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Bridging the explanatory gaps: What can we learn from a biological agency perspective?

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Abstract

We begin this article by delineating the explanatory gaps left by prevailing gene-focused approaches in our understanding of phenotype determination, inheritance, and the origin of novel traits. We aim not to diminish the value of these approaches but to highlight where their implementation, despite best efforts, has encountered persistent limitations. We then discuss how each of these explanatory gaps can be addressed by expanding research foci to take into account *biological agency*—the capacity of living systems at various levels to participate in their own development, maintenance, and function by regulating their structures and activities in response to conditions they encounter. Here we aim to define formally what agency and agents are and—just as importantly—what they are not, emphasizing that agency is an empirical property connoting neither intention nor consciousness. Lastly, we discuss how incorporating agency helps to bridge explanatory gaps left by conventional approaches, highlight scientific fields in which implicit agency approaches are already proving valuable, and assess the opportunities and challenges of more systematically incorporating biological agency into research programs.

KEYWORDS
developmental bias, developmental plasticity, evolutionary innovation, extra-genetic inheritance, missing inheritance, niche construction

INTRODUCTION

As biologists we are keenly aware that, in Richard Dawkins' words, "there really is something pretty impressive about individual organisms".[1] Yet many of the ways we study plants, animals, and other organisms do not fully capture their distinctively flexible, functionally robust capacities as living systems. An explosion of new findings regarding gene regulation, extra-genetic inheritance, and molecular developmental systems has revealed three major explanatory deficits left by prevailing approaches, which focus on the genetic components of organisms as the sole key to understanding development, inheritance and evolutionary innovation. First, the mapping of genotype to phenotype has turned out to be far more indirect and complex than expected, leaving a gap in our ability to explain phenotypic outcomes and hence the causes of individual variation. Second, the developmental information transmitted from parents to offspring is only partially conveyed by shared genes, leaving a gap in our understanding of inheritance. And finally, our understanding of the origin of novel complex traits remains poor, apart from the realization that key evolutionary innovations such as the vertebrate eye, the insect wing, and the mammalian placenta cannot be explained by selection on random genetic mutations per se. Below, we draw on recent research insights to (i) identify these explanatory gaps; (ii) introduce a *biological agency* perspective that emphasizes how the response capacities of organisms shape phenotypic expression, inheritance and trait innovation; and (iii) show how this shift in perspective may help to fill these critical gaps in our understanding.

EXPLANATORY GAP 1: PHENOTYPIC VARIATION

The mid-century discovery of DNA as a protein-specifying molecule led to the confident view of an organism's DNA sequence as a self-contained phenotypic script or "blueprint," more recently studied through the lens of gene regulatory networks.[2] Across biological disciplines, this deterministic view of gene action has justified a primary research focus on genetic elements per se as the basis of phenotypes and their among-individual variation.

In accordance with the expectation of a straightforward mapping from genotypic to phenotypic differences, a key tool for understanding complex human phenotypes has been genome-wide association studies (GWAS) which identify statistical associations between specific genetic variants (usually single-nucleotide sequence polymorphisms) and phenotypes of interest.[3] These variants are considered important because they are understood to determine phenotypic outcomes; they are identified through statistical association but their role is presumed to be a causal, biological one. Hence a major goal of these studies is identifying "disease-susceptibility alleles," that is, the causal variants "that mediate risk of common disease".[4, pp 96,97] Through GWAS, researchers aim to "uncover the underlying molecular mechanisms by which a disease originates, and in particular, identify all relevant genes and gene variants (i.e., *disease causality*)",[5 p1, italics added]. Although genetic architecture and environmental influences are acknowledged to contribute to phenotypes, the prevalence of the GWAS approach reveals a primary research focus on finding the genes 'for' a particular trait or trait variant.

While this statistically powerful approach has identified numerous sequence variant-trait associations, its overall ability to explain phenotypic differences has been surprisingly limited.[6,7] In the case of body weight, for example—a biomedically critical trait in the context of obesity, insulin resistance and type 2 diabetes—115 genetic loci that showed significant statistical association with body mass index (BMI) collectively explained less than 3% of the variation among adults,[8] and a meta-analysis based on an enormous sample of 700,000 individuals (conferring great statistical power) still explained only 6% of BMI variation[9] despite using a high-dimensional correlation matrix that is known to inflate these estimates.[10] While such extremely large studies may incrementally add to the variance explained by identifying additional loci of small effect through sheer statistical force, over 90% of (a) phenotypic variation for BMI and (b) risk of type 2 diabetes remains unaccounted for,[11,12] pointing to a more fundamental issue. Similarly, alleles robustly identified in replicate GWAS studies of asthma, a chronic inflammatory disease that also poses a growing health problem, "account for little of the prevalence" of the disease.[7] And while genetic variants associated with the common (late-onset) form of Alzheimer's disease have been identified at numerous loci, only a modest proportion of disease risk is predictable based on genotype;[13–15] indeed, many individuals who possess multiple genes identified as risk factors reach an advanced age without showing disease symptoms.[16]

The explanatory reach of a gene-association strategy for trait variation may be limited due to its failure to consider the physiological and environmental context of gene expression[6,17] and how the developmental response systems of organisms contextually modulate phenotypes. Biomedical researchers concerned about the limits of the GWAS approach are therefore increasingly calling for conceptually broader studies directly addressing processing pathways that modulate gene function and hence phenotypic outcomes in individuals via complex gene-environment interactions,[18] environmentally-mediated epigenetic modifications,[19,20] and physiological and developmental feedback systems such as microbiome composition, which changes dynamically in response to the individual's diet, behavior, and social environment.[21] These dynamic, context-dependent processes may hold the key to the "dark matter" of phenotypic determination suggested by the explanatory deficits of GWAS– "dark matter in the sense that one is sure it exists, can detect its influence, but simply cannot 'see' it (yet)".[6]

