

A Unified Approach to the Evolutionary Consequences of Genetic and Nongenetic Inheritance

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ABSTRACT: Inheritance—the influence of ancestors on the phenotypes of their descendants—translates natural selection into evolutionary change. For the past century, inheritance has been conceptualized almost exclusively as the transmission of DNA sequence variation from parents to offspring in accordance with Mendelian rules, but advances in cell and developmental biology have now revealed a rich array of inheritance mechanisms. This empirical evidence calls for a unified conception of inheritance that combines genetic and nongenetic mechanisms and encompasses the known range of transgenerational effects, including the transmission of genetic and epigenetic variation, the transmission of plastic phenotypes (acquired traits), and the effects of parental environment and genotype on offspring phenotype. We propose a unified theoretical framework based on the Price equation that can be used to model evolution under an expanded inheritance concept that combines the effects of genetic and nongenetic inheritance. To illustrate the utility and generality of this framework, we show how it can be applied to a variety of scenarios, including nontransmissible environmental noise, maternal effects, indirect genetic effects, transgenerational epigenetic inheritance, RNA-mediated inheritance, and cultural inheritance.

Keywords: transgenerational effects, epigenetic inheritance, gene-culture coevolution, methylation, epialleles.

Introduction

The nature of inheritance was the subject of lively debate throughout the late nineteenth and early twentieth centuries (Sapp 1987; Cook 1999). Since the middle of the twentieth century, however, inheritance theory has been dominated by a simple, analytically tractable model based on Mendelian segregation of DNA sequences (Mayr 1982; Landman 1991). This Mendelian genetic model underpins population genetic theory and forms the basis of the mod-

ern synthesis of evolutionary biology. A common belief is that the inheritance debate was conclusively settled by the weight of empirical evidence demonstrating the exclusive validity of the Mendelian genetic model and the impossibility of non-DNA-sequence-based (nongenetic) inheritance (Mayr 1982; Landman 1991; Cook 1999). In reality, however, evidence of nongenetic inheritance continued to accumulate, despite being largely ignored in the development of evolutionary theory (Sapp 1987; Jablonka and Lamb 1995, 2005).

Observational and experimental data, as well as recent advances in understanding of cell function and development, have revealed many routes (mechanisms) of information transfer across generations that exist alongside the genetic inheritance system. In humans, complex cultural variation affecting virtually every facet of behavior is transmitted through a combination of example and deliberate instruction (Richerson and Boyd 2005; Aldridge et al. 2009). In nonhuman animals with parental care, parents can influence offspring behavior through example (Avital and Jablonka 2000), and research over recent decades has provided numerous examples of such influence (e.g., song learning in birds; Freeberg 2000). In virtually all species, parents influence the environment in which their offspring develop (Roitberg 1998; Freedberg and Wade 2001; Rohlf and Hoffmeister 2005).

Nongenetic inheritance is by no means limited to behavioral influence, however, and parents transmit to their offspring a wide range of biomolecules and compounds, in addition to DNA, whose quality and quantity can influence offspring phenotype (Mousseau and Fox 1998). Novel molecular mechanisms of inheritance have been discovered, such as transmitted variation in DNA methylation patterns, gamete cell wall proteins, and RNA (Ashe and Whitelaw 2006; Rakyen and Beck 2006; Richards 2006; Lalancette et al. 2008; Nowacki et al. 2008; Youngson and Whitelaw 2008). For example, variation in coat color and

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heart morphology can be transmitted over many generations via RNA-based inheritance (Rassoulzadegan et al. 2006; Cuzin et al. 2008; Wagner et al. 2008). Such mechanisms can mediate effects of parental genotype on offspring phenotype (Nelson et al. 2010; Yazbek et al. 2010). Many nongenetically transmitted factors also reflect the influence of parental environment and therefore can sometimes serve as vehicles for the transmission of plastic (acquired) traits. For example, experimental evidence in rodents shows that exposure to endocrine-mimicking substances can give rise to stable transgenerational effects on health and fertility, apparently through modification of DNA methylation patterns in sperm (Anway et al. 2005, 2006; Anway and Skinner 2006). Through such mechanisms, acquired traits such as maternal and paternal condition (Bonduriansky and Head 2007), immunity (Lemke et al. 2004), diet-derived substances and diet preferences (Myers et al. 2005), and plastic antipredator defenses (Agrawal et al. 1999) can be transmitted to offspring.

Despite this growing list of examples of nongenetic inheritance, their varied forms across traits and species lend them all the appearance of being special cases and can lead one to question the generality of such effects. Thought of more broadly, however, all of these specific mechanisms can be viewed as instances of the inheritance of a nongenetic “interpretive machinery” comprising substances, cellular structures, and circumstances that have the potential to influence gene expression and development. All living organisms rely on the inheritance of such nongenetic machinery to make sense of or decode the information present in genes. The inheritance of a cellular machinery is the very least that is required, but all of the inherited factors described above influence how the information encoded in genetic material affects development, and therefore all can be viewed as being part of this interpretive machinery. In this sense, nongenetic inheritance has the same degree of universality as does genetic inheritance.

The recognition that nongenetic interpretive machinery is inherited alongside genetic material is not new (Sapp 1987), but nevertheless, this general aspect of inheritance has not played a significant role in the development of evolutionary theory. There are several reasons for this. One apparent reason is a lack of consensus about a definition of this phenomenon. Many influential authors (e.g., Mayr 1982) have criticized and rejected a concept of nongenetic (or soft or Lamarckian) inheritance involving the transmission of acquired traits via modification of the parental germ-line DNA sequence. However, although modification of the germ-line DNA sequence may be possible (see Steele 1979; Blanden et al. 1998; Steele et al. 1998), most evidence of nongenetic inheritance reflects a class of mechanisms based on the transmission of phenotypic or environmental factors (which can be viewed as an interpretive machinery

for the DNA) alongside the transmission of alleles (Bonduriansky and Day 2009). It is this latter concept of nongenetic inheritance that we consider in this article.

Another reason for the neglect of nongenetic inheritance seems to rest on the implicit assumption that the relevant nongenetic interpretive machinery is largely identical across individuals or that variation in this machinery is entirely determined by genetic variation. As a result, ultimately it is only the genes that matter (Sapp 1987; Dickins and Dickins 2008). However, it is now clear from a growing list of examples (e.g., Agrawal et al. 1999; Lemke et al. 2004; Anway et al. 2005; Rassoulzadegan et al. 2006; Cuzin et al. 2008; Wagner et al. 2008) that these assumptions are not generally true. As we illustrate below, the fact that the interpretive machinery can be inherited separately from genes—and can mutate independent of genes—could have important and unappreciated evolutionary implications.

Other reasons for the neglect of nongenetic inheritance reflect doubts about its importance in long-term evolution. These doubts stem largely from the idea that nongenetically inherited factors lack the stability and combinatorial complexity of genes and therefore cannot, by themselves, account for adaptation and biological diversity (Ridley 1996; Haig 2007; Dickins and Dickins 2008). Of course, few would dispute the central importance of genetic inheritance for evolution, but the relevant question to ask is not whether nongenetic inheritance, by itself, could provide a sufficient basis for evolution but rather whether nongenetic inheritance can influence the course of evolution. Over the past 30 years, several bodies of theory have been developed that illustrate this possibility. These include models of gene-culture coevolution (Cavalli-Sforza and Feldman 1981; Boyd and Richerson 1985; Richerson and Boyd 2005), niche construction (Laland et al. 1996, 1999; Odling-Smee et al. 2003), indirect genetic effects (Wolf et al. 1998), maternal effects (Kirkpatrick and Lande 1989; Mousseau and Fox 1998), inheritance of acquired traits (Pál 1998; Pál and Miklós 1999), and transgenerational epigenetic effects (Jablonka et al. 1992, 1995; Lachmann and Jablonka 1996). Each of these theories has shown, within its own domain, that an extension and generalization of the notion of inheritance can lead to novel evolutionary predictions that were not anticipated within the narrow Mendelian genetic framework of the modern synthesis. To date, however, this work constitutes a rather disparate and loosely connected set of ideas and models.

All of the above considerations suggest that an adequate model of inheritance might profitably be obtained by expanding our current view to allow explicitly for the inheritance of interpretive machinery (broadly construed), alongside genetic material. This would encompass the entire empirically established range of specific inheritance

mechanisms, including transgenerational epigenetic inheritance and genomic imprinting, transmission of diverse cytoplasmic and somatic factors, nutrients, elements of the extraorganismal environment, and the transmission of behavioral variation through learning (Bonduriansky and Day 2009). Our purpose here is to propose such a formal expansion. Our formulation shows that despite the considerable diversity of proximate mechanisms of nongenetic inheritance, they can all be integrated within a relatively simple theoretical framework that reveals their evolutionary consequences.

A General Unified Framework

We consider a situation in which inheritance occurs via a combination of genetic and nongenetic mechanisms. Following definitions introduced previously (Bonduriansky and Day 2009), nongenetic mechanisms are mediated by the transmission to offspring of an element of the parental phenotype or environment. The transmissible factor mediating nongenetic inheritance can be any element of the interpretive machinery that influences development, such as methylation patterns, RNA, resources, behavior/culture, or even some aspect of the ambient environment. In contrast, genetic inheritance is mediated strictly by the transmission of DNA sequences (alleles). Thus, although genes play an essential role in all inheritance phenomena (e.g., the transmission of cultural variation requires a human genome), the above definitions make it possible to distinguish conceptually those phenomena that conform to classic modern synthesis assumptions (i.e., inheritance via Mendelian segregation and transmission of alleles) from phenomena that necessitate a broadening of the concept of inheritance (i.e., maternal/paternal effects, indirect genetic effects, transgenerational epigenetic inheritance and genomic imprinting, cultural inheritance, etc.). All analyses, including simulations and numerical calculations for generating the results, can be found in a zip file (available in the online edition of the *American Naturalist*).

We use g to denote the value of the genetic component, and for the moment we leave the different possible values of g arbitrary. In the examples that follow, sometimes g will be taken as an indicator variable, indicating the presence or absence of a particular gene sequence variant. In other instances, g will be taken as a quantitative character (e.g., breeding value). Similarly, we use h to denote the value of the nongenetic component and allow it to be either an indicator variable or a quantitative character as well. For example, in the former case, it might represent the presence or absence of methylation at a particular location in the genome, while in the latter case, it might represent some measure of the state of the cellular machinery or the level of resources transmitted from parent

to offspring. Variation among individuals in h can either be related to variation in g or be partly or fully independent of g .

