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Using causal models to integrate proximate and ultimate causation

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Abstract Ernst Mayr's classical work on the nature of causation in biology has had a huge influence on biologists as well as philosophers. Although his distinction between proximate and ultimate causation recently came under criticism from those who emphasize the role of development in evolutionary processes, the formal relationship between these two notions remains elusive. Using causal graph theory, this paper offers a unified framework to systematically translate a given "proximate" causal structure into an "ultimate" evolutionary response, and illustrates evolutionary implications of various kinds of causal mechanisms including epigenetic inheritance, maternal effects, and niche construction. These results not only reveal the essential interplay between proximate and ultimate causation in the study of evolution, but also provide a formal method to evaluate or discover non-standard or yet unknown evolutionary phenomena.

Keywords Proximate and ultimate causation · Extended synthesis · Epigenetic inheritance · Niche construction · Causal models · Price equation

Introduction

In 1961, Ernst Mayr published a short article in *Science* that soon became a classic in evolutionary biology as well as in the philosophy of biology (Mayr 1961). In that paper, titled "Cause and effect in biology," Mayr distinguished two notions of causation used in biological sciences. A *proximate cause*, according to Mayr, denotes a developmental, physiological, or chemical mechanism that forms or triggers a particular biological phenomenon, usually in an organism's lifetime.

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Mayr's own example was the migrating behavior of the new world warbler. Its proximate causes include physiological or chemical pathways connecting environmental cues (e.g., day length) to muscular movement, and contribute to the explanation of *how* the migration happens. In contrast, an *ultimate cause* is a historical factor that explains *why* an organism has a given trait rather than another. Why the new world warbler migrates at the end of summer would be explained in terms of the fitness advantage of seasonal migration (e.g., securing food during winter) by the Darwinian theory of natural selection. Mayr believed that these two causal questions pertain to distinct scientific disciplines. Proximate causes are the study subject of "functional biology" including all physiological, cellular, and molecular biologies, while questions about ultimate causes are answered by evolutionary biology.

There is little doubt that they are different questions (although may not be exhaustive; see Calcott 2013). What counts as an appropriate explanation depends on a context (van Fraassen 1980), and in this sense Mayr was certainly right that each subfield in biology may analyze one phenomenon from different research perspectives. But to the eyes of many the distinction further implied that these questions are mutually irrelevant or at least independent so that biologists can study one without the other.[1] Indeed this reading was adopted by Mayr himself, who later used his distinction to defend the autonomy of evolutionary biology from the then burgeoning field of molecular biology (Beatty 1994).

Such a strict division of labor has been under the attack of recent theorists who emphasize the role of developmental or ecological factors played in adaptive evolution (e.g., West-Eberhard 2003; Thierry 2005; Laland et al. 2011, 2012; Sterelny 2013). For instance, developmental plasticity or bias can buffer environmental changes in such a way to regulate or mitigate the influence of natural selection on genetic frequencies (West-Eberhard 2003). Alternatively, organisms may actively reshape their selective regime by choosing, modifying, or even creating the fitness-related environment, the process known as niche construction (Lewontin 1983; Laland et al. 1996, 2000; Odling-Smee et al. 1996). All these phenomena suggest that proximate causes, such as development processes or ecological interactions, play a substantive role in shaping the course of evolution.

The evolutionary significance of proximate causal factors has also been confirmed by mathematical models that incorporate maternal effects (Kirkpatrick and Lande 1989), niche construction (Laland et al. 1996; Odling-Smee et al. 1996), or epigenetic inheritance (Tal et al. 2010). These individual studies, however, do not answer how proximate causation *in general* relates to ultimate causation. Is there a unified framework that includes all of them as special cases and systematically "translates" a variety of proximate causal assumptions into ultimate evolutionary responses? Such a unified framework will not only provide the formal link between the two notions of causation, but also enable us to see when, how, and why a particular causal mechanism matters to evolution.

[1] For discussions about the (mis)uses of the proximate/approximate distinction in biological literatures, see e.g., Amundson (2005), Laland et al. (2011).

The main obstacle for this integrating work is that these two notions of causation are not described in the same language. In particular, evolutionary changes of a population are usually expressed in terms of statistics, such as variances or covariances, rather than its causal features. We need a machinery that translates causal talk describing proximate mechanisms into statistical language representing ultimate evolutionary consequences, and vice versa. To overcome this language barrier this paper relies on *causal graph theory* (Spirtes et al. 2000; Pearl 2000), which provides a formal connection between causation and probability. Section 2 introduces the basic framework and uses it to decompose the Price equation, one of the fundamental principles describing evolutionary change, into a set of underlying causal factors including selection and reproduction. The explicit definition of the basic causal model enables us in Sect. 3 to study evolutionary dynamics under a varieties of causal mechanisms, such as epigenetic or maternal inheritance, niche construction, and nonlinear interactions. The philosophical implications from these extended models are discussed in Sect. 4. First, the causal models obtained in this paper reveal a formal connection between the two concepts of causation distinguished by Mayr. Since "ultimate" evolutionary dynamics are shown to be a function of "proximate" causal mechanisms in each of the above cases, it follows that the two cannot be studied in isolation. Second, this paper answers the call for integrating the two notions of causation (e.g., Thierry 2005; Laland et al. 2011, 2012) by showing *how* such integrations can take place. In particular, the formal representation of proximate causal mechanisms facilitates the discovery of novel evolutionary factors as well as the evaluation of the various claims made by the so-called "Extended Synthesis." Through these analyses this paper establishes both conceptual and methodological links between proximate and ultimate causation.

