Cause and Effect in Biology Revisited: Is Mayr's Proximate-Ultimate Dichotomy Still Useful?

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Fifty years ago, Ernst Mayr published a hugely influential paper on the nature of causation in biology, in which he distinguished between proximate and ultimate causes. Mayr equated proximate causation with immediate factors (for example, physiology) and ultimate causation with evolutionary explanations (for example, natural selection). He argued that proximate and ultimate causes addressed different questions and were not alternatives. Mayr's account of causation remains widely accepted today, with both positive and negative ramifications. Several current debates in biology (for example, over evolution and development, niche construction, cooperation, and the evolution of language) are linked by a common axis of acceptance/rejection of Mayr's model of causation. We argue that Mayr's formulation has acted to stabilize the dominant evolutionary paradigm against change but may now hamper progress in the biological sciences.

In November 1961, Ernst Mayr, Harvard evolutionary biologist and architect of the modern evolutionary synthesis, published what was to become a classic paper on causation. Mayr's "Cause and effect in biology" (*1*) had a massive influence by shaping how most contemporary biologists understand causality and was a major contribution to the philosophy of science (*2*). In this article, Mayr distinguished proximate from ultimate causes. A proximate cause is an immediate, mechanical influence on a trait: say, the influence of day length on the concentration of a hormone in a bird's brain. Ultimate causes are historical explanations; these explain why an organism has one trait rather than another, often in terms of natural selection. Although the proximate-ultimate distinction had been made earlier [e.g., (*3*)], it was Mayr's article that led to its widespread acceptance.

Mayr argued that "functional biologists," such as physiologists, trade in proximate causes because they are interested in showing how systems work. In contrast, evolutionary biologists trade in ultimate causes, because they are interested in why history has produced one system rather than another. The example that Mayr used to illustrate this distinction, avian migration, drew on his early career as a naturalist. Mayr emphasized that, to fully comprehend migration, we need to understand both why birds migrate (its selective advantage) and how they migrate (how they time migration, how they navigate, etc.). How-answers complement why-answers, and vice versa. Fifty years on, Mayr's account of causation has become so ingrained among biologists that few appreciate that it is a scientific convention, that both biologists and philosophers have taken issue with Mayr's stance, and that there are other ways of describing causation (*4*–*9*).

Mayr was acutely aware of the fact that proximate and ultimate accounts of bird migration had been wrongly juxtaposed as alternatives and stressed that "many heated arguments about the 'cause' of a certain biological phenomenon could have been avoided if the two opponents had realized that one of them was concerned with proximate and the other with ultimate causes" [p. 1503 of (*1*)]. This assertion is undoubtedly correct (*10*, *11*), making it even more ironic that his distinction should lie at the center of some of contemporary biology's fiercest debates.

Problems with Mayr's Proximate-Ultimate Distinction

Mayr's migration example was chosen well for its purpose, for it allows a simple proximate-ultimate distinction to be drawn (Fig. 1A). (i) Migration is clearly an evolved behavior, and, because it is expensive, it clearly has some selective explanation. (ii) Because birds evolved from flightless dinosaurs, migration is probably not the primitive condition of bird life, leaving the explanatory baseline relatively unambiguous. (iii) Migration is a response to autonomous, independent features of the environment, features not changed by the fact of migration. To explain migration, it is not necessary, say, to explain the relation between seasonality and Earth's axial tilt. (iv) Researchers can comprehend the physiology of migration without understanding the selection pressures that favored that physiology, and vice versa (*12*). This seemingly helps justify Mayr's (*13*, *14*) stance that researchers could understand evolution without understanding development.