EXPLANATORY GAP 2: TRAIT TRANSMISSION FROM PARENTS TO OFFSPRING

Along with a newly molecular approach to the causes of development, the discovery that chromosomal DNA bears a protein-specifying code provided Mendelian genetics with a precise inheritance mechanism for phenotypic information. Having previously identified the (recombined) nuclear chromosomes as the material passed from generation to generation during sexual reproduction, biologists could at last explain the resemblance of offspring to their parents by presuming that DNA comprises the transmitted developmentalinstructions.[22] The "extent to which phenotypes are determined by the genes transmitted from the parents" or *narrow-sense heritability* (or simply 'heritability'[23]) is estimated from the association between observed trait expression and shared genes of additive (i.e., discrete average) effect, as inferred by the degree of relatedness.[24, p 126] Most directly, when offspring trait values are plotted against their parental mean ('midparent') values, the slope of the regression estimates trait heritability.[23,24] Although such estimates will reflect any inherited factors that may contribute to parent-offspring similarity in the study sample, they are interpreted—as intended—as the result specifically of inherited alleles;[e.g. 25] stretching the inference even further, heritability is often (inaccurately) taken to measure "the genetic contribution to a phenotype"[10] in a developmental, causal sense.[23,26]

Now that GWAS offers the potential to identify the genetic variants that are viewed as the sole basis of inheritance patterns, an unexpected problem has arisen with this model. A case in point is human height, a notably familial trait: across Western societies its heritability is estimated to be c. 0.8.[27] We would expect any shared alleles of average effect that underlie this inherited resemblance to be precisely those revealed by GWAS. Yet even a powerful GWAS meta-analysis of over 250,000 individuals, identifying 10,000 single-nucleotide polymorphisms that contributed additively to height, accounted for only 36% of the heritability estimated from observed variation patterns.[27] In general, researchers have found that GWAS can only partially explain the resemblance of offspring to their parents, a perplexing phenomenon termed "missing heritability"—the extent to which the

evidently heritable portion of major trait variation is not explained by shared genetic alleles.[6] Although ever larger samples and statistical remedies may slightly alleviate this problem,[e.g. 9] it is symptomatic of a broader issue: transmission of specific genetic variants fails to satisfyingly explain either the process or the phenotypic impact of biological inheritance, leaving a second key explanatory deficit.

An experimental example using isogenic plants points to part of what may be missing. In one series of experiments with the common herb *Polygonum*, parent plants of the same genetic line were either drought-stressed or given ample water. When their offspring were grown in identical, dry, conditions, they developed differently: the offspring of drought-stressed parents produced significantly larger and more rapidly-extending root systems than those of the moist-grown parents, an inherited phenotypic effect that resulted not from a genetic difference but in response to parental conditions.[28,29] Numerous studies across animal and plant systems confirm that organisms inherit phenotypic information beyond parental genes alone, including environmentally modulated regulatory effects.[22,30–32]

Maternally derived signaling factors and resources that contribute to phenotypic expression in offspring include hormones, nutrients, stored transcripts, microbiota, and other egg and seed constituents that are influenced by the mother's environmental circumstances.[refs. in 33–35] In addition to these cytoplasmic modes of transgenerational adjustment, biologists are increasingly recognizing the astonishing range of maternally and paternally heritable molecular epigenetic effects on gene expression, including small non-coding RNA's, DNA methylation, and histone acetylation changes that alter chromatin structure and hence transcriptional activity. These regulatory factors may be spontaneous[36] or induced by specific parental cues or stresses, and in many cases are transmitted via gametes,[e.g. 37] sometimes across multiple generations.[reviewed by 38–40] Epigenetic changes due to ancestral environments may lead to major phenotypic effects, including for human health. In a highly cited study of 19th–20th century Northern Swedish population cohorts, poor food supply for paternal grandfathers during the slow-growth phase of their childhood development was associated with a 40% reduced diabetes/cardiovascular mortality risk in their grandsons compared with the population mean, while plentiful grandparental food supply increased the grandsons' mortality risk by 67%.[41] Importantly, heritable environmental effects are readily confounded with genetic factors in most experimental designs,[22] potentially accounting for "a substantial fraction" of phenotypic covariance between parents and offspring.[42, p 448] These extra-genetic inheritance processes may thus account for a considerable portion of the "missing heritability" that has perplexed researchers.

Through these regulatory aspects of inheritance, processes mediated by the parent's encounter with its environment may influence the development, physiology and behavior of its offspring in ecologically important ways.[references in 43–46] For instance, exposure of paternal stickleback fish to simulated predators led to changes in the brain transcriptome of offspring associated with predator-avoiding behaviors,[47] while gravid *Zootoca* lizards exposed to chemical cues from a predatory snake produced offspring with anti-predator traits such as longer tails and risk-averse basking behavior.[48] Similarly, freshwater snails exposed to predator cues produced offspring with increased predator avoidance behavior and thicker shells.[49] Studies of the nematode *C. elegans* provide a richly detailed body of evidence for adaptive transgenerational effects of parental exposures to stress, including increased stress and pathogen resistance and highly specific avoidance behaviors in offspring, that are transmitted in the germline via histone changes and small RNA's.[e.g. 50–51] [reviewed by 53,54] In plants, herbivory-induced maternal and paternal epigenetic effects resulted in increased offspring defense traits in *Mimulus* and *Raphanus*[55,56] and in *Polygonum*, parental drought and shade stress led to distinct methylation-mediated effects on offspring functional morphology.[29,57] Trans-generational effects of environment, mediated cytoplasmically and/or epigenetically, are evidently widespread in natural systems—a 2013 review cited published cases representing 32 biological orders.[58] Yet remarkably little is known about the induction cues and transmission dynamics of these processes,[59,60] leaving a major gap in our understanding of biological inheritance.