Throughout, we use the term “evolution” in the conventional way to refer to transgenerational change in allele frequencies (or, in some cases, change in the population mean phenotype). In line with past usage, we also sometimes refer to cultural evolution or gene-culture coevolution (Cavalli-Sforza and Feldman 1981; Boyd and Richerson 1985; Richerson and Boyd 2005). Although we believe that phenotypic change brought about strictly by nongenetically transmitted factors can be interesting and important in its own right (e.g., see Cavalli-Sforza and Feldman 1981; Lachmann and Jablonka 1996; Odling-Smee et al. 2003), we emphasize effects on evolution in the conventional (genetic) sense in the following discussion in order to illustrate the implications of nongenetic inheritance in terms of existing evolutionary theory.

We model a population of replicating individuals in discrete time and allow for overlapping generations. Individuals might differ in both their genetic and their nongenetic components. We use b to denote the number of surviving offspring produced by an individual in one time step and p for the probability of survival of the parent itself to the next time step. Thus, b can be viewed as the product of the number of offspring produced and the probability that an offspring survives to maturity (here assumed to occur after surviving one time step). Therefore, $W = b + p$ is the total number of individuals produced at the end of a time step (i.e., the parent, if it survives, plus its surviving offspring). The fitness components are assumed to be functions of the genetic and nongenetic values.

The values of g and h in the offspring produced by an individual might differ from those of the individual itself, and the extent to which this is true will depend on the nature of inheritance. We use $g + \Delta g^b$ and $h + \Delta h^b$ to denote the expected values of g and h in the offspring, where Δg^b and Δh^b are the expected differences in these quantities between the parent and its offspring. Likewise, during the process of surviving from one time step to the next, the values of g and h might change in the parent. We use Δg^p and Δh^p to denote the expected difference in g and h after versus before the parent survives one time step.

With these specifications, we can now derive an equation for the change in the mean values of g and h . The mean values of g and h in the next time step are found by calculating the expectation over all individuals in the population, weighted by the fraction that is new offspring versus surviving parents:

$$\begin{aligned}\bar{g}(t+1) &= \frac{E(b) E[b(g + \Delta g^b)]}{E(W) E(b)} + \frac{E(p) E[p(g + \Delta g^p)]}{E(W) E(p)}, \\ \bar{h}(t+1) &= \frac{E(b) E[b(h + \Delta h^b)]}{E(W) E(b)} + \frac{E(p) E[p(h + \Delta h^p)]}{E(W) E(p)},\end{aligned}$$

where we also use overbars to denote expectations. Subtracting $\bar{g}(t)$ and $\bar{h}(t)$ from the above equations, respectively, and defining $\Delta\bar{g} = \bar{g}(t+1) - \bar{g}(t)$ and $\Delta\bar{h} = \bar{h}(t+1) - \bar{h}(t)$, we obtain

$$E(W)\Delta\bar{g} = E[b(g + \Delta g^b)] - \bar{g}E(W) + E[p(g + \Delta g^p)],$$

$$E(W)\Delta\bar{h} = E[b(h + \Delta h^b)] - \bar{h}E(W) + E[p(h + \Delta h^p)],$$

or

$$\bar{W}\Delta\bar{g} = E(Wg) - \bar{g}\bar{W} + E(b\Delta g^b) + E(p\Delta g^p),$$

$$\bar{W}\Delta\bar{h} = E(Wh) - \bar{h}\bar{W} + E(b\Delta h^b) + E(p\Delta h^p).$$

These can be written in the more familiar form

$$\bar{W}\Delta\bar{g} = \text{Cov}(W, g) + E(b\Delta g^b) + E(p\Delta g^p), \quad (1a)$$

$$\bar{W}\Delta\bar{h} = \text{Cov}(W, h) + E(b\Delta h^b) + E(p\Delta h^p). \quad (1b)$$

Equations (1) are versions of Price's (1970, 1972) equation, extended to allow for overlapping generations.

The first terms of equations (1) represent the effect of natural selection on the genetic (eq. [1a]) and nongenetic (eq. [1b]) components. Each is the covariance between an individual's fitness and its genetic or nongenetic value, respectively. For example, all else equal, if this is positive for the genetic component (i.e., individuals with high genetic values also tend to have high fitness), then the average genetic value in the population will increase. Likewise, if this is positive for the nongenetic component, then the average nongenetic value in the population will increase.

The second term in each equation represents the changes in genetic (eq. [1a]) and nongenetic (eq. [1b]) values that occur during transmission from parent to offspring (henceforth termed "reproductive transmission"), reflecting the transmission rules for the factor in question (table 1). The term $E(b\Delta g^b)$ is the fecundity-weighted expected change from parent to offspring in the genetic component. Thus, for example, if g denotes the presence of a particular genotype in asexual individuals, then Δg^b would be 0 unless mutation occurs during reproduction. Analogous considerations hold for the nongenetic component. Notice, however, that the specific magnitude of such changes during transmission will often be different for genetic and nongenetic components. For example, nongenetic components such as methylation states might have a higher mutation rate than genetically transmitted material. Likewise, genetic and nongenetic factors might change in qualitatively different ways during transmission

from parents to offspring. For example, the nongenetic component need not obey the rules of Mendelian segregation, and it might involve important aspects of environmental induction as well.

The third term in equations (1) accounts for any change in genetic (eq. [1a]) and nongenetic (eq. [1b]) values that occurs in parental individuals as they survive from one time step to the next (henceforth termed "survival transmission"). The term $E(p\Delta g^p)$ is the survival-weighted expected change in genetic value in an individual from one time step to the next. It is usually assumed that the genetic value of an individual remains constant throughout its lifetime and, therefore, that $E(p\Delta g^p) = 0$ in equation (1a). On the other hand, nongenetic material might often change during an individual's lifetime, making $E(p\Delta h^p)$ nonzero. Indeed, phenotypic plasticity over an individual's lifetime is a familiar example in which the change in this term is environmentally induced. It is important to note, however, that while technically such changes occur within a generation, equations (1) include them simply as another component of change in the population mean phenotype.

Interactions between Genetic and Nongenetic Inheritance

Although it is not immediately apparent from equations (1), the genetic and nongenetic components of inheritance can interact with each other in subtle and interesting ways. To see why this is so in a general sense, suppose that fitness W is a function of the genetic and nongenetic components and possibly the average value of these components in the population (this allows for simple kinds of frequency-dependent selection). Thus, we have $W(g, h; \bar{g}, \bar{h})$. If we further suppose that both g and h are quantitative characters and that the variation in these characters in the population is relatively small, then we can use a first-order approximation for fitness as $W(g, h; \bar{g}, \bar{h})/\bar{W} \approx 1 + \beta_g(\bar{g}, \bar{h})(g - \bar{g}) + \beta_h(\bar{g}, \bar{h})(h - \bar{h})$, where $\beta_j(\bar{g}, \bar{h}) = (\partial W(\bar{g}, \bar{h}; \bar{g}, \bar{h})/\partial j)/\bar{W}$ is the selection gradient on j . Substituting this into equations (1) gives

$$\begin{aligned}\Delta\bar{g} &= \sigma_{gg}\beta_g(\bar{g}, \bar{h}) + \sigma_{gh}\beta_h(\bar{g}, \bar{h}) \\ &\quad + \frac{1}{\bar{W}}E(b\Delta g^b) + \frac{1}{\bar{W}}E(p\Delta g^p),\end{aligned} \quad (2a)$$

$$\begin{aligned}\Delta\bar{h} &= \sigma_{gh}\beta_g(\bar{g}, \bar{h}) + \sigma_{hh}\beta_h(\bar{g}, \bar{h}) \\ &\quad + \frac{1}{\bar{W}}E(b\Delta h^b) + \frac{1}{\bar{W}}E(p\Delta h^p).\end{aligned} \quad (2b)$$

Here σ_{ij} is the covariance between inheritance components i and j .

The main difference between equations (1) and (2) is that equations (2) split the covariance term into two pieces.

Table 1: Patterns of inheritance and reproductive transmission rules

Inheritance pattern	Mechanisms/agents	Reproductive transmission rules		
		Segregation	Dominance	Environment
Stable hereditary units transmitted by both parents to offspring of both sexes ^A	Autosomal, X-linked, Z-linked alleles	Mendelian segregation	Biallelic expression with various patterns of dominance	Possible influence of F_1 environment on expression in F_1 but not on transmission to F_2
Stable hereditary units transmitted by both parents to offspring of both sexes but expressed in one sex only ^B	Sex-limited alleles	Mendelian segregation	Biallelic expression with various patterns of dominance	Possible influence of F_1 environment on expression in F_1 but not on transmission to F_2
Stable hereditary units transmitted within sex only (mother-daughter or father-son) ^B	Y-linked, W-linked alleles	Within-sex transmission	Monoallelic expression (hemizygoty)	Possible influence of F_1 environment on expression in F_1 but not on transmission to F_2
Parent-of-origin effects (genomic imprinting) ^C	Methylation	Mendelian segregation	Parent-of-origin-dependent expression with various patterns of dominance	Possible influence of F_1 and F_2 environment on parent-of-origin-dependent expression in F_2
Influence of one or both parents' genetically determined phenotypic traits on offspring of one or both sexes (IGE) ^{ABC}	Parental traits	Mendelian segregation of alleles whose expression in F_1 affects phenotype of F_2	?	Possible influence of F_1 environment on expression in F_1 but not on transmission to F_2
Semistable hereditary units transmitted by one or both parents to offspring of one or both sexes ^{ABC}	Methylation patterns (epialleles), RNA (paramutation)	Transmission of maternal and/or paternal phenotype or environment	?	Possible influence of F_1 and F_2 environment on transmission to and expression in F_2 and transmission to F_3
Unstable factors (waning quickly unless reestablished each generation) transmitted by one or both parents to offspring of one or both sexes ^{ABC}	Resources, hormones, behavior, immunity, status, resource patch, etc.	Transmission of maternal or paternal phenotype or environment	?	Possible influence of F_1 and F_2 environment on transmission to and expression in F_2 and transmission to F_3

Note: Proximate agents or mechanisms (e.g., molecular, behavioral) that mediate transmission are shown for each pattern, and shared letters denote patterns that can be difficult to distinguish empirically. Segregation outlines the pattern of transmission and segregation, dominance outlines how maternal and paternal influences interact in offspring, and environment outlines the possible influence of ambient environment. The first three rows represent genetic inheritance, and the last four rows represent nongenetic inheritance. IGE, indirect genetic effect.