However, it has become increasingly clear that other cases are not so simple. When a trait evolves through intersexual selection, the source of selection is itself an evolving character. The peacock's tail evolves through mating preferences in peahens, and those preferences coevolve with the male trait. The ultimate explanation for the male trait is the prior existence of the female preference, proximately manifest in peahen mate-choice decisions, shaped by inherited tendencies and modified by experience throughout development. Likewise, the ultimate explanation for the peahens' mating preferences is the prior existence of variation in the trait associated with fitness. Bird migration seemingly evolves through a unidirectional causal process, as the organism is shaped by selection to "match" features in the external environment. Thus, developmental processes feature only in proximate causal accounts. For intersexual selection, however, causation is reciprocal (Fig. 1B). Proximate mechanisms both shape and respond to selection, allowing developmental processes to feature in proximate and ultimate explanations. In reciprocal processes, ultimate explanations must include an account of the sources of selection (as these are modified by the evolutionary process) as well as the causes of the phenotypes subject to selection.

One ramification of reciprocal causation is that phenotypic plasticity, which is extremely widespread in nature, can generate selection and thus precipitate evolutionary episodes (*15*). It follows that developmental processes can influence the direction of evolutionary change. A second consequence is that, in these cases, the origin of the evolutionary episode is ambiguous. The cycle of causation may have begun with a prior preference or with fitness differences in a trait. Either way, such cycles can originate as an expression of phenotypic plasticity, in which case developmental processes explain the origin of evolutionary change (*7*).

Reciprocal causation extends to other cases where the source of selection on a character is coevolving with the character, for example, many instances of coevolution, habitat selection, social evolution, frequency-dependent selection, and maternal effects. These phenomena contrast with Mayr's paradigm in that acquired characters may not only be aspects of the proximate causes of an individual's development, but also sources of selection and/or novel variation (*7*, *15*–*18*), breaking Mayr's association of the proximate with ontogeny and the ultimate with phylogeny. Many of the growth points in evolutionary theory since 1961 extend the reach of evolutionary biology to phenomena that do not satisfy the simplifying conditions of bird migration. Such phenomena demand a more nuanced conception of biological causation. Furthermore, modern causal modeling methods overcome Mayr's (*1*) concern that biological complexity would make impossible an accurate description of causality as traditionally defined (*19*, *20*) (Box 1).

The Proximate-Ultimate Distinction in Contemporary Debates

Fifty years after the publication of Mayr's classic paper, it is instructive to reflect that several major debates in contemporary biology revolve

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around different notions of causation (Fig. 1). The common pattern to these conflicts is that one, often more radical, group believes that interaction and feedback render processes traditionally characterized as "proximate" relevant to evolutionary questions, whereas the more traditional majority inherit Mayr's position. The former group of researchers sometimes explicitly identify the proximate-ultimate dichotomy as a conceptual barrier to scientific progress (*7*, *9*, *21*, *22*). For instance, West-Eberhard [p. 11 of (*7*)] wrote, "The proximate-ultimate distinction has given rise to a new confusion, namely, a belief that proximate causes of phenotypic variation have nothing to do with ultimate, evolutionary explanation." More frequently, this difference in conceptual frameworks goes unrecognized. As a consequence, this distinction has itself become one of the contested issues, for some of the intellectual descendants of Mayr regard their opponents as confused precisely because they do not use it to frame their work (*23*, *24*).

Evolution and development. The proximate-ultimate distinction cemented the Modern Synthesis's separation of developmental and evolutionary biology. Mayr insisted on a dissociation of evolution and development (*8*), portraying organisms as "programmed" by selection. He described "functional biology" as concerned with the "decoding of the programmed information contained in the DNA code," whereas evolutionary biology studies "the laws that control the changes in these codes from generation to generation" [p. 1502 of (*1*)]. He later [p. 126 of (*13*)] wrote, "All of the directions, controls and constraints of the developmental machinery are laid down in the blueprint of the DNA genotype as instructions or potentialities."

