of phenotypic change, and stable evolutionary states. How strong the effects are will depend on how the non-genetic effects contribute to additive and non-additive sources of phenotypic variance. As a result, it becomes an important empirical task to partition the total additive and non-additive phenotypic variance into its components. This does not necessarily require empirical assessment of transmissibility of variants, but the additive non-genetic variance can be estimated from phenotypic data using pedigrees and experimental designs that decouple different causes of phenotypic covariance between offspring and their biological parents (e.g. [45]). First, partitioning of phenotypic variance into different sources of additive variance is possible through 'double' pedigrees where, for example, the cultural, environmental and genetic inputs to phenotypes are teased apart in complex breeding and cross-fostering designs [46,47]. Second, the logic of how animal models—a tool for studying quantitative genetics of wild populations—deal with maternal, social and shared environmental effects [48,49], can be extended to include similarity matrices that also allow estimating additive effects of epigenetic and social inputs to the phenotype [50]. For the epigenetic case, such matrices can be generated from either sequencing studies (such as bisulfite sequencing revealing methylation marks, for further sequencing methods, see [51], see also [52]) or pedigree methods (e.g. [45]). Third, quantitative genetics (or evolutionary genetics in general) can be studied in experimental systems where some of the sources of parent offspring similarity are manipulated. For example, in inbred or clonal lines [52], mutant strains deficient in certain epigenetic mechanisms, or treatments that erase methylation marks or increase mutation rates [53] can be effective in revealing how epigenetic inheritance contributes to heredity.

The empirical challenges involved in adapting these approaches mean there are still few studies that quantify additive non-genetic variance, despite the fact that epigenetic inheritance and social learning are now recognized as important in a very wide range of organisms (e.g. [54,55]). Perhaps the most comprehensive studies have been done using the model plant *Arabidopsis thaliana*. The reason for this is that plants can be generated that have very low DNA sequence variation but a substantial variation in DNA methylation, which means that the additive genetic variance can be carefully controlled. Growing these plants in a greenhouse established that heritable DNA methylation contributes to heritable phenotypic variation in functionally important characters such as flowering time, root length and disease resistance [56,57]. It is more challenging to conduct such studies in natural populations because populations typically harbour high levels of genetic variation. Nevertheless, since the importance of non-genetic inheritance in evolution stems from its contribution to additive and non-additive phenotypic variance, partitioning of phenotypic covariance is important to the research programme stimulated by the heredity-as-phenotypic-covariance perspective (e.g. [50,52]).

4. Heredity as developmental process

The two previous perspectives on heredity have in common that they treat heredity and development as if they were separable; the inheritance of phenotypes and the generation of phenotypic variation can be considered as if they were two different processes. Screening off development can be desirable not only because developmental processes are highly complex, but also because assuming there are no biases in the introduction of variation can make it easier to grasp how fitness differences contribute to evolutionary change [13,58]. Nevertheless, because development is the process by which phenotypic variants appear, it cannot be screened off completely if the aim is to understand biological evolution. In fact, it is possible to consider parent–offspring similarity (i.e. heredity) as the outcome of the reconstruction of life cycles in consecutive generations, which means that heredity is a phenomenon which requires a developmental explanation [11,59]. Two important features of this heredity-as-developmental-process perspective are that inheritance does not need to be conceptualized as transmission, and that it does not *a priori* assign greater causal relevance to some parent–offspring relations than others (see [9] for further discussion).

The Price equation can be used to illustrate why this developmental perspective on heredity is relevant to understand evolution. In a series of papers, Rice [39,60,61] has developed an approach to evolutionary change that treats fitness and offspring phenotype as random variables. We refer the reader to the original papers for the mathematical derivation and explanations, and focus on the reasons why this body of work is well aligned with a developmental perspective on heredity.

The main advantage of Rice's approach is that it allows the offspring phenotype and fitness to be unknown at the time of reproduction and hence be random variables. This means that the entities of interest have distributions and that the equations for evolutionary change need to track both individual values and the distribution of those values. This has several benefits [39]. First, it emphasizes the role of both the relationship between genotype and phenotype (the genotype–phenotype map) and the relationship between phenotype and fitness in analyses of evolutionary change. Second, it allows consideration of the full shape of the offspring–parent distribution, i.e. moments other than the mean.