The basic framework

As a general framework to study evolutionary consequences of proximate causes, this paper adopts the causal decomposition of the Price equation which is developed elsewhere (Otsuka, forthcoming). The Price equation is a *mathematical theorem* that describes the change in the mean phenotypic value from one generation to another (Robertson 1966; Price 1970). Let Z stand for a quantitative trait, say the body size of an animal.[2] We are interested in how the mean body size in the population, $\overline{Z}$, changes after one round of selection and reproduction. To calculate this using the Price equation, we further need to define the following quantities: (1) the Darwinian fitness W defined as the number of offspring; and (2) the average trait value Z' of offspring produced by each individual. Thus assuming asexuality for the sake of simplicity, if George has four children each having the phenotypic value of 1, 1, 1, and 2, then $w_{George} = 4$ and $z'_{George} = (1 + 1 + 1 + 2)/4 = 1.25$. Provided that these quantities are measured for each individual, the Price equation gives evolutionary change as

[2] Throughout this paper I use uppercase letters to denote random variables and lowercase letters to denote their values.

$$\Delta\overline{Z} = \frac{1}{\overline{W}}\mathrm{Cov}(W, Z') + \overline{Z} - \overline{Z'} \tag{1}$$

where $\mathrm{Cov}(\cdot)$ and the upper bars denote the covariance and the means, respectively.[3] With a slightly different notation, Eq. 1 can be written as

$$\Delta\overline{Z} = \frac{1}{\overline{W}}b\mathrm{Cov}(Z, Z') + \overline{Z} - \overline{Z'} \tag{2}$$

where b is the linear regression of W on Z, which is defined as the covariance between fitness and the trait divided by the phenotypic variance, or $\mathrm{Cov}(W, Z)/\mathrm{Var}(Z)$.[4]

In either form the Price equation divides the overall evolutionary response into several parts, facilitating a component-wise analysis of evolution. Equation 2, for example, identifies four components of evolutionary change, $1/\overline{W}, b, \mathrm{Cov}(Z, Z')$, and $\overline{Z} - \overline{Z'}$. The first two components correspond to selection. The *direction* of selection is determined by the regression coefficient b that measures the (linear) causal influence of the trait on fitness. That is, the trait is favored if $b > 0$, disfavored if $b < 0$ and neutral if $b = 0$. On the other hand, the reciprocal of the mean fitness, $1/\overline{W}$, regulates the *rate* of selection. A lower population mean fitness inflates this term and makes the selective pressure more significant, accelerating the adaptive process. In contrast, if the population as a whole is well adapted the same directional selection will exert only a marginal impact. The rest of the equation concerns reproduction. The covariance between parental and offspring phenotype, $\mathrm{Cov}(Z, Z')$, quantifies their resemblance or the *efficiency* of the reproductive process. Finally, $\overline{Z} - \overline{Z'}$ is the systematic change in phenotypic average due to non-selective evolutionary forces, corresponding to the reproductive *fidelity* or *bias*.[5] These are summarized in Table 1.

Although the Price equation is useful in partitioning the total evolutionary response into different pieces, it serves little if one's interest is in analyzing *causes* of evolutionary change. This is because all the "components" in the Price equation are just statistics, with no indication to the underlying causal structure.[6] Granted, for example, that the reproductive efficiency is expressed by the parent–offspring covariance; but what causal features in the reproductive process underlie this particular statistic? The equation gives no answer. Hence to understand how various kinds of proximate causes affect the evolutionary response through one or more of the four components of the Price equation, we must first identify their causal basis.

In this regard causal graph theory proves particularly helpful, for it provides a formal means to relate statistics to the underlying causal features represented by a *causal graph* and *structural equations* (Spirtes et al. 2000; Pearl 2000). There are

[3] For a derivation of the Price equation, see e.g., Okasha (2006).

[4] Equation 2 does not follow if W and Z are confounded by some common cause (Otsuka, forthcoming). But in this paper we ignore such cases.

[5] To be precise, such a systematic change in phenotypes may include migration as well as selection acting at lower levels, but in this paper I ignore them.

[6] This is the reason that the Price equation does not give a definitive answer to the question of causal agency in multi-level selection (Okasha 2006).

two kinds of statistics appearing in the Price equation, covariance and mean, each of which reflects different features of the underlying causal structure, namely causal connections and causal inputs. Let's take covariance first. An association between two events or properties suggests some causal link. If you find very similar paragraphs in essays of two students, you would naturally suspect some connection: perhaps one copied from the other, they copied from the same source, or both (they refer to the same source *and* one student copied from the other). That is, the essays are similar presumably because there is a directed causal influence from one student to the other, or they have a common cause, say wikipedia. Such causal links are called *treks*. Formally a trek is defined as a sequence of causal arrows that does not contain colliding edges (such as $\rightarrow V \leftarrow$). The above story suggests that a correlation between two variables (two essays) is accounted for by the existence of a trek between them. This intuition proves correct: using Sewall Wright's *method of path coefficients* the covariance of two variables can be obtained by summing the contributions from all the treks connecting them (see "Appendix" for detail). Hence the covariation terms in the Price equation, b and $\mathrm{Cov}(Z, Z')$, are determined by the causal *connection* between the pairs of variables in question.

While a covariance is generated by a causal link (trek), the mean value of a variable is determined by its causal *inputs*. Just as your average monthly budget is a function of your income and spending, the mean fitness of a population is a function of various factors that affect the reproductive outcome of individuals in the population. The way these causal inputs determine the variable in question is specified by the *structural equation*, which in general has the form:

$$V_i = f_i(\mathbf{PA}(V_i)) \tag{3}$$

where $\mathbf{PA}(V_i)$ is all the direct causes of variable V_i. Equation 3 gives the value of V_i as a function of its causal inputs. The means in the Price equation are thus determined by the form of the corresponding structural equations.[7] In the evolutionary biology literature, causal inputs to fitness are represented by the *fitness function*, which usually has phenotype Z and environmental factor E_W as its arguments. On the other hand, the function that determines the phenotypic value from genotype G and another environmental factor E is often called the *genotype–phenotype mapping* or *reaction norm*.