If phenotypes were indeed tightly regulated by genes, with new variants arising solely by random mutation in gene codes, then black-boxing development might be a reasonable stance for evolutionists. Although this conception may fit some traits, it misses others where the development of selectable variation is biased rather than random. Developmental bias is potentially widespread in nature and can contribute to evolutionary stasis [e.g., reducing the likelihood of reversals of digit and limb loss (*25*)] or promote evolutionary adaptation [e.g., inherent features of pelvic development may have facilitated rapid convergent adaptation to postglacial lakes in sticklebacks, (*26*)]. If the proximate biology of a lineage makes some variants more likely to arise than others, these proximate mechanisms help construct evolutionary pathways (*7*, *27*, *28*). Another common theme in evo-devo is an emphasis on the role of developmental plasticity in the formation, preservation, and prevention of novelty (*7*, *29*, *30*). Recent studies of both vertebrates and invertebrates have shown that plastic responses to novel environments can influence evolution by directing the expression of heritable phenotypic variation along particular trajectories (*7*, *16*, *29*).

Thus, proponents of a role for development in evolution argue that variation between

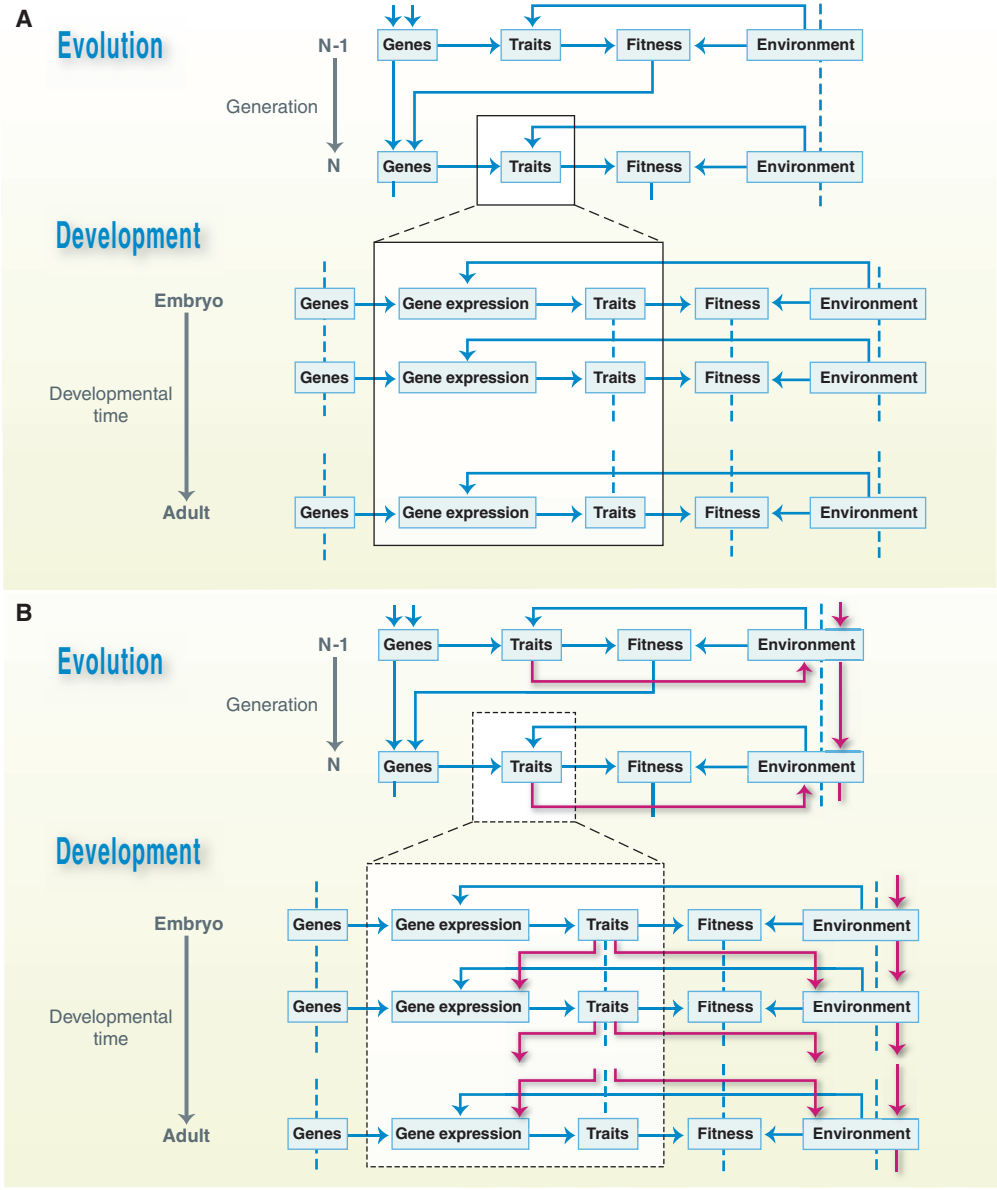

Fig. 1. Graphs depicting the causal pathways involved in the evolution and development of traits. Arrows represent possible causal influences; dashed lines represent features that persist over time. (**A**) Ernst Mayr's perspective. In evolution, genes and environment interact to cause the trait, the trait and the environment cause fitness, whereas the genes are determined by the genes carried by the previous generation and the fitness of individuals in that generation. The process of development is broken down in a similar manner but on a shorter time scale. The present-day trait is independent of other components in the graph conditional on the present-day genes and environment, so an explanation of the proximate cause of the trait must only account for how genes and environment interact in trait development. The ultimate explanation must then account for how the present-day genes and environment themselves were caused, but, because causation is only in one direction from the environment to the trait, the causes of the environment can be treated as an external system, of little