As explained above, it is standard in quantitative genetics to rely on only a single feature of the offspring–parent phenotype distribution, namely the linear slope of regression or additive heritable variance. However, this is only accurate under very specific circumstances that commonly do not

apply even under a purely genetic model [62]. Rice's approach makes it explicit that evolutionary change depends not only on the processes that impact the fitness differences of individuals with different phenotypes, but also on the biological processes that impact the offspring–parent phenotype distribution. Importantly, the crucial role of understanding development is highlighted by examples that demonstrate how the shape of the offspring–parent regression can affect responses to selection systematically, even if only the linear component of the phenotype is under selection [39]. Similarly, it turns out that also higher moments, such as the skewness of the distribution of parent phenotypes, affect response to selection. It is also important to note that the offspring–parent distribution not only changes as a result of reshuffling of standing (e.g. genetic) variation, but also by the developmental processes that give rise to phenotypic variation from genetic mutation, recombination or as individuals encounter novel environments. Thus, this demonstrates that, in principle, the Price equation can be a useful starting point for an evolutionary theory that is concerned with evolutionary novelty [39].

In practice, further theoretical assessment of the evolutionary consequences of non-genetic inheritance entails comparison of evolutionary dynamics under different causal structures or mechanisms that determine the parent–offspring phenotype distribution. Otsuka [63,64] illustrates how the use of causal graphs helps to specify the evolutionary consequences of maternal effects and ecological inheritance using the Price equation. Because the offspring–parent phenotype distribution is determined by the totality of causal effects on development, such approaches could usefully be adopted not only for those who are interested in non-genetic inheritance, but also to study how plasticity or other forms of developmental bias influence evolution [39]. The offspring–parent phenotype distribution will, for example, be affected by any process that generates a within-individual covariance between the mean phenotype and number of offspring, or the population covariance between individual phenotype and individual covariance of fitness and heritability [39]. The latter may be common for nonlinear developmental interactions and when the phenotype depends on both contributions from parents and the environment. As has been pointed out elsewhere [9], such complex interactions appear likely under non-genetic inheritance.

The heredity-as-developmental-process perspective motivates at least two kinds of empirical studies of non-genetic inheritance that may be overlooked under the other two perspectives. First, in contrast with the additive variance approach, quantifying the full offspring–parent distribution becomes of interest. It is well known that heritability varies with, for example, environments, and that heritability and covariance between phenotypes and fitness at least occasionally can be correlated (e.g. [65]). The latter may be common when environment affects both heritability and the selective regime. However, these studies say little about other features of the offspring–parent distribution, such as how commonly there is a nonlinear relationship between phenotypes of offspring and parents, and how in such cases distribution components other than the mean affect response to selection. Surprisingly, despite the very large number of parent–offspring regressions from natural populations that have been published, we are unaware of any systematic study of how commonly the relationship between the phenotype of parents and the phenotypes of offspring is nonlinear.

Second, to understand which features of development are evolutionarily important (and which are not), one also needs to understand how a perturbation to development, for example, through mutation, influence the parent–offspring phenotype distribution under complex genotype–phenotype maps. As demonstrated theoretically by Milocco & Salazar-Ciudad [66], nonlinear gene interactions in development can severely reduce the accuracy of predicted responses to selection using traditional quantitative genetic models. However, it remains poorly understood if there are general properties of developmental systems that make phenotypes more or less evolvable. In addition to theoretical work on this topic (e.g. [67–70]), a greater empirical understanding of proximate mechanisms will be important for at least two reasons. First, it will help to assess the use of traditional idealizations for practical and theoretical purposes. Simplifying assumptions are always necessary, but to make appropriate assumptions, it is necessary to understand what is important to real organisms, and this knowledge will often require mechanistic studies. Second, more knowledge about how phenotypic variation is generated will allow specific models that incorporate the generation of variation, as well as models that explore the consequences of general biological principles of development. There are now many empirical studies of how development shapes phenotypic variability (see [71] for an entry into the literature). By contrast, there are relatively few studies that focus on the role played by non-genetic inheritance, such as the epigenetic and behavioural mechanisms that make some phenotypes more likely to arise and become propagated within populations.