EXPLANATORY GAP 3: THE ORIGINS OF NOVEL, COMPLEX TRAITS

The origin of novel complex traits constitutes a central yet largely unresolved challenge in evolutionary biology.[61] Ever since the founding of evolutionary biology one of the discipline's core motivations has been to understand such elaborate innovations as the vertebrate eye, the insect wing, or the mammalian placenta, traits whose origins transformed the diversity of life on earth. Yet conventional approaches to understanding evolutionary change have provided few opportunities to make significant headway.[62] Of the four evolutionary processes conventionally recognized—natural selection, genetic drift, migration, and mutation, the first three can only sort among existing variants and their distribution within and among populations, but by themselves cannot bring about novel features.[63] This privilege is instead restricted to mutation, yet all attempts to explain the evolution of novel complex traits solely via the coincident origin, spread, and fixation of one beneficial mutation at a time have failed.[61] Not that mutational variation is irrelevant: numerous studies have identified genetic variants that contribute to complex trait development in profound ways.[64] Yet for the most part this work has informed our understanding of pathologies—what makes traits fail to form and function properly—while providing only modest insight regarding how these same traits may have originated in development and evolution.

This problem has only grown through the realization that many complex traits considered evolutionary novelties even by the strictest of definitions (absence of homology and homonomy, *sensu*[62]) consist of component parts and are instructed in development by processes which predate their invention by 10s to 100s of millions of years.[65] For example, butterfly wing patterns constitute a classic example of a morphological novelty, yet what it takes to build them (scales, which are modified hairs, pigments, pathways conveying positional information on the wing surface, etc.) is so ancient as to predate the

evolution of insects.[66] Similarly, insect wings—one of the most spectacular arthropod innovations—develop from serially homologous cell populations present not just in wing bearing segments, but in every segment in the thorax and abdomen, as well as in primitively wingless crustaceans, all equipped and organized by the same, shared, and similarly deeply ancestral gene network.[67] Much novelty in evolution thus appears to be possible without the need to evolve novel genes, pathways, or cell types. Exactly why, how, and when evolutionary innovations occur and unfold the way they do has thus mostly eluded conventional molecular-, population-, and quantitative genetic approaches toward understanding the evolutionary process.[61,68]

BRIDGING THE GAPS—A BIOLOGICAL AGENCY PERSPECTIVE

While these explanatory deficits affect a range of different phenomena—phenotypic determination, inheritance, and the origin of novelties—they originate from a common source: a tendency for our explanations to overlook the contribution of a definitive property of all living systems. Prevailing approaches to the causes of development, inheritance, and innovation, we argue, should be augmented by explanations that fully take into account *biological agency*—ways that organisms themselves actively shape their own structure and function. As scientists, what do we mean by that?

Living systems have evolved to be robust, responsive, flexible, self-synthesizing and self-regulating. This dynamic flexibility is manifest across diverse levels of biological organization, from cells, to tissues, to entire organisms, to reproductive lineages, to social colonies, and throughout a variety of organismal activities—from molecular signaling pathways to morphogenetic, metabolic, immune, endocrine, and behavioral systems. We use the term ***biological agency*** to refer to this suite of robust processes that is constitutive of living systems (See Box 1). Biological agency, in this sense, is the capacity of a system to participate in its own persistence, maintenance, and function by regulating its own structures and activities in response to the conditions it encounters.[69] Attributing agency to a biological system is based on natural, empirically determined processes and connotes neither consciousness nor deliberate intention.

We believe that biology has much to gain by expanding research foci from DNA sequence data per se to include the self-regulating, formative, responsive processes that comprise biological agency. Below we explain how these processes may help to bridge the three major explanatory gaps left by more narrowly gene-focused approaches.

ADDRESSING GAP 1: THE RESPONSIVE PHENOTYPE

In place of a direct "mapping", recent molecular insights have revealed an unexpectedly complex landscape in which the environmental responsiveness of living systems mediates between genes and the development of phenotypes. We now recognize that living systems have evolved to interpret genetic information in a great diversity of context-dependent ways that are mediated by stunningly complex interactive processes.[70–73] Through these interactive pathways, gene activity both shapes and is shaped by the organism's developmental and functional processes. Indeed, as a result of alternative splicing, condition-dependent domains of transcription factors and other signaling proteins, and post-translational modifications, even the most direct level of gene expression is shaped by conditions within and outside the cell, providing for "plasticity, adaptive responsiveness, and developmental versatility".[2, p 1; 74]