biological interest. The only way in which the trait in one generation causes the trait in the next is through fitness (natural selection), so development can be black-boxed. (**B**) A modern developmental perspective. Red arrows denote additional causal influences relative to (A) recognized by fields such as evo-devo and niche construction theory. During development, features of the trait cause changes in both gene expression and environment, which feed back to the developmental process, resulting in a different trait in the adult and modifications of both developmental and selective environments. Development cannot be considered purely proximately causal because it results in additional causal pathways from the trait in one generation to the trait in future generations.

lineages in the extent of modular organization of phenotypes and environmental sensitivity in the expression of those modules contribute to patterns of evolutionary diversification. This could have important implications. If developmental bias is an important factor in the origin of adaptive variation, some of the most celebrated examples of the power of natural selection, such as the strikingly convergent evolution of coordinated traits among different populations of African cichlids, may instead partly be explained by a shared ancestral system of development (*31*).

Niche construction. Other researchers stress that developmental processes bias how organisms modify environmental states. Niche construction theory (*17*, *32*), like developmental systems theory (*22*), is built on a reciprocal view of the interaction of proximate and ultimate factors. Niche-constructing (environment-altering) phenotypic traits of organisms coevolve with recipient traits via organism-modified factors in the environment. For instance, earthworms change the structure and chemistry of the soils in which they live and, by constructing their environment, modify selection acting back on themselves, for instance, influencing their water-balance organs (*17*, *33*). Here again there is reciprocal causation (*17*, *34*): The ultimate explanation of the earthworm soil-processing behavior is selection stemming from a soil environment, but a substantial cause of the soil environment is the niche-constructing activity of ancestral earthworms. Ultimate factors are not stable, autonomous features of the environment; they include labile features of the organisms themselves and their changing effects on their environment.