Table 1 summarizes the above remarks. What concerns us most in this table is the bottom row, for it enables us to "translate" a given causal hypothesis to evolutionary change. To assess the evolutionary response generated by a particular causal structure, we just need to examine each causal feature listed in this row and combine them. To illustrate this, let us take the causal structure underlying the most basic evolutionary equation, the *breeder's equation*, depicted in Fig. 1. The graph reflects the following assumptions: (1) parental fitness W is caused by phenotype Z and environmental factor E_W; (2) parental phenotype Z is caused by its genotype X and another environmental factor E; (3) parental genotype X is faithfully passed to offspring (e.g., without segregation distortion); (4) the transmitted genotype X',

[7] To be precise, to calculate the mean of a variable one also needs to know its marginal distribution, which is also given through the structural equation and the distribution over its causes.

Table 1 Component-wise decomposition of the Price equation

	$\frac{1}{\overline{W}}$	b	$\mathrm{Cov}(Z, Z')$	$+\overline{Z'} - \overline{Z}$
Selection	Rate	Direction	–	–
Reproduction	–	–	Efficiency	Fidelity
Causal basis	Input (to W)	Connection (of W, Z)	Connection (of Z, Z')	Input (to Z, Z')

The top two rows indicate evolutionary components measured by statistics in each column. The bottom row shows the relevant causal relationships/factors that determine each statistics

along with environmental factor E', forms offspring phenotype Z' in the same way as for the parent; (5) and finally, there is no genotype-by-environment or between-environment correlation or interaction.

To derive the evolutionary response from these causal assumptions, we examine each item in the bottom row of Table 1. Let's start with the second and third columns, which concern causal connections. Looking at Fig. 1 we see the direction of selection b is determined by the causal arrow $Z \rightarrow W$, whose effect is usually represented by *selection gradient* β. On the other hand, the reproductive efficiency $\mathrm{Cov}(Z, Z')$ is given by the trek between the parental and offspring phenotypes, namely $Z \leftarrow X \rightarrow X' \rightarrow Z'$. The contribution from this trek is called the *additive genetic effect* and denoted by σ_A^2.

To determine the first and fourth components we examine the causal inputs represented by the structural equations. The mean fitness is simply

$$\overline{W} = \beta\overline{Z} + \overline{E}_W, \tag{4}$$

and the mean phenotypic values are

$$\overline{Z} = \overline{X} + \overline{E}, \tag{5}$$

$$\overline{Z'} = \overline{X'} + \overline{E'}. \tag{6}$$

Under the assumptions of faithful gene transmission ($\overline{X} = \overline{X'}$) and homogeneous environments for the parental and offspring generations ($\overline{E} = \overline{E'}$), Eqs. 5 and 6 entail $\overline{Z'} - \overline{Z} = 0$, i.e., no reproductive bias. The causal structure shown in Fig. 1 thus gives the evolutionary response as

$$\Delta\overline{Z} = \frac{1}{\beta\overline{Z} + \overline{E}_W}\beta\sigma_A^2. \tag{7}$$

This is formally equivalent to the *breeder's equation*, one of the fundamental equations in quantitative genetics and the breeding literature (Lush 1937). Figure 1, therefore, encodes the causal assumptions underlying the breeder's equation.

Arguably Fig. 1 is the simplest causal hypothesis: fitness is determined by a single phenotypic trait, the inheritance is strictly Mendelian, environments are independent and identically distributed, no transmission bias and no nonlinear

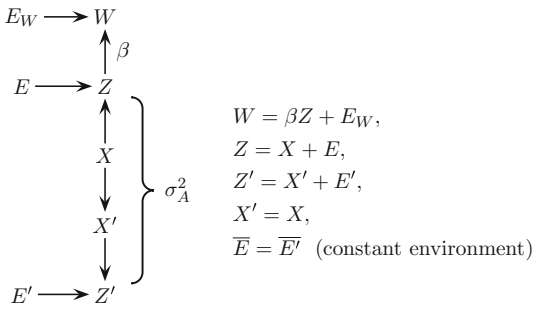

Fig. 1 The causal graph and structural equations underlying the breeder's equation. All causal relations are assumed to be linear, and only one trek ($W \leftarrow Z \leftarrow X \rightarrow X' \rightarrow Z'$) connects the parental fitness and offspring phenotype. For diploid organisms (which consist most if not all application targets of the breeder's equation), the middle part ($\leftarrow Z \leftarrow X \rightarrow X' \rightarrow$) is doubled to account for the contributions from both sexes but this complication is omitted throughout this paper (see Otsuka, forthcoming for detail)

interactions. But it serves as a basis for assessing the evolutionary implication of more complex causal structures/assumptions. In particular, it enables us to examine how various forms of "proximate causes" affect evolutionary or "ultimate causes." In what follows we will see this with four biological examples, namely (1) epigenetic inheritance, (2) maternal effects, (3) niche construction, and (4) nonlinear interactions or development by describing these phenomena in terms of the causal graph underlying the Price equation.