5. Discussion

All models of evolution rely on making the complex tractable. In this paper, we have revisited three perspectives on heredity [9] to illustrate how biologists make use of idealization and abstraction to address new questions. Particular assumptions are often justified on the basis of the aims of the investigator, but may also result from implicit assumptions about how biological systems work or what are the important causes of evolution. The literature on non-genetic inheritance and evolution probably reflects both pragmatic choices and conceptual biases. This is illustrated by the transmission and phenotypic covariance approaches to non-genetic heredity, which retain several key features of the standard representation of evolution by natural selection. For example, Day & Bonduriansky [26] refer to the variants inherited through non-genetic inheritance as the 'interpretative machinery', suggesting that they consider genes to be the primary privileged carriers of hereditary information. Perhaps more importantly, the extension of transmission and quantitative genetic models retain the assumption that the relationship between inheritance and phenotypic variation is such that it is sufficient to focus on the transmissibility of inherited variants or additive variance rather than phenotype development. This makes these approaches well aligned with existing research programmes, and we suggest that this alignment has contributed to making non-genetic inheritance a respectable field of study in evolutionary biology.

The conception of heredity as a developmental process is a more significant departure from traditional notions of inheritance. As a result, it may appear less relevant to

many evolutionary biologists; development is, after all, typically considered a constraint on adaptation rather than a cause. Nevertheless, the Price equation has proved useful to reveal just why development has evolutionary consequences and how developmental processes fit within existing foundational theories (theories that have primarily been concerned with the effects of different forms of selection; [3,39]). The Price equation can be used to draw attention to features of the offspring–parent phenotype distribution that are idealized away in models designed to focus on how natural selection affects phenotypic change. In fact, the mechanisms of non-genetic inheritance, such as parental behaviour, do not only affect the parent–offspring resemblance, but also the generation of variation and individual fitness [9]. It is not always obvious how to interpret the different terms in the Price equation when the traditional assumptions are relaxed. Teasing apart the effects of selection and transmission can be difficult even under strictly genetic inheritance, and increasingly so when allowing cultural transmission of traits [20,22], or modification of environments by organisms [72,73].

The versatile use of the Price equation illustrated in this paper explains why it can be embraced by researchers with a wide range of opinions regarding how radical the departure from genetic inheritance for evolutionary biology (e.g. compare [5, pp. 12–14]; [74,75]). These researchers come to different conclusions regarding the need for conceptual change not so much because they have different standards with respect to the utility of mathematical theory, but because they bring different concepts, perspectives and scientific aims to the study of evolution. The Price equation can be usefully employed to come to terms with these differences; working through the Price equation from its most general form helps to reveal assumptions that lead to differences in interpretative understanding.

One of the four perspectives of heredity introduced above is missing so far, namely the conception that inheritance is about transmission of information between generations [9]. For example, maternal effects are often seen as the outcome of mothers signalling to their offspring, perhaps allowing offspring to adjust their phenotype to match local conditions [76]. While the passing on of information between generations is also a common metaphor for the other perspectives, treating inheritance explicitly in terms of information can be useful. As demonstrated by Shea *et al*. [77], any feature of the parents, including their DNA sequence, physiology and behaviour can carry information about the conditions that the offspring will encounter (see also [78]). This information interpretation is an integral part of transmission-based approaches to modelling how non-genetic inheritance itself evolves (e.g. [79,80]). This makes sense because the maximization of fitness in an uncertain world requires predicting the future through the processing of information, some of it generated by ancestors ([81]; see also the supplementary material in [79]). That this information content itself must be an evolving property is perhaps most evident when heredity is viewed as a developmental process; a developmental perspective is particularly useful when the aim is to study how the evolutionary process itself is evolving (e.g. [82]).

This point about inheritance and information emphasizes that perspectives on heredity do not fall into discrete and mutually exclusive categories, and that individual researchers need not ascribe to any particular perspective. Indeed, the authors of this paper are regularly making use of all four perspectives in their own work. Unfortunately, a diversity of perspectives can make the literature on non-genetic inheritance and evolution unwieldy and difficult to navigate. Drawing attention to different perspectives on heredity, and the theoretical and empirical research programmes they motivate, should make it easier to structure and organize a growing body of literature. While we have only briefly touched upon the insights provided by different models, all the perspectives that we have discussed in this paper have identified important evolutionary consequences of non-genetic inheritance. We anticipate that further work in this area will reveal many more insights, and that further use of the Price equation will help to expand this research in directions that have so far been little explored.

Data accessibility. This article has no additional data.

Authors' contributions. H.H. and T.U. formulated the idea and wrote the paper together.

Competing interests. We declare we have no competing interests.

Funding. H.H. was supported by the Kone Foundation. T.U. was supported by a Wallenberg Academy Fellowship from the Knut and Alice Wallenberg Foundations and a research grant from the John Templeton Foundation (grant no. 66501).

Acknowledgements. We are grateful to two anonymous reviewers for helpful comments on the paper.

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