Niche-construction theorists, like developmental biologists, view phenotypes (and hence their environmental modification) as underdetermined by genes. The changes that organisms bring about do not flow only from their adaptations, but also derive from plasticity, byproducts, and acquired characters and are often the collective output of multiple species (*17*, *34*). Moreover, these changes spill over to drive evolution in other species (*35*). For instance, human cultural practices, such as planting crops, domesticating animals, processing food, and living in cities, have generated selection for alleles that aid the digestion of starch, carbohydrates, proteins, and other novel features of our postagricultural diets (*36*, *37*). They also select for alleles that confer resistance to diseases (e.g., malaria and smallpox) inadvertently promoted by these practices (*36*, *38*). Ecological resources manufactured or modified by organisms can accumulate over generations to affect selection on descendant populations, a legacy known as "ecological inheritance" (*17*, *39*). At the extreme, phenomena such as sediment bioturbation or the accumulation of shell beds can accumulate over geological time, modulating macroevolutionary patterns and diversity (*40*). This ecological inheritance supplements other extragenetic forms of inheritance, including epigenetic inheritance, maternal and paternal effects, and cultural inheritance, all of which are now known to modify selection on descendants (*21*, *41*) and to affect evolutionary dynamics (*17*, *39*, *42*). The evolution of malaria resistance is very different from the evolution of migration. The evolving populations alter their environments, inadvertently exposing themselves to increased disease threat (e.g., creating breeding grounds for mosquitos) and responding genetically to that threat, but also through phenotypically plastic responses encompassing further environmental modification [as in cultural learning to manufacture DDT (*43*)]. Proximate and selective factors interact, each modifying the other in series.

Human cooperation. The evolution of cooperation is the subject of a multifaceted debate with many issues at stake, one of which is explaining human cooperation. One camp maintains that large-scale human cooperation is unique (*44*–*48*) and offers cultural evolution and gene-culture coevolutionary explanations for this puzzle. Their approach is typically implemented by using formal models, frequently reliant on multilevel selection (*44*, *47*–*49*), with explanations that stress ontogenetic processes such as imitation, teaching, or strong reciprocity (cooperation enforced through punishment). Their opponents question the argument that humans are special (*23*, *50*) and use an inclusive-fitness rather than a multilevel-selection modeling approach (*23*, *50*, *51*). Much of the debate has focused on technical issues and the relative merits of multilevel versus inclusive fitness frameworks. Less appreciated is a fundamental difference in causal concepts between the camps.

West and colleagues (*23*) argue that cultural transmission (often integral to multilevel-selection models of cooperation) is an aspect of proximate, not evolutionary, biology. They explicitly criticize Fehr, Boyd, Richerson, and others, because their "approach mixes up two different questions (how and why)" [p. 243 of (*23*)]. In their view, Fehr and others misconceive a proximate hypothesis as a solution to an ultimate question. Their opponents think this is mistaken. Those criticized explicitly endorse reciprocal accounts of causation (*44*–*46*, *52*); for instance, Efferson *et al*. provide evidence that "cultural processes can reshape the selective pressures facing individuals and so favor the evolution of behavioral traits not previously advantaged" [p. 1844 of (*52*)]. These authors regard teaching, imitation, and punishment as modifying selection and hence influencing biological evolution. Here, social learning creates developmental bias and/or shapes natural selection pressures, allowing genetic and cultural variation to coevolve and plastic responses to trigger evolutionary episodes. Once again, ontogenetic processes are part of the evolutionary explanation.

Cultural evolution. Matters become even more complex with cultural evolution, where many researchers see alternatives to natural selection as the ultimate process responsible for a character's design (Fig. 2). Aspects of human cognition and society—features of language, reading, writing, norms, cooperative behavior, institutions, and technology—are viewed as fashioned by cultural evolution, encompassing generations of social learning, teaching, and innovation (*21*, *44*, *53*, *54*).

There are many forms of cultural evolution, which differ in transmission pattern and in whether differentially fit individuals are biological organisms, groups, or cultural traits. But none fit Mayr's simple paradigm. For example, in one view, culture allows acquired characteristics to be transmitted between individuals at varying rates. In this view, cultural knowledge itself differentially reproduces. This allows differential social learning and transmission to generate design, in a manner parallel to that resulting from the natural selection of genes (*44*, *54*, *55*). Indeed, archaeologists and historians have documented many design features emerging through a long series of refinements of existing technology, from projectile

Box 1. Causal modeling and observational data.