Equations (2) illustrate that selection acts on the genetic and nongenetic components of inheritance both directly and indirectly. The first term of equation (2a) is the variance in the genetic component, multiplied by the selection gradient on genes, and accounts for direct selection on genes. The second term of equation (2a) is the covariance between genetic and nongenetic components, multiplied by the selection gradient on nongenetic material, and accounts for indirect selection on genes. Evolution of the

genetic component can occur indirectly if selection acts on the nongenetic component, provided there is a statistical association between genes and nongenetic material. An analogous interpretation holds for transgenerational change in the nongenetic component in equation (2b).

In addition to correlated responses to selection, equations (2) reveal that nongenetic inheritance can affect the evolutionary dynamics of genetic inheritance (and vice versa) directly through the selection gradients. For ex-

ample, in equations (2), the selection gradient for the genetic component, β_g , is a function of the average genetic and nongenetic components in the population. As a result, changes in the nongenetic composition of the population can directly alter the adaptive landscape of genes and thereby have long-term effects on evolution. An example below, based on gene-culture coevolution, will illustrate this phenomenon.

There can also be interactions between genetic and nongenetic inheritance through the other two terms. For example, the expected change in the genetic component from parent to offspring might be affected by methylation level if high methylation suppresses transposon activity and thus mutation (Johannes et al. 2009). Likewise, some genetic patterns might be more likely to acquire methyl groups than others, making the expected change in the nongenetic component dependent on genotype. An example of this involving epialleles is presented below.

Clearly, the diversity of inheritance mechanisms—that is, proximate pathways mediating the effects of parents on offspring (see Bonduriansky and Day 2009)—is very large. However, these mechanisms engender a much more limited array of inheritance patterns, that is, unique combinations of reproductive transmission and survival transmission rules (table 1). The theoretical framework provided by equations (1) can therefore be used to investigate the evolutionary consequences of a great diversity of inheritance mechanisms, regardless of the proximate details of transmission. As the examples presented below will illustrate, characterizing the effects of any kind of nongenetic inheritance simply requires the specification of three ingredients (corresponding to the three terms in eqq. [1]): (1) how genetic and nongenetic values affect individual fitness; (2) the reproductive transmission rules: how genetic and nongenetic values change during transmission from parent to offspring; and (3) the survival transmission rules: how genetic and nongenetic values change when an adult survives from one time step to the next. Thus, for example, phenomena as distinct as cultural and epigenetic mechanisms of inheritance can, in some circumstances, be regarded as functionally equivalent in terms of their influence on the course of genetic evolution.

Examples

The above results provide a general mathematical framework within which one can understand the role of nongenetic inheritance in evolution and how it interacts with genetic inheritance. To gain a deeper understanding of the potential evolutionary consequences of nongenetic inheritance and to appreciate the breadth of the above formalism, we now consider a series of examples. All are based on the general model introduced above and are presented

in order of increasing complexity. We simplify matters by focusing on populations with nonoverlapping generations (i.e., $p = 0$).

Pure Noise

Consider a situation in which an environmentally induced nongenetic factor affects the phenotype within generations but is not transmitted to offspring. This is the case of conventional within-generation phenotypic plasticity or environmental noise. We start with this example to illustrate the connection between conventional plasticity and the examples of nongenetic inheritance that will follow.

We model a quantitative trait z whose value is made up of the sum of a genetic component, g (the breeding value), and some nongenetic deviation, h , that is acquired anew in each generation (i.e., it is not transmitted from parent to offspring). The mean value of h is denoted h_e and is allowed to vary as a function of the environment. To employ the above framework, we need to specify fitness, reproductive transmission, and survival transmission. We consider these in reverse order. Since $p = 0$, there is no adult survival, and thus survival transmission is nonexistent. For reproductive transmission, we assume that there is nothing that biases the genetic values that are transmitted from parent to offspring (e.g., no mutational bias or meiotic drive) and that reproduction is asexual. Therefore the term $E(b\Delta g^b)$ will be 0 (i.e., offspring are genetically identical to their mothers). On the other hand, because the nongenetic component of the trait is not transmitted to offspring, and because the average value of this component of the trait is h_e for all genotypes, we have $\Delta h^b = h_e - h$.

To complete the model specification, we next need to specify fitness, but some insights can already be gained without yet making any additional assumptions. So far, equations (1) become

$$\bar{b}\Delta\bar{g} = \text{Cov}(b, g), \quad (3a)$$

$$\begin{aligned} \bar{b}\Delta\bar{h} &= \text{Cov}(b, h) + E(b\Delta h^b) \\ &= \text{Cov}(b, h) + E[b(h_e - h)] = 0. \end{aligned} \quad (3b)$$

This illustrates the fact that in the absence of directional change in the environment itself, the average environmental component does not change over time. As a result, given that the trait is additively determined by both g and h (i.e., $z = g + h$), any change in the mean trait value over time is entirely due to change in the mean breeding value; that is, $\Delta\bar{z} = \Delta\bar{g}$.

To take things slightly further, we can partially specify fitness by using the simplifications employed in the derivation of equations (2). This shows that the average breed-

ing value—and thus the average trait value—evolves according to

$$\Delta \bar{z} = \sigma_{gg} \beta_g(\bar{g}, \bar{h}) + \sigma_{gh} \beta_h(\bar{g}, \bar{h}). \quad (4)$$

Moreover, if fitness b depends only on the phenotype, $z = g + h$, rather than on g and h individually, then $\beta_g = \beta_h \equiv \beta_z$. Furthermore, there will be no covariance between the genetic and the nongenetic component of the trait (i.e., $\sigma_{gh} = 0$), and thus equation (4) reduces to the familiar breeder's equations from quantitative genetics, $\Delta \bar{z} = \sigma_{gg} \beta_z$ (Lande 1976, 1979).

Taking the specification of fitness further still, suppose there is stabilizing selection on the phenotype z . This can be modeled by assuming that an individual's fecundity is related to its phenotype according to the function $b(z) = \exp(-s(z - \theta)^2/2)$. Here θ is the phenotype with the maximum possible fecundity and s is a measure of the strength of selection. If the variance in z is small, then the selection gradient can be approximated as $\beta_z = s(\theta - \bar{z})$. Consequently, the mean breeding value—and thus the mean phenotype in the population—evolves as $\Delta \bar{z} = \sigma_{gg} s(\theta - \bar{z})$. Assuming that the genetic variance remains roughly constant over the time frame of interest, the mean phenotype then approaches its equilibrium value of θ geometrically (fig. 1).

Maternal Effects

The next simplest example allows the environmental component of the trait, h , to be inherited from parent to offspring. This is the case of classic maternal effects, where mothers transmit material (e.g., resources) in addition to genetic material to their offspring.

Consider the situation modeled by Kirkpatrick and Lande (1989), in which a quantitative trait z is determined by an individual's breeding value plus a quantity proportional to its mother's phenotype. The only difference from the above model comes from a change in reproductive transmission. The genetic component is the same as before, but the nongenetic component, $E(b\Delta h^b)$, now differs. Specifically, the offspring now inherits, on average, the nongenetic value $mz = m(g + h)$ from a parent with phenotypic value $z = g + h$, where m is a constant of proportionality that scales the effect of a mother's phenotype on its offspring (Bonduriansky and Day 2009). As a result, instead of $\Delta h^b = h_c - h$, we now have $\Delta h^b = m(g + h) - h$. The general equations are then

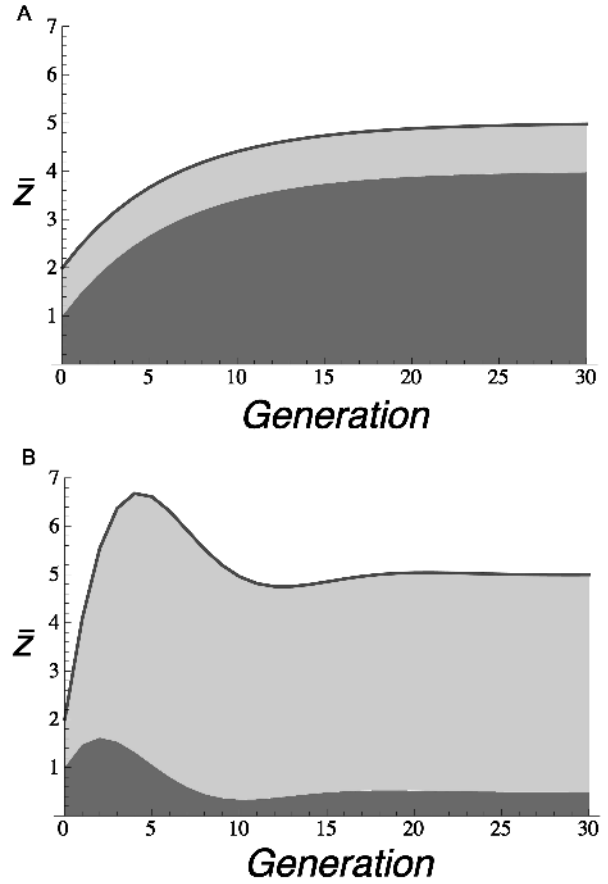


Figure 1: Plots of the evolutionary dynamics of a trait z for the models of pure noise (A) and maternal effects (B), using the selection gradient $\beta_z = s(\theta - \bar{z})$. Different shading represents that part of z made up of genetic (dark gray) and nongenetic (light gray) components. The equilibrium trait value is $\theta = 5$ in both cases, and the initial trait value is $\bar{z} = 2$, with equal genetic and nongenetic contributions. Parameter values: $\sigma_{gg} = 1$, $\sigma_{gh} = 0.05$, $\sigma_{zz} = 2$, $s = 0.15$, $\theta = 5$, $h_c = 1$, $m = 0.9$.

$$\bar{b}\Delta \bar{g} = \text{Cov}(b, g), \quad (5a)$$

$$\begin{aligned} \bar{b}\Delta \bar{h} &= \text{Cov}(b, h) + E(b\Delta h^b) \\ &= \text{Cov}(b, h) + E\{b[m(g + h) - h]\} \\ &= m\text{Cov}(b, z) + \bar{b}(m\bar{z} - \bar{h}). \end{aligned} \quad (5b)$$

Note that the change in the average nongenetic component across generations is no longer 0 (cf. eqq. [3b], [5b]).