These flexible mediations are not minor "tweaks" to a genetically determined outcome—rather, they suggest a set of dynamically reciprocal pathways in which gene activity both shapes and is shaped by the organism's regulatory developmental and functional processes. Food availability regulates neuronal *daf-7* mRNA expression to either stimulate or inhibit development of larval nematodes.[75] Circadian rhythm-associated genes in *Drosophila*[76] and mice[77] are activated in response to perception of natural light/dark cycles, while light influences numerous functionally important aspects of gene expression in bacteria and yeast.[78] In plants, gene activity changes in response not only to perception of light, temperature and humidity but vibration and touch as well.[79,80] In many reptiles, the developmental response of offspring to nest temperature and other incubation conditions determines their sex,[81,82] evidently through differential activation of genes encoding steroid-producing enzymes,[83] and influences adult traits such as body size and running speed.[84] Brain-mediated acoustic, tactile, and visual stimuli influence gene expression and RNA synthesis in birds and mammals.[references in 46] Epigenetic regulatory mechanisms are implicated in many of these context-dependent modulations of gene activity,[discussed by 85–88] including diet-based effects in mammals.[59,89] In animals, the individual's response to signals from its (host-influenced) microbiome can in turn influence such complex behaviors as mating preferences and social interactions, which in turn mediate microbiome composition and transmission.[90] Clearly, any 'translation' of genotype into phenotype takes place through "intricate networks of cause and effect that are mediated by an organism's physiology, behavior, and interactions with the environment",[70, p 738] response networks that are themselves influenced in subtle ways by genomic differences.

This unlooked-for flexibility of gene expression results in what has long been recognized as environmentally contingent or *plastic* phenotypic outcomes for aspects of development, physiology, life-history, and behavior in all living systems.[91,92] Crucially, many such plastic responses are functionally appropriate to the particular conditions that elicit them, providing a mode of adaptation at the individual level.[reviewed in 45,46] For example, allocational, morphological or physiological shifts that increase nutrient uptake capacity may allow a plant in poor soil to maximize or even maintain its growth rate and eventual reproduction.[93] Similarly, in certain fish species gills are "remodeled" so as to increase respiratory surface area in individuals that spend several days in hypoxic water,[94] and small mammals at high altitudes develop lungs with increased alveolar surface area.[95] Phenotypes elicited in particular environments may of course also

Box 1: Biological Agency: What it is, and is not

What agency is

Agency is a dynamical property of a system.[162] It consists in the system's capacity to transduce, configure, and respond to the conditions it encounters. Crucially, agential systems are capable of maintaining functional stability in response to conditions that would otherwise compromise their viability. Agency is implemented through the influence that the system as an integrated whole exerts on the structure and activities of its component parts, and through the agent's influence on its external milieu. Often enough, the maintenance of stability elicits novel structures, functions and activities. Thus, for agential systems, novelty and stability are two sides of the same coin; they are both the consequence of the system's functionally adaptive dynamics. These adaptive dynamics have a distinctive signature or behavioral profile. Agents typically behave in ways that promote the attainment or maintenance of their persistence or viability. Thus, agency is an observable, predictable, explainable feature of the system's behavior.

This diagnostic signature of agency is observable at a variety of levels of biological organization, including the context-responsiveness of developmental, metabolic, immune, and endocrine processes. Agency manifests in the adaptive plasticity of development and phenotypic accommodation—adjustments that modify the organism's experience of environmental stresses[46]–as well as the manipulation by organisms of their external environments in ways that facilitate normative development and maintain fitness.

"Agential dynamics" is the study of the difference that the agency of systems makes to biological phenomena. One can measure the range of conditions across which an agent is resiliently robust and quantify an agent's repertoire of activities. One can predict a system's potential for adaptive novelty and model the capacity of a system to search "viability space".[163] Moreover, agency underwrites a distinctive mode of explanation; because an agent is capable of attaining and maintaining stable endpoints that reliably secure its stability, one can cite the stable endpoint to which the system tends in explaining its activities. As such, agential dynamics can form an indispensable element of the biologist's toolkit.

What agency adds

The agency perspective complements and augments existing approaches to modeling biological systems such as systems biology and reaction norms. Systems biology depicts the dynamics of a system as a set of trajectories through an abstract configuration space, but it does not explain why the configuration space has the topology it has. The agency perspective demonstrates that the possible trajectories are various ways that the system has of attaining its stable end states. Moreover, unlike systems theory, the agency perspective can capture the dynamic and reciprocal relation between a biological system and its configuration space. As an organism responds to its conditions, it structures and alters the configuration space; this reciprocity between configuration space and system is unique to organisms. The initiation of functionally adaptive adjustments or morphological novelties through developmental plasticity are just such examples of an organism both responding to and altering its own configuration space. This feedback in turn results in agency-influenced effects on selective trajectories that can suggest new evolutionary implications.

For their part, reaction norm studies plot patterns of phenotypic response as deterministic genetic outcomes. An agency perspective expands this approach by making room for recognizing, and thus studying and measuring, how norms of reaction themselves may be further modulated—for instance, in response to inherited environmental influences. In the process genotypic norms are re-conceptualized not as fixed products of previous selection, but rather as actively generated by the ways that organismic processes elicit specific gene actions in response to the conditions organisms experience.

What agency is not

Agency is neither an "intellectual" phenomenon, nor a "merely mechanical" one. Ascribing agency to a system in no way imputes to it intentions or desires. The association of agency with mindedness is understandable, but nevertheless misguided. To be sure, the cognitive and conative capacities of humans are paradigms of agency. But thinking is an extremely sophisticated, rarefied form of agency. Genuine agency is manifest in any living system that is capable of responding adaptively to its conditions, including unicellular organisms.[164] Nor does agency entail any form of providential design.