Extending the basic model

In this section I extend the basic causal structure underlying the breeder's equation (Fig. 1) to study the evolutionary consequence of various types of proximate causal mechanism, such as epigenetic inheritance, maternal effects, niche construction, and nonlinear interactions. For each of these mechanisms I first describe the corresponding causal graph and structural equations and then calculate the evolutionary response following Table 1. This will reveal how and through which components of the Price equation these "proximate" causes affect "ultimate" evolutionary trajectories, establishing a systematic connection between these two notions.

Epigenetic inheritance

The causal graph in Fig. 1 and thus the breeder's equation (Eq. 7) are based on the strict Weismanian assumption that restricts carriers of hereditary information to genes alone. Recent studies, however, have provided ample evidence that various epigenetic materials are also transmitted during reproduction (e.g., Jablonka and Lamb 2005). At the molecular level, for example, phenotypic information may be stored in the form of DNA methylation, histone modification, RNA regulation or

cell structures, which can be more or less stably transmitted across generations and contribute to phenotypic resemblance.

Epigenetic mechanisms are "proximate causes" par excellence—they are chemical processes that happen during an organism's lifetime. These proximate mechanisms, however, may affect evolution by introducing an extra pathway connecting the parental and offspring phenotypes. The quantitative contribution of the epigenetic pathway to the parent–offspring resemblance was studied by Tal et al. (2010). Let C denote the state of an epigenetic factor (say methylation mark) of a parent, and C' be its average among the offspring. Parents pass their epigenetic state to offspring with probability (or ratio coefficient) $1 - \nu$, which Tal et al. call the *coefficient of epigenetic transmissibility*. Alternatively, offspring that did not receive epigenetic marks from their parents may acquire one from the environment, for example by heat stress. These assumptions are summarized by the causal graph in Fig. 2.

From this graph we immediately see that the epigenetic inheritance, as modeled by Tal et al. (2010), affects the reproductive components of the Price equation (the third and fourth columns of Table 1). First, the newly created trek $Z \leftarrow C \rightarrow C' \rightarrow Z'$ contributes to the parent–offspring resemblance, $\mathrm{Cov}(Z, Z')$. Using the trek rule (see "Appendix"), the contribution from this path can be calculated to be $\sigma^2_{epi} := (1 - \nu)\mathrm{Var}(C)$. This value quantifies the effect of the epigenetic pathway on the efficiency of the reproductive system. Second, the fidelity of the reproductive process may be affected by loss or acquisition of the epigenetic mark in the offspring generation, which can be thought of as a mutation in the epigenetic factor. Due to this epigenetic mutation the causal inputs to the parental and offspring phenotypes may no longer be same, as is seen from the structural equations for Z and Z' in Fig. 2. Simple algebra shows that $\overline{Z} - \overline{Z'} = \nu(\overline{E}_C - \overline{C})$, hence the reproduction is biased whenever the mean acquisition rate of a new epigenetic mark differs from the mean epigenetic state in the parental generation. Taking these two points into account, the overall evolutionary change under epigenetic inheritance becomes

$$\Delta\overline{Z} = \frac{1}{\overline{W}}\beta\left[\sigma^2_A + \sigma^2_{epi}\right] + \nu(\overline{E}_C - \overline{C}). \tag{8}$$

This equation entails a different evolutionary dynamic than the basic breeder's equation (Eq. 7). As we have seen, this difference is attributed to the additional "proximate" causal factors in the process of reproduction. These epigenetic factors affect the efficiency and fidelity of the reproductive system and thus the respective statistical components in the Price equation. Epigenetic inheritance therefore provides the first instance where proximate causes affect ultimate causation.

Maternal effects

Another well-known and perhaps ubiquitous form of non-genetic inheritance is maternal effects. In many species, especially mammals, pre- and post-natal care provided by parents has strong influences on the offspring phenotype. Body size in

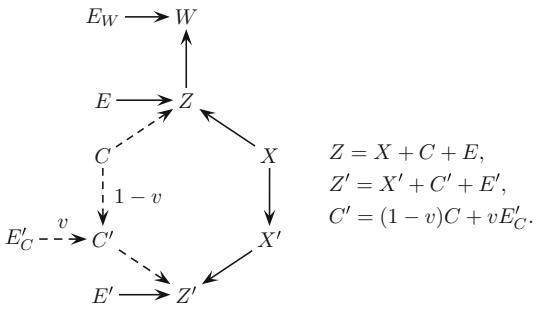

Fig. 2 The causal graph underlying the epigenetic inheritance model analyzed in Tal et al. (2010). The newly introduced causal connections are indicated by dashed arrows. Only those structural equations different from Fig. 1 are shown

mammals, for example, may be affected positively by maternal lactation performance but negatively by litter size. These non-genetic contributions of parents are known to significantly affect evolutionary trajectories in theory (Feldman and Cavalli-Sforza 1976; Kirkpatrick and Lande 1989), in the laboratory (Cheverud 1984) and in nature (McAdam and Boutin 2004).

In a causal graph, maternal effects can be represented with a direct causal influence from the parental to offspring's traits, $Z \to Z'$, with its linear path coefficient m expressing its strength.[8] In the same way, we assume that a mother's phenotype is also affected by her grandmother. If reproduction and thus maternal care happen after selection, this grand-maternal effect is represented by a causal arrow into the mother's phenotype from the grandmother's phenotype after selection, $Z^*_{GP} \to Z$. Figure 3 gives the causal graph reflecting all these pathways.