If we now use the above approximation for fitness and assume that b depends only on the phenotype z (as in Kirkpatrick and Lande 1989), equations (5) reduce to

$$\Delta \bar{g} = (\sigma_{gg} + \sigma_{gh})\beta_z, \quad (6a)$$

$$\Delta \bar{h} = m\sigma_{zz}\beta_z + m\bar{z} - \bar{h}. \quad (6b)$$

Notice that because the genetic and nongenetic components now both change across generations, we can no longer model evolutionary change with a single variable (we note that Kirkpatrick and Lande [1989] present an equivalent formulation that makes use of a single equation with a time lag, but this also involves two variables since it tracks two successive values of the mean phenotype). As a result, the partitioning in equations (6) reveals that nongenetic inheritance decouples change in the mean phenotype from change in the mean genetic value. Moreover, there will now typically be some covariance between g and h , and thus the evolutionary dynamics of the genetic component of the population are different from the case of pure noise. Positive covariance will increase the speed of evolution, while negative covariance will decrease it.

To further illustrate the effects of nongenetic inheritance, suppose, as above, that the selection gradient is given by $\beta_z = s(\theta - \bar{z})$. In this case, equations (6) become

$$\Delta \bar{g} = (\sigma_{gg} + \sigma_{gh})s(\theta - \bar{g} - \bar{h}), \quad (7a)$$

$$\Delta \bar{h} = m[\sigma_{zz}s(\theta - \bar{g} - \bar{h}) + \bar{g} + \bar{h}] - \bar{h}. \quad (7b)$$

Figure 1B illustrates that the transient dynamics of model (7) differ from those of the traditional model involving pure noise because phenotype and genotype are decoupled in a way that allows the mean phenotype to change over generations without changes in the mean genotype.

For the assumptions made in this model (specifically, that both fitness and the extent of nongenetic inheritance depend only on an individual's phenotype), the equilibrium mean phenotype with nongenetic inheritance is the same as that from the traditional model with genetic inheritance alone. More generally, however, nongenetic inheritance will also influence the equilibrium value, as shown in some of the examples below. Even in the current example, however, the equilibrium mean phenotype is composed of different underlying factors in the two cases. In the case of pure noise, $\hat{g} = \theta - h_c$ and $\hat{h} = h_c$, whereas in the case of maternal effects, $\hat{g} = (1 - m)\theta$ and $\hat{h} = m\theta$. In both cases, the mean phenotype is $\hat{z} = \theta$, but they differ in the extent to which this mean phenotype is comprised of genetic versus nongenetic factors. This could have implications for the sensitivity of the mean phenotype to changes in the ambient environment.

Indirect Genetic Effects

Indirect genetic effects (IGEs) of parents on their offspring can also be viewed as a special case of nongenetic inheritance. We restrict attention to “vertical” (parent-offspring) IGEs because these conform to the conventional definition of inheritance as the influence of parents on

offspring (Bonduriansky and Day 2009). Such vertical IGEs can be defined as the effect of a parent's genotype on its offspring, mediated by the interaction of the parent's phenotype and the development of the offspring (Wolf et al. 1998).

Our example of IGEs is similar to that of maternal effects in that both involve the “transmission” of some nongenetic factor that affects the development of the offspring phenotype, in addition to offspring genes. The distinction between the two is that for an IGE, the mediating nongenetic factor is exclusively a function of parental genotype. Although this is a subtle distinction, it can lead to different predictions about transgenerational change in the nongenetic component of the trait.

To model IGEs in the above framework, we simply need to modify the reproductive transmission term for nongenetic inheritance, $E(b\Delta h^b)$. As a simple example, rather than assuming that $\Delta h^b = m(g + h) - h$, as in maternal effects, suppose that $\Delta h^b = mg - h$ instead (i.e., the nongenetic component that an offspring receives is proportional to its parent's breeding value). In this case, we have

$$\bar{b}\Delta \bar{g} = \text{Cov}(b, g), \quad (8a)$$

$$\bar{b}\Delta \bar{h} = m\text{Cov}(b, g) + \bar{b}(m\bar{g} - \bar{h}), \quad (8b)$$

or, using the above approximation for the selection gradient,

$$\Delta \bar{g} = (\sigma_{gg} + \sigma_{gh})\beta_z, \quad (9a)$$

$$\Delta \bar{h} = m(\sigma_{gg} + \sigma_{gh})\beta_z + m\bar{g} - \bar{h}. \quad (9b)$$

All else equal, the genetic component evolves in the same way as it does with maternal effects, but now the change in the nongenetic component is different, as can be seen by comparing equations (6b) and (9b).

Epialleles

In this example, we consider discrete genetic and nongenetic variants, motivated by the discovery of epialleles (i.e., heritable alternative methylation states). We show that when the methylation state affects the phenotype, the inheritance of such nongenetic factors can alter both the dynamics and the outcome of evolution. This example suggests the possibility of quite complex genetic-epigenetic interactions.

We model a single locus with two alleles (e.g., A and a), along with a single nongenetic factor that can be inherited in two discrete states (methylated and unmethylated). In the context of equations (1), we use the indicator variables $g = 1$ to denote the presence of allele A ($g =$

0 denotes allele a) and $h = 1$ to denote the methylated state ($h = 0$ denotes the unmethylated state). We then need to specify the three model components. As before, we ignore survival transmission. For reproductive transmission, we assume that genetic mutation is negligible and that alleles segregate in a Mendelian fashion. We also assume that the methylation state of an allele is transmitted faithfully to offspring with probability τ . Conversely, with probability $1 - \tau$, there is a lack of fidelity, and offspring with genotype i then end up with methylation state j with probability γ_{ij} (where $\gamma_{i1} + \gamma_{i2} = 1$).

Before specifying the third model component (i.e., fitness), one can show that equations (1) reduce to

$$\bar{b}\Delta\bar{g} = \text{Cov}(b, g), \quad (10a)$$

$$\bar{b}\Delta\bar{h} = \text{Cov}(b, h) + (1 - \tau)(M - D) \quad (10b)$$

(section A in the zip file), where $M = x_{10}b_{10}\gamma_{11} + x_{00}b_{00}\gamma_{01}$ is the overall rate of methylation and $D = x_{11}b_{11}\gamma_{10} + x_{01}b_{01}\gamma_{00}$ is the overall rate of demethylation, both conditional on the parental methylation state not being transmitted. More specifically, x_{ij} is the frequency of individuals with genotype i and methylation state j , and therefore the two terms of M account for the spontaneous methylation of both unmethylated genotypes, whereas the two terms of D account for the spontaneous demethylation of both methylated genotypes.

Notice that because there is no genetic mutation, and because of Mendelian segregation, there is no transmission bias in genes (i.e., alleles are transmitted in a perfectly faithful way; $E(b\Delta g^b) = 0$). On the other hand, methylation state is not always transmitted faithfully, resulting in the extra term in equation (10b), $E(b\Delta h^b) = (1 - \tau)(M - D)$. Specifically, with probability $1 - \tau$, there is unfaithful transmission, and the effect this has on the average level of methylation in the population depends on the difference between the net methylation and demethylation rates, $M - D$.

To take this example further, suppose that the fitness effect of carrying allele A is s_g , the fitness effect of being methylated is s_h , and the fitness effect of having both is $s_g + s_h + s_e$, where s_e is the synergistic or “epistatic” effect of having both. Specifically, s_e will be nonzero whenever the fitness effect of carrying the A allele depends on its methylation status. Equations (10) then become

$$\Delta\bar{g} = \sigma_{gg} \frac{s_g + \kappa_h s_e}{2\bar{b}} + \sigma_{gh} \frac{s_h}{2\bar{b}}, \quad (11a)$$

$$\Delta\bar{h} = \sigma_{gh} \frac{s_g}{2\bar{b}} + \sigma_{hh} \frac{s_h + \kappa_g s_e}{2\bar{b}} + (1 - \tau)(M - D) \quad (11b)$$

(section A in the zip file), where $\kappa_h = \bar{h} + \sigma_{gh}/\bar{g}$ is the probability of the locus being methylated, conditional on

carrying the A allele (and, analogously, $\kappa_g = \bar{g} + \sigma_{gh}/\bar{h}$). Equations (11) are now in the same form as equations (2). Notice, however, that unlike equations (2), the gradient of direct selection on g in equation (11a) (i.e., $(s_g + \kappa_h s_e)/2\bar{b}$) differs from the gradient of indirect selection on h in equation (11b) (i.e., $s_g/2\bar{b}$) by the term $\kappa_h s_e$. This term is analogous to epistatic selection in multilocus population genetic models. Such epistatic selection was implicitly ignored in the approximation used to derive equations (2).

From equations (11), we can again see that selection on genes can have an indirect evolutionary effect on the dynamics of methylation and vice versa. The first term in equation (11a) illustrates that allele A will change in frequency as a result of direct selection acting on this allele. At the same time, the second term in equation (11a) illustrates that allele A will also change in frequency through selection acting directly on methylation, provided that methylation patterns are nonrandomly associated with the alleles (i.e., $\sigma_{gh} \neq 0$).

Model (11) is still relatively general and can be used to explore the transgenerational dynamics of epialleles under a wide variety of assumptions. For example, in the absence of faithful transmission, the methylation status of offspring might depend entirely on genotype. This has been referred to as obligatory epigenetic variation (fig. 1 in Richards 2006) and would have $\gamma_{00} = 1$ and $\gamma_{11} = 1$ (i.e., methylation state is entirely determined by genotype). Alternatively, some genotypes might allow for variation in methylation patterns but not others. This has been referred to as facultative epigenetic variation (fig. 1 in Richards 2006) and would again have $\gamma_{00} = 1$ but would leave γ_{11} (and thus $\gamma_{10} = 1 - \gamma_{11}$) arbitrary. In the extreme case, methylation status might develop entirely independently of genotype, a form of variation that has been called pure epigenetic variation (fig. 1 in Richards 2006). This would have $\gamma_{00} = \gamma_{10}$ instead.