Most biologists are taught that correlation does not imply causation and that randomized experiments are the only way reliably to infer the presence and direction of a causal link between variables. This is inaccurate. Rather, "a simple correlation implies an unresolved causal structure" (*19*). Statistical methods now exist that allow researchers to translate a causal hypothesis into a corresponding model and thus to distinguish between competing causal hypotheses by using observational data. The first stage is to express a causal hypothesis as a directed graph (*20*), in which variables are connected by edges (lines) representing direct causal effects (Fig. 3). Directed graphs are a useful means to express complex causal relationships economically (e.g., Figs. 1 and 2). However, researchers can also translate these into statements about which variables will be observationally independent conditional on other variables by using a property called d-separation (*19*, *20*).

Once competing causal hypotheses are translated into statistical models, one can assess the evidence for each by using standard methods of statistical analysis or compare competing hypotheses by using information theoretic or Bayesian criteria. The approach is related to path analysis, developed by the evolutionary biologist Sewall Wright. Wright used directed graphs to describe causal relationships between variables and linear regression to estimate the size (path coefficients) of each effect. Structural equations modeling (SEM) is an extension of path analysis that includes latent (unmeasured) variables. These approaches can be seen as a subset of the causal modeling approach, although many SEM users do not recognize the causal interpretation that can be given to their models (*20*). For an introduction to causal modeling, see Shipley (*19*).

points to the electric motor (*55*). These refinements did not result from differences in inclusive fitness.

For instance, languages are learned and culturally transmitted across generations and vary considerably between societies. Language scholars are polarized over whether specific design features, or regularities, of languages are best understood as the product of biological [e.g., (*56*, *57*)] or cultural (*58*–*60*) evolution. A recent study from the latter school concluded, on the basis of a phylogenetic analysis of languages, that "at least with respect to word order, cultural evolution is the primary factor that determines linguistic structure, with the current state of a linguistic system shaping and constraining future states" [p. 79 of (*61*)]. Similarly, laboratory studies of language learning demonstrate that linguistic structure can emerge through repeated bouts of cultural transmission involving selective retention of easily learned symbol-meaning combinations, leading some linguists to portray iterated learning as an alternative to natural selection for design features of language (*58*, *59*). Other linguists have criticized cultural evolution explanations for linguistic structure because "cultural transmission is a proximate mechanism" and follow Mayr in maintaining that "an ultimate explanation would have to explain why the production of such utterances produces (or does not produce) inclusive fitness benefits" [p. 43 of (*24*)].

This difference in perspective is manifest more generally in debates between evolutionary psychologists and cultural evolutionists (*62*). Evolutionary psychologists characterize cultural influences on development as operating like a (proximate) switch (akin to the buttons on a jukebox) to shift behavior and cognition from one preestablished program to another, with each context-dependent strategy fashioned by natural selection (*63*). In contrast, cultural evolutionists view culture as a historical knowledge-gaining process and therefore as a legitimate source of ultimate explanations for acquired human characters (*44*, *53*, *55*). The ideas of cultural group selection (*44*) or selfish memes (*64*) illustrate in different ways the fact that researchers cannot safely treat culture merely as a proximate system, for the mechanisms link back to evolution through the nonrandom creation of new variation (*52*).

Does Mayr's Proximate-Ultimate Distinction Remain Tenable?

There is obviously far more to the above disputes than the issues raised here, and we do not suggest that alternative notions of causation are the sole or even primary bone of contention. Nonetheless, it would seem that these seemingly separate disputes, among the most prominent in contemporary biology, are linked by a common axis of acceptance/rejection of Mayr's account of causation.

In one important respect, Mayr's stance has been vindicated. Mayr's concern that proximate and ultimate explanations should not be regarded as alternatives remains entirely valid today and is an important and useful heuristic that applies broadly across biological disciplines. There will always be how and why questions, and their answers will always be complementary rather than conflicting. That said, many recent debates show that Mayr's portrayal of his developmentalist critics as "muddled" (*8*), like similar arguments made by his intellectual descendants, is too simple. For instance, it is apparent that researchers' views on the evolution of culture critically depend on their assumptions about causality. Cultural evolutionists tend to view natural selection and cultural evolution as providing competing ultimate explanations, whereas evolutionary psychologists and linguists with a more nativistic perspective see the discussion as centered around alternative proximate accounts, often with greater or lesser amounts of innate structure shaping cultural learning. The same holds for debates over evo-devo, niche construction, and cooperation, where advocates of reciprocal causation propose alternatives to conventional evolutionary explanations in which ontogenetic processes are relevant to ultimate questions. In each case, the protagonists' stance follows logically from their model of causation.