Neither are agents "mere machines". The principal difference between agents and machines is that the dynamics of a mere machine can be exhaustively explained by appeal to the structure and activities of its parts.[143] The dynamics of machines can be captured exclusively in the component-to-system mode of explanation. The dynamics of an agent further requires the system-to-component mode of explanation. In order to understand why the components of an agential system have the properties they have and interact in the ways that they do, we must understand the ways in which the agent as a system regulates the properties and interactions of the components in pursuit of its goals.

be maladaptive, for instance those expressed under new or extreme conditions that were not part of the organism's evolutionary past.[96] Certain disease states may thus be better understood as resulting from the body's response systems when confronted by novel cues and conditions.[97] Furthermore, a growing body of work suggests that even when encountering novel conditions, developmental systems may generally be biased toward producing functionally integrated, adaptive phenotypes.[98,99]

Understanding the development of phenotypes and their variation thus requires attending to the intricate, environmentally sensitive processes that actively generate and shape them. Research focused on these response processes may provide substantial new causal insights. In the case of body weight, for instance, maternal diet and the resulting uterine environment guide DNA methylation and hence transcriptional regulation in the developing fetus in ways that substantially shape outcomes; in a study of two human cohorts, methylation status of a single gene region in newborn umbilical tissue explained 26% of the variance in body fat at age nine.[100] Maternal overnutrition, obesity, or exposure to environmental chemicals such as bisphenol A (BPA) lead to epigenetic regulatory changes that increase offspring risk of obesity and diabetes.[12] In addition to these direct impacts of the uterine environment on fetal development and consequently childhood BMI and metabolism, epigenetic changes in maternal or paternal germ cells due to parental diet, BMI, insulin resistance, smoking during early adolescence, or chemical exposure all may contribute to adiposity and diabetes risk in F_2, F_3, or even later-generation progeny.[41,101–104] These investigations are building a new, "multigenerational" understanding of the developmental causes of obesity and metabolic disease.[12,59] The key to closing the phenotype gap may lie in part in shifting to an agency perspective in which organisms as responsive systems influence and integrate the effects of their genetic, epigenetic, developmental and environmental processes.

Biomedical researchers are also taking a response-systems approach to early-onset asthma, as a result of the recent discovery of an association between risk of this inflammatory disease and the composition of a child's gut and lung microbiomes (which jointly modulate the development and function of the immune system, for instance via circulating bacterial metabolites that promote T cell differentiation).[105 and references therein] These physiologically active communities of bacteria and fungi are themselves shaped by pre- and post-natal environmental experiences and are thus potentially amenable to therapeutic manipulation. Alzheimer's Disease research is also turning to a "new perspective" that focuses on the dynamic, environmentally context-dependent changes to gene regulation that underlie the multiple processing pathways involved in disease development, including cholesterol metabolism, *Tau* and *Amyloid B* protein processing, immune response and inflammation[], and the environmentally sensitive activity of microglia, the primary immune cells of the brain.[106] In these and other fields, a focus on the organism's dynamic processes rather than on genes alone is providing essential causal insights to phenotypic outcomes, revealing new potential therapeutic targets.

ADDRESSING GAP 2: MODULATED ASPECTS OF INHERITANCE

As documented in a flood of new insights into parent-environment effects and epigenetic transmission, the process of inheritance comprises unexpected complexity and nuance relative to the neo-Mendelian model of heredity as transmission of "the DNA sequence alone"[22] (Danchin et al. 2011). Cytoplasmic and epigenetic factors induced in response to parental environments influence phenotypic expression in offspring, as do heritable stochastic epigenetic 'marks', while both the induction and the phenotypic impact of these factors are influenced by genotype.[32,36,107] Furthermore, the developmental impact of such parent-environment effects generally varies from one progeny environment to another,[e.g. 49,57,108–110] revealing an interactive effect of parent-and-progeny conditions on each genotype's phenotypic expression.

This leads to the central point that an organism's phenotypic response to its immediate environment—its *norm of reaction*– is not as expected a fixed property of its DNA sequence, but instead is modulated by all of the regulatory information the individual has inherited, including cytoplasmic and epigenetic factors resulting from previous environments.[28] In consequence, instead of a expressing a genetically-determined conditional response, the developing individual integrates these various types of information through dynamic, real-time nuclear and cellular processes. These integration systems themselves vary genetically (i.e., genotypes as well as populations differ in parent environment x offspring environment interactions,[107,109]) indicating the potential for them to evolve under natural selection.[99,111–113] Such studies suggest that the key to filling the inheritance gap may lie in identifying the capacities of organisms to modulate and transmit phenotypic information to their descendants, and better understanding how those descendent individuals draw on this information in their own genetic and environmental contexts.

An agency perspective on inheritance that focuses on these capacities may uncover unexpected coping systems in animals and plants to novel environmental challenges as well as limits to those means of coping. In several marine systems, transgenerational regulatory effects may pre-adapt offspring to stresses associated with global change.[114 and references therein] When parental anemonefish are exposed to high concentrations of dissolved carbon dioxide, their progeny develop normally in elevated CO_2, although progeny of unexposed parents have sharply reduced growth in such conditions.[115] Similarly, sea urchins exposed to low pH before spawning "pre-load" their larvae with protective transcripts such as heat shock proteins and antioxidants, resulting in pre-acclimated progeny that can better survive in these conditions.[116] Juveniles of a common reef fish were able to acclimate successfully to elevated water temperatures simulating future marine conditions (+3°C) as a result of inherited methylation changes to genes involved in oxygen physiology that were induced in parents exposed to high temperatures.[117] In stickleback fish, the effects of simulated ocean warming in grandparent and parent generations varied from positive to negative depending on the timing and duration of

the stress,[118, see also 47] a reminder that determining the potential for inherited effects to provide rapid adaptation will require a great deal more empirical study.