From the theoretical formulation presented here, it is clear that obligatory, facultative, and pure epigenetic variation are merely three points on a continuum of possibilities of how epialleles might behave. Systematic analysis of the evolutionary consequences of different possibilities is beyond the scope of this article, but as an illustrative example, consider an extreme form of pure epigenetic variation in which the locus in question is normally methylated regardless of the allele present. Recent data (Teixeira et al. 2009) has shown that methylation states can sometimes be transmitted faithfully for multiple generations after being experimentally manipulated, and we can use the above model to explore how such nongenetic inheritance affects the ability of a newly advantageous allele to spread.

Given that the locus in question is normally methylated, we have $\gamma_{11} = 1$, and we obtain a model in which, with

probability $1 - \tau$, remethylation occurs after offspring formation (i.e., the offspring state is methylated regardless of parental state). We assume that methylation simply suppresses gene expression, and thus the methylated state alone (i.e., in the absence of mutant allele A) has no fitness effect (i.e., $s_h = 0$). On the other hand, allele A alone (i.e., in the absence of methylation) is assumed to be advantageous ($s_g > 0$). Finally, when both allele A and methylation are present, the gene is suppressed, and thus again there is no fitness effect. As a result, there is epistatic selection (specifically, $s_e = -s_g$). Equations (11) then reduce to

$$\Delta \bar{g} = \sigma_{gg} \frac{s_g(1 - \kappa_h)}{2\bar{b}}, \quad (12a)$$

$$\Delta \bar{h} = \sigma_{gh} \frac{s_g}{2\bar{b}} - \sigma_{hh} \frac{\kappa_g s_g}{2\bar{b}} + (1 - \tau)M, \quad (12b)$$

where $M = (1 - \bar{h})b_0$ and b_0 is the average fecundity of all unmethylated individuals.

Equation (12a) reveals that only direct selection acts on the A allele, and this is given simply by the product of the genetic variance at the A locus and the selection gradient. Only when methylation is absent (which occurs with probability $1 - \kappa_h$) does the presence of the A allele affect fitness. The first term of equation (12b) represents indirect selection on methylation through additive selection on allele A . It is the product of the covariance between the presence of allele A and methylation, and the additive component of selection on allele A . The second term in equation (12b) is the direct selection on methylation, which arises solely from epistatic effects. Only when allele A is present (which occurs with probability κ_g) does the presence of methylation affect fitness. Finally, the third term in equation (12b) represents the effects of remethylation. Note that as a further check on the formulation of model (12), when selection is turned off, the frequency of allele A is unchanging, but the frequency of methylation increases geometrically over time according to $\Delta \bar{h} = (1 - \tau)(1 - \bar{h})$, as we would expect.

Now suppose an unmethylated mutant A allele appears, and consider the ensuing evolutionary dynamics. A linear stability analysis, coupled with numerical simulations (section A in the zip file), shows that the fate of the A allele depends on the quantity $(1 + s_g/2)\tau$. This is the expected fitness of a rare, unmethylated A carrier weighted by the probability of its offspring also not being methylated. If this quantity is < 1 , the mutant A allele nevertheless increases in frequency, but remethylation quickly becomes complete and neutralizes the allele before it reaches fixation. In terms of equations (12), once methylation reaches 100% (i.e., $\bar{h} = 1$), we have $\sigma_{gh} = 0$, $\sigma_{hh} = 0$, $\kappa_g = \bar{g}$, and $M = 0$, making $\Delta \bar{h} = 0$. At the same time, we have

$\kappa_h = 1$ (the probability of an A allele being methylated is 1), and therefore $\Delta \bar{g} = 0$, regardless of the frequency of allele A . As a result, a polymorphism at the genetic locus is attained, where both alleles are methylated and thus neutral (fig. 2A).

If $(1 + s_g/2)\tau$ is larger than 1, then remethylation is infrequent enough that allele A not only increases in frequency initially but also reaches fixation as well (i.e., $\bar{g} = 1$). In terms of equations (12), this gives $\sigma_{gg} = 0$ and thus $\Delta \bar{g} = 0$. At the same time, we also have $\sigma_{gh} = 0$ and $\kappa_h = \bar{h}$, and therefore the methylation level equilibrates (i.e., $\Delta \bar{h} = 0$) when the last two terms of equation (12b) balance each other. At this point, a polymorphism of methylation is attained, where persistent de novo remethylation in each generation is countered by the higher reproductive success of unmethylated individuals (fig. 2A). Thus, there is a critical remethylation–fitness combination, below which a neutral genetic polymorphism results and above which a methylation polymorphism occurs as a result of a selection–remethylation balance (fig. 2B).

Even with this relatively simple pure form of epiallele (sensu Richards 2006), the evolutionary outcomes are substantially different from those that neglect this form of nongenetic inheritance. In the absence of nongenetic inheritance, the advantageous allele always spreads to fixation. With low-fidelity inheritance of methylation patterns, however, the advantageous allele increases in frequency initially, but it reaches a neutral polymorphism, at which point all variation in phenotype is hidden by methylation (fig. 3A). With higher-fidelity inheritance of methylation patterns, the advantageous allele then reaches fixation, but variation in the phenotype is nevertheless maintained through a stable epiallele polymorphism at which selection is balanced by remethylation (fig. 3B). Thus, low fidelity results in genetic variation but a uniform phenotype, while high fidelity results in genetic uniformity but nevertheless variation in the phenotype. In both cases, it is ultimately the pattern of variation in epialleles that determines the pattern of variation in phenotype. As a result, the dynamics of phenotypic change are decoupled from the evolutionary dynamics of the genotype (fig. 3). It is also interesting to note that if environmental perturbations can potentially cause demethylation, then with low fidelity this will release previously hidden genetic (and phenotypic) variation on which selection can act, whereas with high fidelity it will potentially remove (epiallelic) variation that would otherwise exist.

RNA Inheritance

With only slight changes in the above example, we can also model the evolutionary consequences of RNA inheritance (Ashe and Whitelaw 2006; Rassoulzadegan et al.

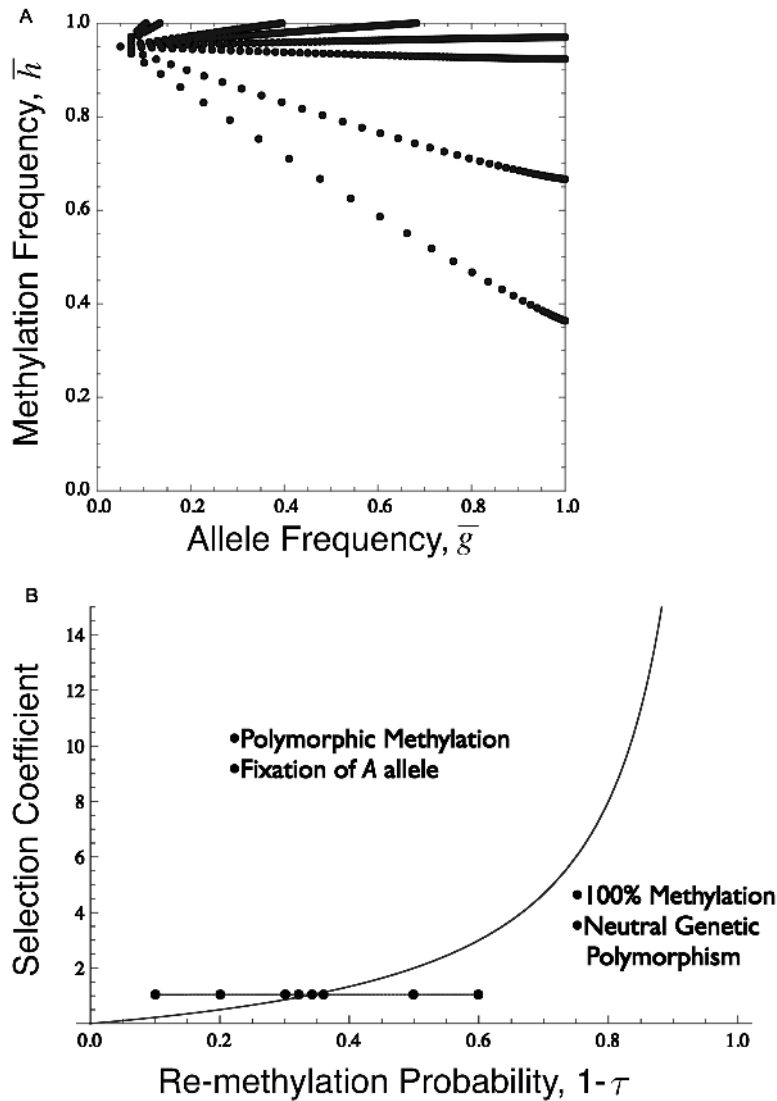


Figure 2: Remethylation dynamics and the spread of advantageous alleles in model (12), with $s_g = 1$; initial conditions $\bar{g}(0) = 0.05$, $\bar{h}(0) = 0.95$, and $\sigma_{gh}(0) = -0.0475$; and different values of $1 - \tau$. The critical value of $1 - \tau$, below which fixation of *A* occurs, is $1/3$. *A*, Phase plane in allele and methylation frequency space. Eight different evolutionary trajectories are shown. Values of $1 - \tau$ from bottom to top are 0.1, 0.2, 0.3, 0.32, 0.34, 0.36, 0.5, and 0.6. *B*, Values of $1 - \tau$ and s_g that yield different evolutionary outcomes. Parameter choices corresponding to the eight evolutionary trajectories in *A* are indicated with circles.

2006, 2007; Suter and Martin 2010). Here, RNAs (which originate as allelic transcripts) can be transmitted to offspring independently of the alleles themselves and affect offspring phenotype. We show that in this case, the non-genetically transmitted factor influences the strength (but not the sign) of selection on genes and can thereby affect the rate of evolution. This example illustrates how, even in single-trait models, the presence of nongenetic inheritance can bring about highly complex evolutionary dynamics that may be difficult to explain under the assumption of purely Mendelian genetic inheritance.