From this figure we note that maternal effects, like epigenetic inheritance, affect only the reproductive process, i.e., the third and fourth components of the Price equation (Table 1). First, the direct influence from a mother to offspring introduces an additional trek that contributes to the parent–offspring phenotypic covariance by $\sigma^2_m := m\mathrm{Var}(Z)$. In addition, the fact that a parent and offspring have different mothers and thus receive different amounts of maternal care may result in a reproduction bias. According to the structural equations in Fig. 3, this difference can be given by $m(\overline{Z^*}_{GP} - \overline{Z})$, where $\overline{Z^*}_{GP}$ is the post-selection mean phenotypic value in the grandparental generation. This gives the evolutionary response as:

$$\Delta\overline{Z} = \frac{1}{\overline{W}}\beta(\sigma^2_A + \sigma^2_m) + m(\overline{Z^*}_{GP} - \overline{Z}). \tag{9}$$

One notable difference from the epigenetic case (Eq. 8) is that the reproductive bias (second term) under maternal effects becomes nonzero if and only if there is an adaptive evolution in the *previous* generation such that $\overline{Z^*}_{GP} \neq \overline{Z}$. This means that a population may continue to evolve even after selection ceases to exist, provided it was operative in prior generations (Kirkpatrick and Lande 1989). Such an

[8] On the other hand, an effect of litter size can be represented by drawing a causal arrow from parental fitness W to Z' (not shown in the graph), since by definition fitness is nothing but litter size. For the sake of simplicity in this paper we limit our attention to the univariate evolution of the maternal care trait alone, but the extension to include the simultaneous evolution of the care trait (e.g., lactation) *and* its beneficiary (e.g., body size) is straightforward.

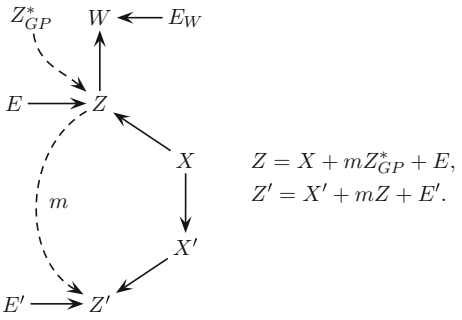

Fig. 3 Maternal effect. Z^*_{GP} is the grandmother's phenotype after selection. This follows from the assumption that reproduction happens after selection, and thus that only those who survive selection can rear offspring

evolutionary momentum is one salient consequence of maternal effects not observable in the standard genetic model.[9] The causal approach, therefore, illustrates the way the proximate interactions between parents and offspring alter evolutionary response and produce the novel evolutionary dynamics.

Niche construction and ecological inheritance

In the traditional picture, organisms play only a passive role in adaptive evolution, environmental factors "shaping" their genotype and phenotype but not vice versa. In many cases, however, organisms are also active agents selecting, altering, or even creating the very environment they live in (Lewontin 1983). Ant nests, mole holes, spider webs, and beaver dams are conspicuous examples where organisms construct their own niche and alter important selective parameters such as temperature or the accessibility to food. Through such *niche construction* organisms may actively influence their evolutionary fate (Odling-Smee et al. 1996; Laland et al. 2000). In addition, some of the constructed niches such as ant nests or beaver dams may persist and serve for several generations via *ecological inheritance*.

Let R denote a niche or environmental resource. Then niche construction is represented by a causal arrow from phenotype Z to R, with its strength measured by the linear path coefficient λ_2 (Laland et al. 1999). The persistence/inheritance of the environmental resource between generations, on the other hand, is expressed by an edge from R to R', the resource in the offspring generation, with the depletion rate of λ_1. The causal graph depicting this simple scenario of niche construction is shown in Fig. 4.

While epigenetic inheritance and maternal effects concerned reproduction, niche construction mainly influences selection, i.e., the first and second components of the Price equation (Table 1). First, niche construction creates an additional pathway through which the phenotype affects fitness, so that the total fitness contribution of

[9] Kirkpatrick and Lande (1989) further showed that this term equals $m\left[\Delta\overline{Z}_{GP} - \mathrm{Var}(Z)\beta_{GP}\right]$, where $\Delta\overline{Z}_{GP}$ and β_{GP} are the evolutionary response and selection gradient in the previous generation, respectively. To derive this from Eq. 9, note that the mean after selection in the grandparent generation is given by $\overline{Z}^*_{GP} = \overline{Z}_{GP} - S_{GP}$ where $S_{GP} := \mathrm{Cov}(W_{GP}, Z_{GP}) = \mathrm{Var}(Z_{GP})\beta_{GP}$ is the *selection differential*. Their result follows from Eq. 9 by noting $\Delta\overline{Z}_{GP} := \overline{Z} - \overline{Z}_{GP}$ and assuming a constant phenotypic variance between generations, i.e., $\mathrm{Var}(Z_{GP}) = \mathrm{Var}(Z)$.

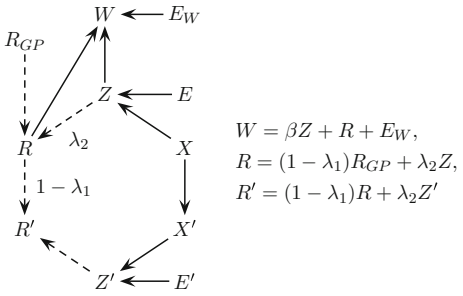

Fig. 4 Niche construction and inheritance. R_{GP}, R, and R' are the environmental resources (niches) of the grandparental, parental, and offspring generations, respectively. The notation follows Laland et al. (1999) with an important simplification that here only one quantitative trait, Z, is considered, whereas Laland et al. analyzed nonlinear fitness interactions of two loci (each for niche construction and fitness). The basic causal structure, however, remains the same

the trait becomes $b = \beta + \lambda_2$. Next, the constructed niche regulates the strength of selection through the weighting factor, $1/\overline{W}$. Assuming the environmental resource is shared by every individual in the population (hence R is a group or contextual variable) this factor is $1/(\beta\overline{Z} + R)$. Adaptive evolution under niche construction is thus expressed as:

$$\Delta\overline{Z} = \frac{1}{\beta\overline{Z} + R}(\beta + \lambda_2)\sigma_A^2 \tag{10}$$