Mayr's proximate/ultimate distinction has proven problematic because it builds on an incorrect view of development that fails to address the origin of characters and ignores the fact that proximate mechanisms contribute to the dynamics of selection. As a general conceptual framework for biology, reciprocal causation may now prove more useful than a unidirectional characterization, because it is better placed to accommodate the insights of developmentally minded evolutionists. This is not to suggest that all biological phenomena are reciprocally caused but rather that unidirectional selection is a special case of reciprocal causation where feedback is negligible (Fig. 1). Although reciprocal causation already features in biological explanations, it is typically viewed as applicable solely to special cases (e.g., sexual selection and coevolution). In contrast, the aforementioned debates suggest that reciprocal causation may be a very general, perhaps even universal, property of biological systems. We suggest a change in the default setting of evolutionary theory: from a default in which reciprocal causation is viewed as unusual or atypical, requiring special explanation, to a default in which straight-line causation is viewed as unusual, an atypical case where reciprocal impacts are minor enough to be ignored.

Should Mayr's proximate-ultimate dichotomization be abandoned? We see Mayr's view as

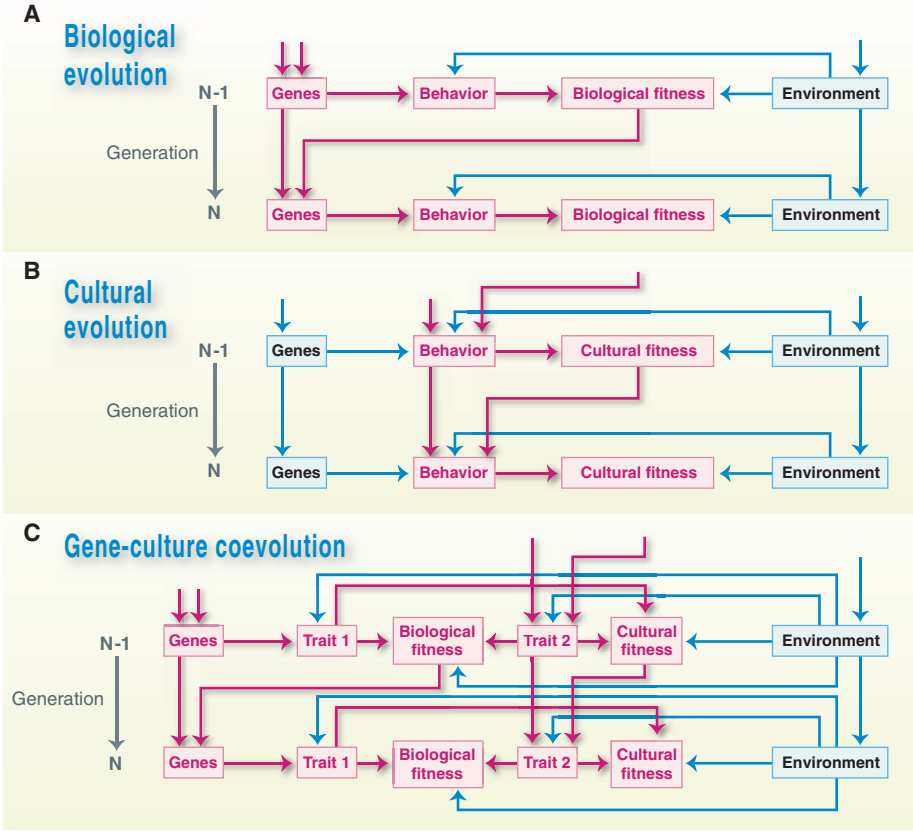

Fig. 2. Alternative evolutionary processes. (**A**) Biological evolution: The ultimate explanation for the behavior is its effect on biological fitness. (**B**) Cultural evolution: The behavior can be inherited from the previous generation through intergenerational cultural transmission and differential cultural selection. Here, the ultimate explanation for the behavior is its effect on cultural fitness. (**C**) Gene-culture coevolution: Genetically and culturally inherited traits coevolve, with each trait affecting the fitness of the other. [For illustration, trait 1 might be lactose absorption and trait 2 dairy farming or milk use (*43*).] Inheritance pathways are shown in red. For any given data set, causal modeling can be used to establish whether a particular causal influence is operating.

having two components, one of which is valid and valuable and the second of which is frequently taken to follow from the first, but does not. The first component is that proximate and ultimate explanations should not be confused as alternatives. We agree. Biologists will always require different answers to how and why questions. The second component is that ultimate hypotheses cannot invoke proximate processes and are solely concerned with biological evolution. Here, we disagree. Progress within biology demands dismantling of Mayr's identification of proximate with ontogenetic