Consider a single locus with two alleles that each code for two different suites of RNA transcripts. It is these transcripts that determine the phenotype of an individual and thus its fitness. The alleles are inherited in a perfectly faithful, Mendelian way as before, but there is also some probability τ that an individual's suite of RNA transcripts is also passed on to its offspring. Failing that, we assume that offspring develop RNA transcripts specific to their genotype.

Using the indicator variables $g = 1$ to denote allele *A* again and now $h = 1$ to denote the suite of RNA tran-

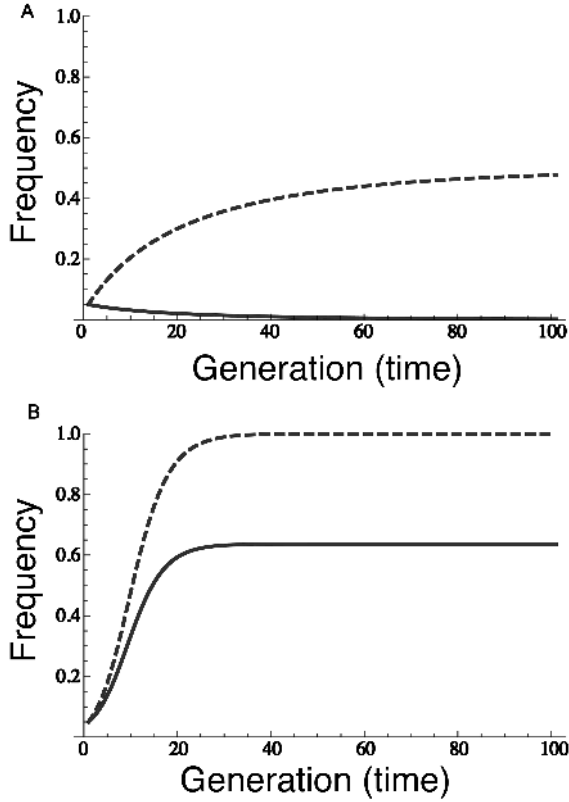


Figure 3: Remethylation dynamics and the spread of advantageous alleles in model (12), with $s_g = 1$ and initial conditions $\bar{g}(0) = .05$, $\bar{h}(0) = .95$, and $\sigma_{gh}(0) = -.0475$. Solid line is the frequency of the advantageous phenotype (i.e., the phenotype resulting from an unmethylated A allele), and dashed line is the frequency of the A allele. *A*, High remethylation probability; $1 - \tau = 0.35$. Allele initially spreads but reaches only an intermediate frequency because it is silenced by methylation. Consequently, the phenotype reverts to the ancestral state. *B*, Low remethylation probability; $1 - \tau = 0.1$. Allele spreads to fixation, at which point a stable phenotypic polymorphism is maintained through the presence of epialleles in a selection-remethylation balance.

scripts specific to allele A (which we will also refer to as the A phenotype), we can specify the three model ingredients as follows. As before, survival transmission is neglected. Likewise, because there is no genetic mutation, and because of Mendelian segregation, we have $E(b\Delta g^b) = 0$. Reproductive transmission of the RNA transcripts is analogous to the obligatory epiallelic variation (sensu Richards 2006) mentioned above, and therefore model (11) can again be used with the modification that $\gamma_{00} = 1$ and $\gamma_{11} = 1$, yielding $E(b\Delta h^b) = (1 - \tau)(M - D)$, where $M = x_{10}b_{10}$ and $D = x_{01}b_{01}$. Finally, fitness is entirely determined by the suite of RNA transcripts, and therefore $s_g = 0$ and $s_e = 0$, reducing equations (11) to

$$\Delta \bar{g} = \sigma_{gh} \frac{s_h}{2b}, \quad (13a)$$

$$\Delta \bar{h} = \sigma_{hh} \frac{s_h}{2b} + (1 - \tau)(M - D) \quad (13b)$$

(section B in the zip file).

Equations (13) reveal that the frequency of allele A evolves solely through indirect selection; selection acts directly on the suite of RNA transcripts (i.e., the phenotype), and the alleles responsible for these transcripts experience this selection only through their association, σ_{gh} , with the transcripts. The frequency of the RNA transcripts themselves changes through direct selection and through reproductive transmission.

Equations (13) show that the phenotype and its genetic underpinning can evolve somewhat independently. The genes ultimately cause the phenotype, but because the phenotype can also be inherited independently, the two are decoupled. In fact, if selection is weak relative to the probability of RNA inheritance (i.e., s_h is small relative to τ), then the dynamics of the covariance, σ_{gh} , are fast relative to allele frequency change. We can then use this covariance to calculate the quasi-equilibrium value of $\kappa_g = \bar{g} + \sigma_{gh}/\bar{h}$, which is the probability that an individual carries the A allele, given that it has the A phenotype.

Under reasonable assumptions, the quasi-equilibrium value is $\kappa_g \approx \bar{g}$ when RNA inheritance is nearly perfect ($\tau \approx 1$; section B in the zip file). That is, when RNA inheritance is very faithful (i.e., every offspring inherits the RNA, regardless of the alleles it inherits), the association between carrying the A allele and having the A phenotype quickly breaks down, and the probability of carrying the A allele is then independent of phenotype (and equal to the frequency of A in the population). On the other hand, when RNA inheritance is very rare, virtually all individuals with the A phenotype will carry the A allele (fig. 4).

How does the occurrence of RNA inheritance affect the evolutionary stability of a population fixed for a particular allele/RNA combination? A linear stability analysis shows that, provided the A phenotype is selectively advantageous, the invasion of the mutant allele (and its associated RNAs and phenotype) is always possible (section B in the zip file). Because of the decoupling of DNA and RNA inheritance, however, there are different ways in which invasion can occur.

If RNA inheritance is negligible, then in the absence of selection the quasi-equilibrium covariance is given by $\sigma_{gh} = \sigma_{gg}$ (section B in the zip file). As a result, equation (13a) becomes $\Delta \bar{g} \approx \sigma_{gg} s_h / 2b$. Evolution of the genetic component of the population then proceeds exactly as predicted from standard population genetics ($\tau = 0.01$ in fig. 4). Selection still acts only on the RNA type that is

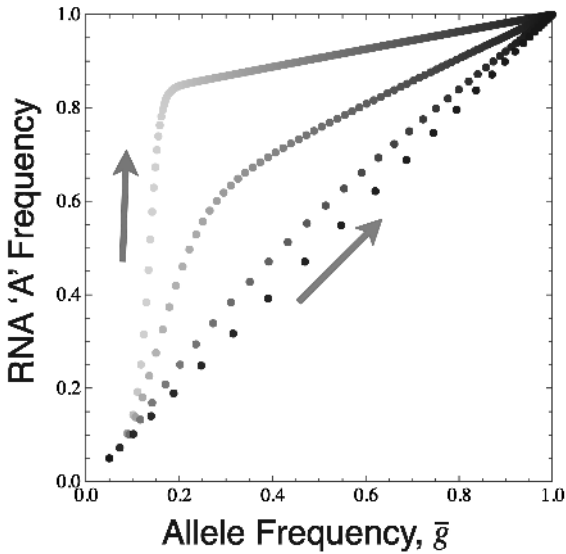


Figure 4: Phase plane in allele and RNA frequency space for model (13), with $s_g = 1$; initial conditions $\bar{g}(0) = .05$, $\bar{h}(0) = .05$, and $\sigma_{gh}(0) = .0475$; and different values of the fidelity of RNA inheritance, τ . Four different evolutionary trajectories are shown, with arrows indicating the direction of change. Values of τ from top to bottom are 0.95, 0.85, 0.65, and 0.01. Shading indicates the probability that an individual carries the *A* allele, given that they have the *A* phenotype (i.e., α), from 0 (white) to 1 (black). Thus, darker shading corresponds to a stronger association between genotype and phenotype.

expressed, but because RNA type is completely linked to genotype, it is as if selection were acting directly on the alleles. This is a standard assumption of most population genetics models. Thus, if a mutant *A* allele appears, it will spread through the population, along with its linked RNA type.

If RNA inheritance is nearly perfect, then the genetic component of the population is largely irrelevant because it is the inherited RNA transcripts that determine the phenotype. Selection then drives a rapid increase in frequency of the *A* phenotype with very little evolutionary change in allele frequency ($\tau = 0.95$ in fig. 4). A quasi-equilibrium frequency of the RNA-induced phenotype is then attained, at which point there is a slow evolutionary increase in allele frequency, along with a gradual fixation of the corresponding RNA type (fig. 4).

For intermediate levels of RNA inheritance, the dynamics fall between these two extremes. Interestingly, the initial rate of invasion of a mutant type is highest for either perfect or negligible RNA inheritance, and it reaches a minimum value at intermediate fidelity (fig. 5). This can also be seen in figure 4, where the spacing of the points (i.e., the evolutionary change in one generation) in the

initial stages of invasion is smallest for intermediate values of fidelity. For very low fidelity, invasion occurs just as in standard population genetic analyses, as described above. As fidelity increases, however, the tight quasi-equilibrium association between allele *A* and the selectively advantageous *A* phenotype begins to break down. This decreases the effective strength of selection on the mutant gene because it begins to decouple genotype from phenotype. As fidelity increases to very high values, the genotype-phenotype coupling breaks down completely, making the allele effectively neutral. As this happens, however, the higher fidelity of RNA inheritance means that the phenotype itself begins to act as a stably inherited unit, thereby once again increasing the rate of invasion. Thus, at the extremes, the initial invasion of the mutant phenotype is fast. However, when fidelity is low, this phenotype is mediated entirely by genotype, whereas when fidelity is high, it is largely independent of genotype (fig. 4).