It should be noted that R in Eq. 10 keeps changing across generations as the environmental resource is supplemented by niche construction in each generation and depleted through an incomplete ecological inheritance. This has several important consequences. First, differential amounts of environmental resources among generations may generate a similar kind of evolutionary momentum as we saw in the case of maternal effect (Laland et al. 1996, 1999). Second, an accumulating resource (bigger R) counteracts the selection measured by β, bearing out our intuition that with a poor "scaffolding" the phenotype of each individual is the key determinant of its fitness and thus strongly selected, while a well-constructed niche mitigates the selective pressure. In addition this change in the rate of adaptive evolution affects the rate of resource accumulation. Thus niche construction may create evolutionary feedbacks between organisms and their environment. And finally, if environmental resource R is shared by every or most members of the group, as in a beaver dam, it may introduce selection at the group level. In particular, constructing a beneficial niche ($\lambda_2 > 0$) that incurs some cost to the individuals ($\beta < 0$) can be considered a type of altruistic trait, disfavored by individual selection but favored by group selection.

Evolutionary consequences of niche construction were studied in the pioneer works of Laland et al. (1996, 1999). Their analyses employed two-locus population genetics models and considered various sorts of nonlinear fitness functions. Such additional complexities in the causal mechanism enabled them to study richer evolutionary patterns than the one discussed here. For example, if fitness is a

nonlinear function of the phenotype and the resource, the accumulating niche may change not only the rate but also the direction of selection, resulting in more complex evolutionary trajectories. Our analysis, however, showed that even the simplest form of niche construction is enough to produce novel evolutionary dynamics which differ significantly from those obtained from the standard model. In addition, the simplicity has its own virtue in revealing *why* niche construction matters to evolution—it creates a new causal pathway from the phenotype to fitness and alters the fitness function, thereby affecting the selective components in the Price equation.[10] The causal model, therefore, reveals the essential feature of the proximate causal structure through which niche construction influences the ultimate cause of evolution.

Nonlinear interactions

The above discussions have focused on evolutionary consequences of introducing novel causal mechanisms, such as epigenetic, maternal, or ecological inheritance. By doing so we have assumed that all causal factors act additively and independently. For example, the structural equations for parental and offspring phenotypes in Fig. 2 assume that genotype X and epigenetic mark C make independent contributions to the phenotype, without one changing the activity of the other. This, of course, is unrealistic with most epigenetic factors including methylation that necessarily interacts with the target gene by suppressing its expression. In general, we expect various causes in nature to interact with each other in such a way that one factor regulates the causal contribution of the other. Under *dominance* or *epistasis*, the genetic effect of one allele is a function of (an)other allele(s). Genetic effects on a phenotype may also be dependent on some external/environmental factor, the phenomenon called *phenotypic plasticity* (Pigliucci 2001; West-Eberhard 2003). Finally, the fitness of an organism is always a product of an interaction between the phenotype under selection and an environmental selective pressure, say temperature or predator abundance (Wade and Kalisz 1990; Glymour 2011).

These nonlinear interactions may not introduce additional causal pathways in a causal graph but do alter the form of structural equations, which may lead to more complex evolutionary patterns. If a cause acts in a nonlinear fashion, its contribution depends on its value as well as that of other causes. The fitness contribution of the running speed of a zebra, for example, is partly determined by the speed of nearby predators, another important cause of the zebra's fitness. Hence interactions make the nature of causal relationships specific to local conditions/configurations. In the context of evolutionary biology, this means that each local population may evolve more or less differently.

To see this more closely, let us consider dominance and epistasis, i.e., nonlinearity in the genotype–phenotype mapping. How does it affect the Price equation? First, a nonlinear relationship between Z and Z' means that the

[10] This entails that a nonlinear fitness function is *not* essential for a niche construction model to produce non-standard evolutionary dynamics.

reproductive efficiency, $\mathrm{Cov}(Z, Z')$, may differ among local populations. This is because the association between the two variables now depends on the local distribution of these variables (Fig. 5). Hence if two local populations have more or less different genetic distributions, they may respond differently even to the same selection pressure (Wade 1992). Moreover, the nonlinearity enhances the strength of drift by affecting the reproductive fidelity—the fourth component of the Price equation. Recall this term is given by the difference in the mean phenotype between parents and offspring. If the genotype–phenotype mapping is linear, these means are just functions of the mean of genotypes X and X', as seen above. But under nonlinearity they are affected by higher moments (variance, skewness etc.) as well, and these statistics are known to be extremely sensitive to sample variations (e.g., McCullagh 1987). Since the transmission of genes from parents to offspring is nothing but a sampling process, nonlinear genotype–phenotype mappings may magnify this sampling fluctuation into a larger phenotypic deviation between parents and offspring, resulting in stronger drift. Moreover, the divergence is further amplified as population/sample size becomes smaller.