processes and ultimate with evolutionary processes (*65*). It is now vital to recognize that developmental processes frequently play some role in explaining why characters possess the properties that they do, as well as in accounts of the historical processes that explain their current state. To the extent that researchers view the proximate/ultimate distinction as a barrier to the satisfactory integration of evolution and development [e.g., (*7*–*9*)], it is largely because of the widespread, but mistaken, tendency to treat this second component as logically following from the first.

The commonalities of the above debates also raise rich issues concerning the history and philosophy of science, for instance, over how conceptual frameworks channel thinking and hinder paradigm shifts. It would seem that the manner in which biologists think about causality has acted like a meta-theoretical conceptual framework to stabilize the dominant scientific paradigm. Violation of the proximate-ultimate distinction became a theme in Mayr's rejection of the claims of developmentally minded critics of the Synthesis (*13*, *14*), and similar arguments continue to be made (*24*). Mayr's unidirectional characterization of causation encourages focus on single cause-effect relations within systems rather than on broader trends, feedback cycles, or the tracing of causal influences throughout systems (*8*, *9*, *17*). It may also hinder the empirical investigation of evolutionary causes if the role of proximate processes goes unrecognized. This has consequences not only for biologists' ability to break new ground and integrate subfields within biology, but also influences biologists' view on how their discipline is connected to other sciences, including the humanities. The fact that humans (and other animals) learn culturally is indeed part of their proximate biology, but it is also an aspect of our evolutionary biology. The biological sciences might now be better served by a new "reciprocal" conception of causation.

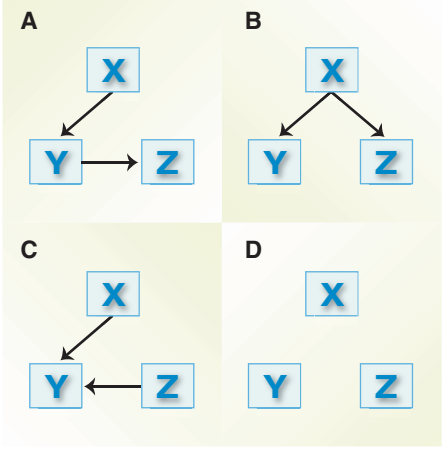

Fig. 3. Causal (directed) graphs showing different causal relationships between three variables. In (A) to (C), X is a direct cause of Y, meaning that changes in X will result in changes in Y irrespective of the behavior of any other variables in the graph. In (**A**), X is an indirect cause of Z, because changes in X will only induce changes in Z by causing changes in Y. The d-separation property enables us to say that in (A) X is independent of Z conditional on Y; in (**B**) Y and Z are independent conditional on X; in (**C**) X and Z are unconditionally independent; whereas in (**D**) all variables are independent regardless of conditioning. These four hypotheses could be distinguished by using observational data.

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