Macroevolution and Long-Term Divergence

This example will illustrate how an interaction between a genetically inherited trait and a nongenetically inherited trait can contribute to long-term evolutionary divergence. We model the interaction between a genetically inherited factor and the interpretive machinery that affects how this factor is expressed. The interpretive machinery is genetically determined as well, but it can also be inherited independently of the alleles that determined its properties. This example will show that, even though genetic change may be necessary for long-term differentiation and stability of lineages, nongenetic inheritance can potentially

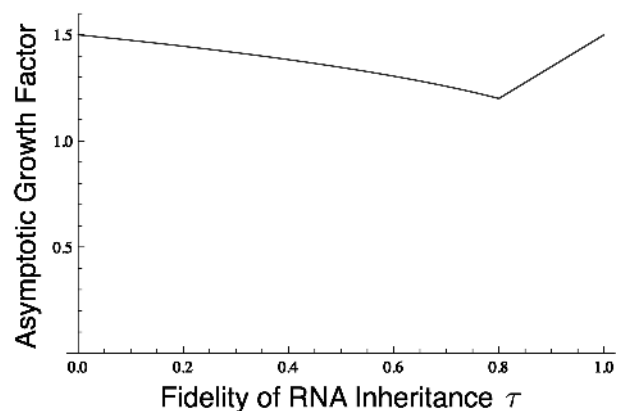


Figure 5: Asymptotic growth factor of an invading advantageous type, as measured by the dominant eigenvalue from a linear stability analysis of model (13). Plot corresponds to figure 4 (i.e., a stability analysis of equilibrium $\bar{g}(0) = 0$, $\bar{h}(0) = 0$, and $\sigma_{gh}(0) = 0$, with $s_g = 1$).

influence the course of genetic differentiation and thereby shape biological diversity. Furthermore, it illustrates that attributing species differences to either genetic or nongenetic inheritance alone can be very difficult.

Consider again a sexual organism with two loci (A and B) and where we explicitly model the inheritance of an interpretive machinery. Suppose that one locus, B, is genetically uniform and that the other locus, A, has two possible alleles (A and a) that code for two different states of the interpretive machinery. Different interpretive machinery results in locus B being interpreted differently and thus will give rise to different phenotypes. Thus, an individual's phenotype is determined by the interpretive machinery that it inherits from its parent (for simplicity, we assume that an individual can inherit this machinery from either parent, e.g., via RNA inheritance; Rassoulzadegan et al. 2006).

During the process of inheritance of the interpretive machinery, we suppose that with probability ρ the machinery transmitted to offspring is "reset" to be that coded for by the parental genotype at the A locus. Conversely, with probability $1 - \rho$, the machinery is simply transmitted intact as it was inherited by the parent, regardless of its genotype.

Now suppose that the species in question is fixed for allele a and the corresponding interpretive machinery and that it colonizes a new environment in which the phenotype arising from machinery A is favored. An analysis similar to that of the previous model can be conducted (section C in the zip file) to show that the evolutionary dynamics in this case are qualitatively the same as in that example. If the reset probability ρ is high (i.e., parents are likely to transmit interpretive machinery that corresponds to their own genotype at the A locus), then evolutionary divergence in this incipient species occurs through both genotype and phenotype since they are coupled. If the reset probability is low, so that the interpretive machinery is transmitted as an independent factor, then evolutionary divergence occurs initially through divergence in the interpretive machinery, followed much later by genetic divergence.

In both cases, at the end of the process, we have a population that has diverged in both genotype and interpretive machinery, and this divergence is stable in the long term. Moreover, it would then appear that the genetic divergence underlies the phenotypic divergence because the newly fixed allele codes for the newly fixed interpretive machinery, and it is this machinery that gives rise to the new phenotype. But this view can be too simplistic. When the reset probability is low, most of the phenotypic divergence occurs initially with very little corresponding genetic divergence. In fact, after initially inducing the selectively advantageous interpretive machinery, allele A can

even be lost through stochastic extinction, and the population can still undergo substantial, stable, phenotypic divergence (fig. 6). Thus, patterns of divergence at equilibrium can be misleading. Both genetic and nongenetic inheritance underlie the basis for divergence in this example when the reset probability is low. Indeed, nongenetic inheritance arguably contributes more to the long-term stability of the divergence in this case, because populations perturbed away from equilibrium evolve back toward it more quickly in terms of the interpretive machinery than they do in terms of genetic composition.

Gene-Culture or Gene-Environment Coevolution

Our final example uses a case of gene-culture coevolution—the evolution of lactase persistence in milk-using human populations—to illustrate an interaction between a genetically inherited trait and a nongenetically inherited trait whose expression is sensitive to the ambient environment (i.e., plastic). It captures the insight that a nongenetically inherited trait can influence both the strength and the sign of selection on a genetically inherited trait

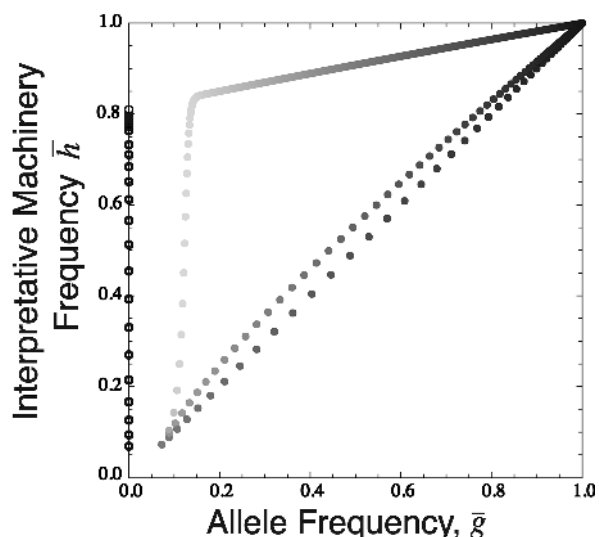


Figure 6: Phase plane in allele and interpretive machinery frequency space. Model is as described in section D in the zip file (available in the online edition of the *American Naturalist*) and has parameter values as in figure 4 (i.e., $s_g = 1$ and initial conditions $\bar{g}(0) = .05$, $\bar{h}(0) = .05$, and $\sigma_{gh}(0) = .0475$). Four different evolutionary trajectories are shown. The three in the interior have values of ρ from top to bottom of 0.05, 0.5, and 0.99. Shading indicates the probability that an individual carries the A allele, given that they have the A machinery, from 0 (white) to 1 (black). Thus, darker shading corresponds to a stronger association between genotype and phenotype. The fourth trajectory along the boundary (open circles) shows divergence in machinery alone for $\rho = .05$.

and thus influence the direction of long-term evolution (Feldman and Cavalli-Sforza 1989; Laland et al. 1996, 1999; Richerson and Boyd 2005). Such an interaction between inheritance systems appears to have played a fundamental role in human evolution (Richerson and Boyd 2005; Laland et al. 2010) and may be equally important in the evolution of other species (Odling-Smee et al. 2003; Jablonka and Lamb 2005; Bonduriansky and Day 2009). For instance, the example presented here easily generalizes to other systems of coevolution between nongenetically transmitted host or diet preferences and genes that influence the ability to exploit the host or food. Likewise, similar examples arise in the coevolution of nongenetically transmitted displays of male quality and genetically determined mating preferences.

Consider a situation involving the spread of the lactase persistence allele in conjunction with the spread of cow domestication and the use of cow's milk in the adult diet (Swallow 2003; Gerbault et al. 2009). In most human populations, as in other mammals, lactase (which facilitates digestion of the milk sugar lactose) is secreted in infancy, but secretion stops at weaning. However, in human populations that began to use milk in the adult diet thousands of years ago, a mutation that causes lactase to be secreted throughout life (lactase persistence allele) has spread. The joint spread of the culture of milk use in adulthood and the evolution of the lactase persistence allele provides a clear case of how the interaction of genetic and nongenetic inheritance systems can influence the direction of long-term evolution (Feldman and Cavalli-Sforza 1989; Richerson and Boyd 2005).

Suppose that there are two alleles segregating at a single locus (e.g., a wild-type allele and a lactase persistence allele), along with two cultural states (e.g., an ancestral state and one in which cows are domesticated and milk is available for use in the adult diet). Central to this example will be the fact that in terms of fitness, certain cultural states are better suited to certain genotypes: an optimal combination is having the lactase persistence allele along with the cultural practice of using milk in the adult diet. We can construct a model for this situation again by specifying the three model ingredients.

As before, we will model a sexual population, and for simplicity, we ignore survival transmission. Likewise, we assume that there is Mendelian segregation and no genetic mutation. Cultural state is transmitted from parent to offspring with probability τ and in a way that is independent of genotype. With probability $1 - \tau$, the offspring instead develops a cultural state independent of that of its parent as follows. With probability λ the offspring correctly figures out the cultural state best suited to its genotype (in terms of fitness), which we refer to as self-learning. With probability $1 - \lambda$, it instead learns from the population,

taking on state 1 (here assumed to be the use of milk in adult diet) with probability κ and state 0 (no use of milk in adult diet) with probability $1 - \kappa$.

Using the indicator variable $g = 1$ to denote the lactase persistence allele and $h = 1$ to denote cow domestication, we can again employ model (11) with the additional specifications $\gamma_{11} = \lambda + (1 - \lambda)\kappa$, $\gamma_{10} = (1 - \lambda)(1 - \kappa)$, $\gamma_{00} = \lambda + (1 - \lambda)(1 - \kappa)$, and $\gamma_{01} = (1 - \lambda)\kappa$. Furthermore, we assume that the probability of learning domestication from the population, κ , is proportional to the frequency of domestication at that time, \bar{h} , with proportionality constant ζ . To specify fitness, we suppose that $s_g = s_k = -s$, meaning that having the lactase persistence allele alone or cow domestication alone is maladaptive (both with the same cost s , for simplicity), and we define $s_e = 2s + \eta$, where η is the selective advantage of having both the lactase persistence allele and cow domestication.

With this setup, we can determine the conditions under which an ancestral population can both evolve lactase persistence and acquire a culture of milk use in the adult diet, by analyzing the stability of the equilibrium $\bar{g} = 0$, $\bar{h} = 0$. Because having the lactase persistence allele or milk-use culture alone is selectively disadvantageous, and because these genetic and nongenetic factors are inherited somewhat independently, the selective advantage of individuals having both must be large enough for evolution to occur. Section D in the zip file demonstrates that the critical value of the selective advantage, η , above which evolutionary invasion occurs is given by

$$\eta^* = 2 \frac{s[2 - 2\lambda(1 - \tau) - \tau]}{s\tau + 4\lambda(1 - \tau)}.$$

The strength of selection needed for evolution depends very strongly on both the fidelity of transmission, τ , and the probability of self-learning, λ (fig. 7). Self-learning always reduces the strength of selection required because it always increases the chance that mutant individuals will have both the lactase persistence allele and be milk users. The effect of the fidelity of parent-offspring cultural transmission, however, is more complex. If the probability of self-learning is low (specifically, less than $s/(2 + s)$), then high-fidelity cultural transmission aids evolution. If the probability of self-learning is high, however, then high-fidelity cultural transmission is detrimental because, left to their own devices, individuals will figure out the appropriate cultural state instead. Indeed, the best scenario for the spread of the lactase persistence allele and milk-use culture is to have very low-fidelity cultural transmission and a very high probability of self-learning (fig. 7).