Broadening the search for the heritable causes of disease to include epigenetic and cytoplasmically transmitted effects is a second major area of possible advance[6,19] for instance as heritable factors in cancers;[119,120] obesity, metabolic, and cardiovascular disease[121,122] and response to stress.[123,124] Including these inheritance processes may considerably enhance the limited success of GWAS studies to explain the inheritance and distribution of disease phenotypes,[125] particularly when their interactions with current environment and genotype are considered. Although to date studies of inherited epigenetic effects in humans are limited, a recent cohort study found that infant growth in height—a strongly familial trait in which less than 25% of variance is explained by even the largest GWAS studies[9]—was influenced by the fathers' prenatal nutrient environment.[126] Even more unexpectedly, initial studies of pregnant women exposed to lead during gestation demonstrated substantial changes to methylation state at over 400 loci (including those close to brain-development related gene regions) in their children's blood and in the fetal germ cells of their daughters, suggesting eventual transmission to grandchildren as well.[127] Clearly investigating these extra-genetic aspects of inheritance may be of tremendous benefit to human health.

ADDRESSING GAP 3: THE CONSTRUCTIVE NATURE OF INNOVATION

Surprisingly, many of the most promising breakthroughs in understanding the genesis of evolutionary novelty have occurred not in evolutionary biology itself, but through the comparative study of development and, more recently, the interface of developmental biology and ecology.[45] Examining development across taxa, environmental contexts, and levels of biological organization has led to several key realizations. First, organismal development has revealed itself to be a highly modular process, whereby phenotypic diversity is facilitated through the context-dependent re-use and re-assembly of an otherwise remarkably limited pool of genes, developmental pathways, cell types, and morphogenetic processes.[64,128] Second, organismic development has emerged as a highly constructive process, where a given aspect of phenotype formation builds upon a pre-existing phenotype created during previous stages of development.[129,130] The modularity, constructive nature, and context responsiveness inherent in all of development is now changing our understanding of what matters in the origin of novel, complex traits in ontogeny and evolution.

Modularity and context-responsiveness of development undergird several fundamental requirements for the evolutionary origin of novel traits. These developmental properties provide trait *integration*: during vertebrate development muscle precursors migrate randomly, but are maintained only in positions relative to concurrently forming bones.[131] Motor neurons proliferate abundantly during early developmental stages but are maintained only if they manage to innervate muscles.[132] The vascular system simply expands into empty space during early embryogenesis, but is stabilized subsequently through its attraction to hypoxic conditions.[133] In each instance, complex and discrete developmental processes integrate with each other through reciprocal interactions, thereby forming higher order levels of organization, yet without the need for a higher order organizer. Rather, integration emerges through the context-responsive action of component developmental processes.[134]

Modularity and context-responsiveness also facilitate *robustness*. Developmental systems respond to changes in context by falling apart only in the most extreme cases; generally, they react by adjusting subsequent rounds of phenotype construction, often in a functionally adaptive manner.[99] For example, perturbations to bone growth in vertebrates are accommodated by subsequent rounds of phenotype construction that adjust the corresponding attachments of ligaments and muscles, the commensurate placement of motor neurons, and the proper balancing of mechanical load across the entire muscular-skeletal system.[131] Even massive experimental perturbations are often compensated depending on the complexity of the developmental system already in place: for example, downregulation of *orthodenticle*, a transcription factor involved in patterning head formation is lethal in embryonic development across bilaterians, yet in later developmental stages the same perturbation is developmentally accommodated, causing heads to reorganize dramatically yet retain functionality.[135]

Because modularity allows developmental processes to respond to perturbations in a manner that yields adjusted but nevertheless robust and integrated complex phenotypes, living systems are afforded the ability to adjust to stressful environmental conditions—including conditions never before encountered—in ways that may bring about significant innovation, yet without initially requiring genotypic changes. *Polypterus* fish reared in a terrestrialized environment in which fish are forced to walk on their pectoral fins rather than swim, adjust—within a lifetime—not just their behavior, gait and posture but also their skeletal features, in ways that parallel the fossil record of tetrapods' ascendance onto land.[136] Tadpoles exemplifying the ancestral detrivorous life style and associated gut morphology will adjust the latter if forced to consume a carnivorous diet, in ways that partly parallel evolved changes in specialized carnivorous lineages.[137] Examples such as these suggest that interactions between developmental systems and environmental circumstance may bias the production of phenotypic variation in the face of novel or stressful environments toward functional, integrated, and possibly adaptive variants.[99] If so, novel phenotype production may precede, rather than follow, changes in genotype.[138] This does not diminish the importance of genes and genetic variation in the origin of evolutionary innovation: genes and their products are integral resources in enabling the modularity, self-organization, and context responsiveness of development. Similarly, selection of genetic variation within populations—whether arising from cryptic genetic variation made visible in novel environments or generated anew though novel mutations—plays a critical role in stabilizing and refining newly induced phenotypes in subsequent generations. But recognizing the creative role played by developmental systems in generating phenotypic variation does shift our emphasis away

from mutations as the sole source of evolutionarily significant new traits toward understanding how evolutionary innovation can also be significantly fueled by the self-constructing, self-regulating, and self-adjusting nature of developmental systems.

THE AGENCY PERSPECTIVE

In each of these cases, a persistent explanatory deficit may be partially or substantially filled by more fully appealing to a distinctive feature of organisms, the capacity of their constituent systems to respond adaptively to their circumstances. We call this explanatory strategy the "agency perspective". This approach begins with the observation that organisms are agents, and that recognizing their agency helps us to understand how organisms develop, function, and evolve. In this context, an agent is a system that is capable of attaining and maintaining a stable, viable endstate, by mounting adaptive (i.e., functionally appropriate) responses to its circumstances. These endstates are the agent's "goals". It is of the utmost importance to note that the concept of a goal, or of goal-orientation, carries no connotation of purpose or mindedness. A goal is simply a state that a system reliably tends to attain or maintain by making adaptive responses across a range of conditions.[139] As such, agency—goal-orientation— is recognized as an observable, measurable natural feature of any system's dynamics. Understanding that an agent has the capacity to implement those activities that conduce to its goals allows us to predict and explain its behavior (see **Box 1**: *What agency is and what it is not)*.