It must be emphasized that a nonlinear genotype–phenotype mapping does *not* automatically entail no or even little additive genetic variance.[11] To the contrary, a linear parent–offspring relationship in each local population is totally consistent with, and even predicted from, a nonlinear genotype–phenotype mapping (see Fig. 5 right). Under nonlinearity, however, the nature of such relationships may vary across populations and generations: the response in one population at one time may be totally different from that of another population and/or at different generations. In other words, nonlinearity makes evolution a local process, determined by the conditions specific to each population. The idea of local evolution is at the heart of Sewall Wright's *shifting balance theory* (Wright 1930). In contrast to Ronald Fisher who viewed the evolutionary process as one large panmictic population moving toward the global optimum through gradual changes, Wright held that evolution mostly takes place in subdivided populations of smaller size. Since small populations are prone to random drift, this would help them to effectively "explore" the adaptive landscape to attain different local maxima. As we have seen, strong dominance and epistasis, which Wright thought to be a ubiquitous feature of organisms, promote differential explorations and random walks in the phenotypic space, facilitating subpopulations to explore a broader range of possibilities.

The Fisher–Wright debate has arguably been one of the biggest controversies in modern evolutionary biology since its conception (e.g., Coyne et al. 1997, 2000; Wade and Goodnight 1998; Goodnight and Wade 2000). The debate has surrounded two different conceptions about evolution, i.e., gradual adaptive processes tending toward the global optimum on Fisher's side and local adaptation and dispersal on Wright's side. As the above discussion makes clear, this dissidence in the nature of evolutionary processes largely hinges upon the differential assumptions about the genotype–phenotype mapping. In other words, one of the great controversies about ultimate causation in modern evolutionary biology was partly about proximate

[11] This point is often made by the distinction between the "functional" or "biochemical" epistasis and "statistical" epistasis (Wade 1992).

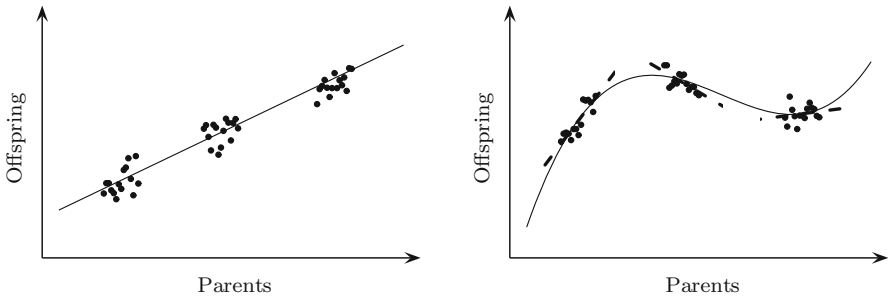

Fig. 5 Under nonlinearity, the efficiency of the reproductive process, $\mathrm{Cov}(Z, Z')$, depends on local genotypic compositions. The two graphs plot hypothetical offspring phenotypes against the mid-parent's phenotype, under different genotype–phenotype mappings. The parent–offspring associations remain constant across all three "subpopulations" (clouds of points) for the linear genotype–phenotype mapping (left), but differ radically under nonlinearity (right). Note however, that even with the nonlinearity the parent–offspring relation *in each subpopulation* is virtually linear (as seen from regression lines)

causation. Far from being irrelevant, therefore, proximate mechanisms have been a major concern in evolutionary genetics since the Modern Synthesis, at least in the minds of its founders.

Discussion

In the introduction I identified the chief obstacle for integrating proximate and ultimate causation to be the "language barrier": that the two notions are not stated in the same language. The previous sections employed causal graph theory to close this gap in some prominent cases where proximate causal structures affect evolutionary trajectories, namely epigenetic inheritance, maternal effects, niche construction, and nonlinear interactions. The causal approach, however, is not restricted to these specific examples but in principle can be applied to any evolutionary phenomena described by the Price equation. Table 1 tells us that the linear evolutionary response ultimately rests on four causal components. Hence if we want to know the evolutionary consequence of a particular mechanism, the basic strategy would be to (1) build a causal graph for the mechanism in question, (2) estimate or specify structural equations, and then (3) calculate each of the four components using the structural equations and the trek rule. This set of rules enables a systematic translation from any type of proximate mechanism represented by a causal model into the ultimate evolutionary response described by the statistics in the Price equation.

The formal connection between proximate and ultimate causation reveals the crucial dependence of the latter on the former. Since evolutionary response is calculated from the underlying causal structure, it is imperative to identify the

proximate mechanism to study or evaluate any evolutionary process.[12] This is most evident in the Fisher–Wright debate, where the conflicting views of adaptive evolution reflect to a large extent different conceptions of the genotype–phenotype mapping, namely whether genes contribute linearly or nonlinearly to phenotypes. This is ironic given that Mayr, in the upsurge of molecular biology spurred by Watson and Crick's discovery of the DNA structure in 1953, employed his proximate/ultimate distinction to defend the autonomy of evolutionary biology as an independent scientific discipline (Beatty 1994). The very framework he was defending—the Modern Synthesis—or at least its theoretical core was in fact contingent upon specific assumptions about the proximate mechanism of gene expression, which is best investigated with molecular techniques! This fact also speaks against those theorists who wish to downplay the role of development in the study of evolution.[13] It is sometime said that the modern genetics "black-boxes" developmental processes. Black-boxing, however, is not the same as "doing away with." Any evolutionary model makes a certain assumption about developmental processes, on which its theoretical results crucially depend. Developmental mechanisms, therefore, are far from irrelevant but are core ingredients of evolutionary models.