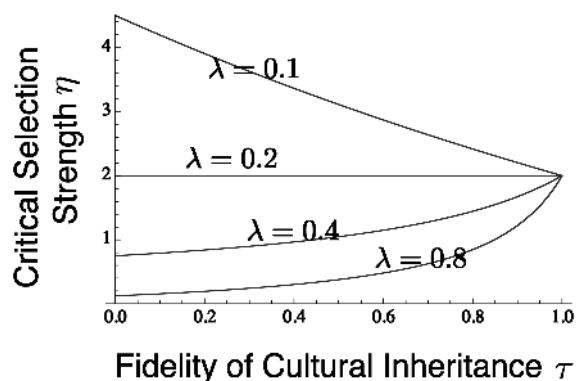


Figure 7: Critical strength of selection acting on individuals both carrying the lactase allele and being domesticators, η^* , as a function of the fidelity of cultural inheritance from parent to offspring, τ , and the probability of self-learning the correct genotype-specific cultural state, λ . Lower values of η^* mean that evolution of both the lactase allele and cow domestication can proceed more readily; $s = 0.5$.

Discussion

Recent reappraisals of the nature of inheritance (Jablonka and Lamb 1995, 2005; Bossdorf et al. 2008; Bonduriansky and Day 2009) suggest that the Mendelian genetic model of inheritance—the traditional basis of evolutionary analysis—should be expanded to encompass nongenetic forms of inheritance. We have developed a general synthetic framework for modeling evolution based on an expanded concept of inheritance encompassing both the Mendelian transmission of alleles (genetic inheritance) and the diverse range of known nongenetic inheritance mechanisms (Bonduriansky and Day 2009). This framework can be used to revisit many evolutionary questions in light of recent advances in the understanding of inheritance.

Although several bodies of theory have been developed in an effort to expand the concept of inheritance, most of these are regarded as having only local relevance for certain taxa or traits. For example, gene-culture coevolution theory is assumed to apply only to humans (but see Avital and Jablonka 2000), whereas the evolutionary importance of transgenerational epigenetic inheritance is questioned because few of the available examples relate to ecologically relevant traits and contexts (Bossdorf et al. 2008). Conversely, niche construction theory encompasses phenomena that fall outside the conventional purview of inheritance, such as the transmission of ecological parameters that affect all individuals within a cohort (Odling-Smee et al. 2003; Bonduriansky and Day 2009). Consequently, it is still widely assumed that Mendelian genetic principles represent the only universal mechanism of inheritance and thus provide a sufficient foundation for evolutionary theory.

The general framework developed here is based on Price's (1970, 1972) equation and provides a way to integrate an expanded concept of inheritance, comprising both genetic and nongenetic inheritance, with evolutionary theory. We show that the diversity of proximate inheritance mechanisms can be subsumed within an analytically tractable formalism by specifying three parameters for the genetic and nongenetic components of inheritance: (1) effects of transmissible variants on individual fitness, (2) rules governing the transmission of these variants from parents to offspring (reproductive transmission rules), and (3) rules governing changes in individual phenotypes over individual lifetimes (survival transmission rules). These parameters can be specified for any proximate mechanism of inheritance, allowing for phenomena as diverse as culture and gene regulation to be encompassed within a common analytical framework. The examples considered above illustrate how this framework can be adapted to reflect various assumptions about inheritance by modifying the terms in equations (1). We note that Helanterä and Uller (2010) have independently suggested that Price's equation might be used to classify different kinds of inheritance, but their approach differs somewhat from that presented here.

Importantly, the framework embodied by equations (1) makes it possible to investigate the evolutionary consequences of different assumptions about inheritance without the need to specify the proximate details of the inheritance mechanisms involved. Different mechanisms can give rise to similar inheritance patterns and follow similar reproductive transmission rules (table 1). Furthermore, recent studies have revealed many intriguing examples of nongenetic inheritance whose proximate basis remains poorly understood (Anway et al. 2005; Pembrey et al. 2006; Nelson et al. 2010; Yazbek et al. 2010). The framework described here makes it possible to model such phenomena on the basis of a characterization of the three parameters specified above, irrespective of the molecular, developmental, or behavioral mechanisms that actually mediate the effects of parents on offspring. Nonetheless, our framework also shows that different patterns of inheritance (i.e., distinct combinations of reproductive transmission and survival transmission rules), in combination with the effects of transmissible variants on fitness, can engender different evolutionary outcomes and thus illustrates the need to include all relevant patterns of inheritance in evolutionary models.

Our examples illustrate why the incorporation of nongenetic inheritance within evolutionary models leads to otherwise unexpected outcomes: nongenetic inheritance alters evolutionary predictions because it differs from genetic inheritance in the nature of the reproductive transmission rules and, perhaps, survival transmission rules.

Nongenetic inheritance thus engenders distinct inheritance patterns that, in turn, give rise to otherwise unexpected patterns of evolutionary change. First, some mechanisms of nongenetic inheritance allow for the transmission of acquired traits. This includes the transmission of adaptive (facultative) plastic responses, such as antipredator defenses (e.g., Agrawal et al. 1999), as well as the transmission of nonadaptive plastic responses, such as pathologies (Anway et al. 2005). Second, nongenetic inheritance allows for the transmission of factors (such as RNAs or methylation patterns) that may arise spontaneously (i.e., without obvious environmental triggers) or as a consequence of genetic mutations. Such factors can then be transmitted independently of genetic variation and via non-Mendelian reproductive transmission rules (as in paramutation; Ashe and Whitelaw 2006). Third, phenotypes that reflect a nongenetically inherited component may be more plastic (i.e., more sensitive to environmental heterogeneity and fluctuations and more likely to change over individual lifetimes). These properties of nongenetic inheritance result in a decoupling of transgenerational phenotypic change from genotypic change. Such decoupling can have interesting consequences for evolution because the phenotypic mean and variance can influence selection on genes. This makes possible many different types of interactions between genetic and nongenetic inheritance, and as our examples demonstrate, such interactions can influence both transient evolutionary dynamics and long-term evolutionary trajectories. In the most general sense, the incorporation of nongenetic inheritance can influence evolution for the same reason as the inclusion of an additional relevant Mendelian genetic locus, except that nongenetic inheritance can engender a much greater range of inheritance patterns than a Mendelian locus and thus bring about a greater range of possible evolutionary outcomes.

Most of our examples are based on the assumption that nongenetically inherited factors can have some degree of transmission fidelity across multiple generations, such that a trait transmitted nongenetically from parents to offspring has some probability of being passed on by the offspring to their own offspring. This assumption is well supported empirically (see Bonduriansky and Day 2009). For example, Anway et al. (2005) showed that a low-fertility phenotype acquired through exposure to an environmental factor can be transmitted through the male line for several generations in the absence of the inducing environmental factor. Likewise, Yazbek et al. (2010) showed that a mutant allele in the parents can produce an IGE that confers obesity resistance in two generations of descendants that lack the mutant allele. In humans, a great variety of cultural variants can be transmitted over many generations. Such stability can arise in two ways: (1) when a nongenetically

transmitted factor (e.g., a diet-derived substance) is actually transferred across multiple generations, subject to dilution at each transmission step, and (2) when a nongenetically transmitted factor promotes its own reestablishment in each generation (as in the case of RNA-mediated paramutation, or cultural inheritance). The second case is of greater interest because it can result in transmission over many generations without a waning of the effect via dilution. Indeed, some cultural variants can become amplified over several generations (e.g., an increment in parental literacy can engender a greater increment in offspring literacy), and such positive-feedback effects may be possible under other mechanisms of inheritance as well. However, none of our examples assume that the nongenetically transmitted factor is as stable as a gene, illustrating that the relative transience of nongenetically transmitted factors does not prevent them from influencing the course of evolution.

Our examples deliberately explore simple cases in order to illustrate how the general framework can be adapted to reflect various assumptions about the nature of inheritance and encompass previous models (such as maternal effects, IGE, or cultural evolution models) as well as recently discovered phenomena (such as transgenerational epigenetic inheritance and RNA inheritance). These examples represent one- and two-trait systems. However, the general framework can be readily extended to represent more complex systems involving multiple traits influenced by different mechanisms of inheritance (including different mechanisms of nongenetic inheritance) that bring about distinct inheritance patterns. Such complex systems may be required in modeling sexual coevolution or host-parasite coevolution. The general framework can also be extended to model the evolution of a single trait influenced by more than two distinct mechanisms of inheritance. For example, human diet choice and health may be influenced by a complex combination of genetic variation, cultural inheritance, and transgenerational epigenetic inheritance (Hatchwell and Grealley 2007; Stöger 2008; Krebs 2009).

In addition to evolutionary questions, our framework can also be applied to problems in medicine and public health, where the importance of nongenetic inheritance is becoming increasingly apparent (Gluckman et al. 2007, 2009; Hatchwell and Grealley 2007; Stöger 2008). For example, genome-wide association studies have consistently failed to account for the heritability of some diseases, pointing to a gap in understanding called the missing heritability (Manolio et al. 2009). In principle, nongenetic inheritance could account for the missing heritability (Manolio et al. 2009; Slatkin 2009; Nelson et al. 2010), and we will explore this possibility more completely in a forthcoming article.

Conclusions

Many areas of evolutionary biology have traditionally neglected nongenetic inheritance, relying instead on the assumptions of purely Mendelian genetic inheritance. We believe that a reexamination of these assumptions could lead to important advances in our understanding of evolution. Likewise, nongenetic inheritance is increasingly seen to have implications for human health (Gluckman et al. 2007, 2009; Hatchwell and Grealley 2007), necessitating theoretical tools to investigate the inheritance of complex traits such as obesity and diabetes (Manolio et al. 2009; Slatkin 2009). The general framework presented here provides new tools for the analysis of evolution and phenotypic variation in light of an expanded concept of inheritance.

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