The benefits of the agency perspective

One crucial benefit of the agency perspective is that it offers an enhanced understanding of the internal (sub-agential) activities of a system. Although these processes are again in no way conscious or deliberate, agents pursue their dynamics by controlling their component parts and processes. The influence of living systems over their components is seen in all aspects of life: organisms synthesize the materials they are constituted of; they transduce the effects of their environments; they regulate the structure and function of their genes and genomes. It follows that we do not adequately understand the components of an agential system until we understand the ways in which the system regulates its structures, activities and relations in pursuit of the system's stable endstates. The agency perspective utilizes this dependence of a system's components on the dynamics of the whole. Even when the system's regulation of its sub-agential components is ultimately deleterious (as in the cases of asthma and Alzheimer's surveyed above), the agent's capacity to regulate those components is required in order to explain their activities and the eventual outcome.

In this way, the agential perspective offers a system-to-component direction of explanation that is in stark contrast to the prominent mode of explanation in the natural sciences. Typically, explanations of complex phenomena in the natural sciences proceed from the 'mechanism perspective'. In adopting the mechanism perspective, we often explain the activities of a system by decomposing it into its parts.[140–142] The properties, activities and interactions of the parts are taken to explain the dynamics of the system as a whole.[143] The mechanism perspective uniquely provides a component-to-system direction of explanation. As such, the mechanism perspective is always available for complex entities, and it is indispensable. Any complex system—living or non-living—operates in the way it does because of the properties and interactions of its components. However, mechanistic explanation may not exhaust all we want to know about the dynamics of a system.

A complement to mechanism

There are two related features of agential systems that suggest that standard mechanistic explanations can be augmented by agential explanations: context sensitivity, and goal-directedness. The components of agential systems exhibit a significant degree of context sensitivity in their structure and activities. The dynamics of the system, after all, requires the components to respond differently in different circumstances. The strategy of mechanistic decomposition, by contrast, involves either assuming the context insensitivity of the parts.[140–142] or holding contexts constant. Where the properties and activities of the parts are context *in*sensitive, a given component-to-system explanation will apply across a wide range of circumstances. This is the case with most mechanical, non-living systems. But where the properties and activities of the parts are highly context sensitive, each component-to-system explanation will apply to only a limited range of cases.

This brings us to the second distinctive feature of agential systems: the properties and activities of their parts are context sensitive in a specific and systematic way. Agential systems are goal-directed (though not in any deliberate way, as explained above). The system as a whole, as it pursues its goals, modulates the activities of its parts and processes in ways that bias the system toward the attainment of the goal in predictable (and empirically explicable) ways. At the same time, the system's components are sensitive to the shifting contexts provided by the goal-directed activities of the entire system. The system-to-component explanation afforded by the agential perspective explains why, in any given context, the components have the properties they have. In agential systems, this explanation cannot be furnished from the mechanism perspective.

It is important to note that the mechanism perspective (component-to-system) and the agency perspective (system-to-component) are not antagonistic or competing explanatory strategies. Rather, they are reciprocal and complementary. They are reciprocal in the sense that the component-to-system explanation accounts for the ways in which the dynamics of the whole depends upon the structure and activities of the parts, and the system-to-component direction explains the way the properties of the parts depend upon the dynamics of the entire system.[see 144 on circular causation] They are complementary in the sense that each perspective explains something important about the dynamics of the system that the other cannot. In order to understand the

Box 2: How can an agency perspective be incorporated into contemporary research programs?

Expanding research programs to include the processes emphasized by an agency perspective requires approaches for detecting and manipulating the context-responsive, self-constructing, and self-adjusting processes characteristic of living systems. Such approaches include:

Incorporate environmental variability into experimental design: Regulatory networks, developmental trajectories, trait expression, and interactions between organisms such as hosts and their microbiota must be tested not just in a uniform "control" environment, but in a realistic range of possible conditions. To evaluate prospects for future adaptation, testing an organism's responses to predicted future conditions will be a critical complement to conservation biology assessments of genetic variation per se.

Expand studies of transgenerational inheritance to include non-genetic sources of heritable variation: Accounting for inherited developmental information beyond genotype alone will require experiments that vary parental conditions, as well as multigeneration studies testing for meiotically persistent epigenetic influences. Similarly, incorporating the role of non-random environmental modifications through niche construction within and across generations promises to identify previously underrecognized sources of heritable variation and avenues for adaptation and diversification.[e.g. 164,165]

Examine the reciprocal interactions between development and environment: Conventional perspectives view the environment primarily as an autonomous source of information separate from, and external to, the organism. Agency perspectives additionally recognize environments as shaped by organismal action both *developmentally* (as each stage of phenotype construction builds on the developmental environment created by preceding stages) and *ecologically* (as organisms actively shape the ecological conditions experienced by themselves, their offspring, and eco-system members). Incorporating agency into modern research programs thus calls for studies that emphasize the simultaneously plastic and robust nature of development on one side, and the reciprocal interactions between agential systems and their environments.