The study of evolution shall benefit much from a tool for representing the underlying causal structure. That was the original motivation for Wright's introduction of the *method of path analysis* (Wright 1921, 1934). This paper follows his path and highlights the usefulness of the causal modeling approach to analyze evolutionary consequences of various causal mechanisms. Without an appropriate method, evaluating evolutionary consequences of a particular causal structure would be impossible or at least liable to errors. Based only on inspections of the statistical functions in the Price equation, for example, Helanterä and Uller (2010) claimed that epigenetic inheritances reduce the parent–offspring similarity due to variation in epialleles. By arguing so, however, they overlooked the fact that epigenetic inheritance creates a new causal pathway (trek) between parents and offspring that positively contributes to their resemblance. It is easy to show with our epigenetic causal model (Fig. 2) that the reduction of the overall heritability (the regression of the mid-parental phenotype on the average offspring phenotype) due to an additive epigenetic factor occurs if and only if the narrow-sense heritability (the ratio of the additive genetic variance to the phenotypic variance) is greater than the coefficient of epigenetic transmissibility (Tal et al. 2010), i.e., $h^2 > 1 - v$. This conclusion, however, is hardly attainable if one lacks a proper method to connect the Price equation to the underlying causal structure.

[12] The dependence relation may go the other way around, when one considers that organismal structures themselves are products of evolution. The relationship in reality is hence "reciprocal," as Laland et al. (2011) note.

[13] One such example can be found in the opening remark of Maynard Smith's *Evolution and the Theory of Games*, where he claims "One consequence of Weismann's concept of the separation of germ line and soma was to make it possible to understand genetics, and hence evolution, without understanding development. [...] We can progress towards understanding the evolution of adaptations without understanding how the relevant structures develop" (Maynard Smith 1982, p. 6).

The unified causal framework presented in this paper offers a common platform to evaluate evolutionary consequences of various mechanisms. The non-standard causal mechanisms treated in this paper often come under the heading of the "Extended Synthesis" (Pigliucci 2007; Pigliucci and Muller 2010). The advocates of the new synthesis criticize the traditional framework for failing to address these novel mechanisms that have been shown, at least in theory, to affect evolutionary trajectories. In one sense, this can be understood as a plea for reconsidering the "proximate" causal basis of "ultimate" evolutionary models established by the Modern Synthesis. It is still an empirical question, however, *to what extent* these novel mechanisms matter to evolution. In fact, few would deny that epigenetic factors or niche construction may affect evolution: the question is how significant these effects are. The causal approach suggests one way to tackle this question, since building a causal model for a specific evolutionary phenomenon enables us to identify relevant parameters and to evaluate their evolutionary consequences. To assess evolutionary implications of epigenetic or maternal inheritance, for example, the coefficient of epigenetic transmissibility $(1 - v)$ or maternal effects (m) proves essential, as seen from Figs. 2 and 3, respectively. In addition to the evaluation of these known mechanisms, the systematic translation from underlying causes to evolutionary changes also opens up the possibility of exploring other causal mechanisms that may generate yet unknown evolutionary dynamics.

This last point brings us to another potential use of causal models, the causal search. The past few decades have seen the development of algorithmic procedures to infer the underlying causal structure from observational data (Spirtes et al. 2000; Pearl 2000). These methods have been applied to discover causal networks among phenotypes and environmental factors (e.g., Shipley 2000; Valente et al. 2010, 2011), but also can be used to search for evolutionary factors discussed in this paper. In the case of niche construction, for example, it might be difficult to identify which aspect of the constructed or modified environment is actually contributing to adaptive evolution. Is it the size, location or quality of the niche that matters? Do they affect fitness through regulating temperature, mating success, or the accessibility to food? If relevant measurements are made (which, granted, is not at all a trivial task), one can apply a search algorithm to determine potential causal factors, which may be followed by a more detailed experimental study. Identified and estimated causal pathways can then be incorporated into a causal model to calculate the impact on evolutionary response. In this way, the causal approach provides a seamless framework from the discovery and estimation of proximate causal factors to the assessment of their evolutionary implications.

Conclusion

Mayr's distinction between proximate and ultimate causation has exerted a huge influence in biology as well as the philosophy of biology. Although the distinction has been criticized by a number theorists who argue for the integration of the two concepts, their formal relationship has remained unknown presumably due to the difference in the languages with which these concepts are represented. The present

paper employed causal graph theory to overcome this language barrier, providing a systematic procedure to translate any form of proximate causal mechanism into the ultimate evolutionary consequence. The technique was illustrated with some prominent evolutionary mechanisms including epigenetic inheritance, maternal effects, niche construction, and nonlinear interactions. The results from these examples establish a close connection between proximate and ultimate causation, and show the crucial need for understanding a proximate mechanism in the study of evolution. Different causal hypotheses predict different evolutionary outcomes, and one of the biggest controversies over the nature of "ultimate" evolutionary process, the Fisher–Wright debate, actually hinges on the type of proximate causal mechanism under consideration. These two notions, therefore, are far from irrelevant but rather strongly connected. The causal approach taken in this paper highlighted the formal aspect of this connection. Further investigations on this relationship will benefit our understanding of complex evolutionary phenomena.

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Appendix: The trek rule

For a linear system the covariance of two variables can be obtained by the method of path coefficients (Wright 1934), also known as the *trek rule*. A *trek* is any non-overlapping sequence of edges between two variables that does not contain a *collider* where two edges on the path collide at one variable (e.g., $\rightarrow V \leftarrow$). A trek thus defined is equivalent to a pair of directed paths that share the same source (but note that one of the pair may be empty). For each trek, we can calculate the *trek coefficient* by multiplying the variance of its source and all the linear coefficients on the edges constituting the trek. The trek rule states that the covariance of two variables equals the sum of trek coefficients over all the treks connecting them. That is, if $\mathbf{T}$ is the set of all the treks between X and Y and β_{ti} is the linear coefficient of the ith edge on $t \in \mathbf{T}$,

$$\mathrm{Cov}(X, Y) = \sum_{t \in \mathbf{T}} \sigma_t^2 \prod_{i \in t} \beta_{ti}$$

where σ_t^2 is the variance of the source of trek t.

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