Develop additional model systems conducive to experimental assessment of agency processes: More model systems must be developed, or existing model systems need to be expanded to include, assays and approaches for manipulating agency processes within generations (e.g., developmental plasticity) as well as transgenerationally (e.g., non-genetic inheritance).

dynamics of a living system we need to understand both how the components together produce the system's behavior, and how the system's dynamics regulates the components.

Returning to the explanatory deficits surveyed above, we can see that in each case there is enough empirical work available to suggest that the lacuna may be filled by providing an explanation of the system-to-component direction of influence: the agency perspective. Taken together, the studies we have surveyed suggest that the development of phenotypes is under the active control of the developing organism. The organism marshals the resources of its developmental system: (i) to mount integrated responses to changes in conditions; (ii) to guide trait transmission from parents to offspring beyond what genomes alone can accomplish, and; (iii) to facilitate the emergence of novelties without requiring an initiatial genetic change. These flexible responses provide adjustment to the individual's external conditions—as in the case of *Polygonum* plants to mount a transgenerationally stable response to drought stress—and to the internal environment created by the developing organism itself, allowing *Polypterus* fish, for instance, to produce pectoral limbs suitable for terrestrial locomotion. Throughout, genes and genomes are essential as one of several critical sources of information and other resources, but it is the dynamic, robustly adaptive nature of the organism's "physiology, behavior, and interactions with the environment"[73] that mediates between genotype and phenotype.

THE PROMISE OF INCORPORATING AN AGENCY PERSPECTIVE

An agency perspective points to new lines of investigation that aim to determine how the flexible and reciprocal response processes that characterize organisms may contribute to their adaptive, resilient, and innovative features (see **Box 2**: *How can an agency perspective be incorporated into contemporary research programs?*). While this represents a substantial shift in focus compared with prevailing gene-based approaches, this perspective is implicit in several current research avenues that are already starting to bridge persistent explanatory gaps and provide new applications.

Studies of the metabolic, cellular, and immunological adjustments that take place in response to microbial symbionts are opening new possibilities from crop plant productivity and disease resistance[145,146] to cancer treatment.[147] Also in cancer medicine, new studies show that the problem of progressively emerging drug resistance may result from the ability of the cancer-cell signaling network to adapt plastically to a given drug (without any genetic change), giving rise to new combinatorial strategies to derail this response network[148] or to strengthen the body's own tumor-suppressing metabolic and immune responses.[149] Another exciting area of medical research involves organoids, miniaturized and simplified versions of an organ produced in vitro.[150] Initiated either from stem or

differentiated cells, organoids self-organize their three-dimensional architecture, reaching levels of complexity and functionality that mimic some of the structural characteristics and dynamic behaviors of an organ. Recognizing the agential abilities of organoids to self-build, self-organize, and self-maintain has opened up critical new opportunities for drug testing, disease modeling, the production of human organ transplants, and the study of human development.[151]

Alongside more conventional approaches (for instance studies of allelic variation for herbivore or pathogen resistance), agency perspectives are also increasingly present in ecology and evolution. As natural populations confront rapid environmental changes, researchers are focusing on immediate and transgenerational plasticity as potential sources of adaptive rescue.[152,153] Plastic responses to environmental conditions are also under study as possible sources of the morphological innovations that fueled early crop and livestock domestication.[154] In Maize, for instance, the "profound" architectural and reproductive changes that distinguish cultivated Maize from its wild progenitor, Teosinte, resulted not from novel mutants but from the response of a complex epistatic network to the atmospheric CO_2 and crowded planting conditions encountered during the species' early cultivation.[155] Similarly, recent experiments with the soil bacterium *Myxococcus* raise the exciting possibility that plastic responses to physical and nutrient substrate properties rather than a novel mutation may explain the origin of microbial multicellularity.[156] Behavioral ecologists are studying how behavior takes shape in response to the environmental inputs the animal receives from its parents as well as throughout its own life-cycle;[157] evolutionary ecologists are including the active roles of organisms in modifying their own ecological circumstances and hence creating feedbacks on their development, physiology, and behavior, and on the selective pressures that shape their further evolution.[158,159] Evolutionary theory is moving beyond deterministic gene-based models to test the potential selective role of flexible response processes within and across generations.[e.g. 31,160,161] An agency perspective may thus prove especially valuable for evolutionary biology because conventional approaches focused on genetic variation leave explanatory gaps regarding the very things we need to know to understand the evolutionary process—phenotypic variation, inheritance, and the origin of novel traits.

CONCLUSION

A strict focus on genetic variants has been enormously productive in terms of both basic and applied biology; it has led to detailed knowledge of molecular signaling pathways, remarkable tools for genetic engineering, identification of specific human variants with major impact on disease risk, and robust determination of phylogenetic history and relationship. Yet recent findings have underscored critical gaps in knowledge that remain despite these achievements. In short, one cannot fully explain why genes (and other component factors) have the effects they have unless one takes into account the way in which the systems they are embedded in regulate their own structure and activities. It is this dynamic, system-level adaptive responsiveness that constitutes biological agency, a characteristic feature of living systems. Agency offers biology a distinctive explanatory strategy, the *agency perspective*, in which the dynamics of the system, and the activities of its components, are explained by appeal to the agent's adaptive responsiveness. This perspective can complement and enrich gene-based approaches by revealing how the flexible response processes that characterize organisms contribute to their adaptive, resilient, and innovative features. As contemporary biologists seek to meet urgent challenges in human health and biodiversity conservation, shifting our perspective to emphasize the formative response capacities of organisms could be a transformational step toward bridging persistent gaps in our understanding, leading to new lines of investigation and new insights to living systems.

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There are no data available.

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