Genes as cues: phenotypic integration of genetic and epigenetic information from a Darwinian perspective

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The development of multicellular organisms involves a delicate interplay between genetic and environmental influences. It is often useful to think of developmental systems as integrating available sources of information about current conditions to produce organisms. Genes and inherited physiology provide cues, as does the state of the environment during development. The integration systems themselves are under genetic control and subject to Darwinian selection, so we expect them to evolve to produce organisms that fit well with current ecological (including social) conditions. We argue for the scientific value of this explicitly informational perspective by providing detailed examples of how it can elucidate taxonomically diverse phenomena. We also present a general framework for linking genetic and phenotypic variation from an informational perspective. This application of Darwinian logic at the organismal level can elucidate genetic influences on phenotypic variation in novel and counterintuitive ways.

Development and cue integration

The textbook depiction of genes as ‘recipes’ that determine organismal phenotypes is increasingly difficult to sustain in the modern biological sciences [1,2]. Phenotypic plasticity – the ability of a genotype to produce distinct phenotypes as a result of nongenetic influences during development – may be ubiquitous in multicellular organisms [1,3]. Such nongenetic influences (here referred to collectively as epigenetic) can include environmental cues and ‘parental effects’ (including vertical cultural inheritance and DNA-methylation patterns) [1,3,4], which often reflect parental experience of the local selective environment [5]. However, it is underappreciated that genes themselves can also act as cues of the current environment [5–9]. If there is restricted gene flow among local environments with differential fitness effects of alleles in different environments, allele frequencies will vary spatially [10]. Therefore, an individual’s genotype will statistically contain information about (correlate with) local environmental conditions and can be regarded as a genetic cue. In effect, genes at polymorphic loci provide information that the phenotypic states they trigger have had local success [5–7,10]. Furthermore, at the level of developmental mechanisms, there is considerable overlap in how environmental cues and genetic variation determine phenotypes [1,11].

Here we aim to provide a general framework for thinking about how potential cues are integrated during development to maximise the fit of the phenotype to current ecological (including social) conditions. Such integration will be favoured by Darwinian selection if the cue integration system is itself under genetic control [7]. For instance, a polymorphic ‘genetic cue’ locus might influence the hormonal regulation of phenotypes, either by encoding transcription factors that modulate gene expression at other loci [12] and influence circulating hormone levels or by influencing hormone receptors [11,13]. Similarly, developing phenotypes can be modulated by epigenetic parental effects (e.g., genomic imprints, maternal effects) and the state of the local environment. By influencing transcription in target tissues, hormone receptors can ‘integrate’ these inputs [14,15], thereby guiding phenotypic development [14]. In summary, evolutionary change of developmental systems occurs via selection on modifier loci (e.g., that influence tissue-specific hormone receptor densities), fine-tuning responses to developmental cues. Modifiers might often be regulatory genes.

Adaptive cue-integration systems of the sort outlined above will take any available sources of information (epigenetic and genetic) into account in determining phenotypes. Our framework predicts that the relative weights put on each source of information should depend on environmental characteristics, such as its temporal stability, and on cue accuracies. If correlations among allele frequencies at a cue locus and local ecological conditions provide greater predictive accuracy than environmental cues, genetic polymorphism can be favoured, along with genes that are selected to modify phenotypic development appropriately for each genetic morph [7] (such ‘specific’ modifiers are known; e.g., from studies of sex determination [16]). Thus by taking such an explicitly informational approach...
we can predict epistatic effects among genes determining the cue integration (developmental) system and other genes that provide cues.

This informational perspective offers a powerful way to understand how genetic and epigenetic influences are integrated during development. Since this perspective was introduced [6,7,10] it is increasingly being used to interpret a wide variety of biological phenomena [3,5,17–21]. Here we promote the scientific value of this approach by outlining the underlying logic and detailing how it can elucidate taxonomically widespread phenomena. We show how rigorously applying Darwinian logic at an organismal level (i.e., assuming selection favours developing phenotypes that process information to maximise their fit to their local environment) can help to explain genetic influences on phenotypic variation in novel and counterintuitive ways.

**Being alive can be informative**

Central to the idea that genes can be used as developmental cues of the forthcoming environment is the existence of persistent genetic variation with alleles differing in frequency in different environments [7,22]. If the ability to cope with local environments is to some degree controlled genetically and conditions remain stable enough across generations (e.g., individuals are likely to inherit parental environments and do not disperse too far away to reproduce), the fact that an individual exists suggests that it is likely to be in an environment to which it is well adapted. This is because most of the individuals of its genotype are likely to be born into such ‘good’ habitats precisely because genotype fitness (the rate at which it is copied) is maximised where it is best matched to environmental conditions. Thus, over generations, genotype members will accumulate disproportionately in environments to which they are well suited [10,21]. We call this demographic accumulation the ‘Multiplier Effect’ (ME) and have demonstrated how it can explain the evolution and maintenance of ostensibly paradoxical unconditional strategies such as natal philopatry (attempting to breed in natal habitats) [10]. We briefly illustrate the main insights (modelling details can be found in [10]).

**Case study: natal philopatry**

Consider an organism with discrete, non-overlapping generations with a 1-year generation time. The environment contains many breeding sites, some of which are good (it is well suited to), others poor. Sites change quality over time but site quality (good or poor) is positively correlated between years. During development individuals receive environmental cues of current site quality. Individuals can either attempt to breed on their birth site or choose another breeding site at random. After breeding the individual dies and its offspring face the same decision.

Consider first a genotype that ignores environmental cues and always attempts to breed at its birth site (i.e., is natailly philopatric). Since good sites produce more surviving offspring than poor sites, by being natailly philopatric individuals of the genotype increase their chances of breeding on a good site. Over generations this effect amplifies (the ME [10]). This results in a higher proportion of individuals breeding on good sites at demographic equilibrium than would be expected by chance given the frequency of good sites in the environment. Therefore, breeding on birth sites is the best thing for individuals to do unless environmental cues provide very strong evidence that sites are poor. In other words, natal philopatry maximises fitness unless environmental cues are highly accurate (Figure 1). In informational (Bayesian) terms [23,24], the probability that an offspring came from a good site acts as the Bayesian prior and the posterior probability is the probability of a good site given this prior and the cue. Since an individual that does not attempt to breed at its natal site chooses a site at random, natal philopatry is optimal provided the posterior probability exceeds the proportion of good sites in the environment.

As Figure 1 shows, the likelihood that natailly philopatric individuals came from good sites (the Bayesian prior) depends strongly on the ratio of surviving offspring on the two site types. This ratio might depend on other aspects of the genome. If variation in these other aspects were maintained, it would be adaptive to have a cue integration (e.g., developmental) system that based its ‘decision’ on whether to disperse on both the cue value and cues provided by these other genetic elements. In other words, one might expect epistasis between the genes controlling the cue integration system and those affecting the ratio of surviving offspring produced on different patches.

There has been a recent effort to link ideas about the ME [10] to a branch of population genetics theory that has its roots in Fisher’s thinking about mutation–selection balance [21]. According to the Reduction Principle (RP),
populations near an equilibrium between selection and any ‘transformation processes’ (e.g., mutation, dispersal, recombination) will evolve less transformation because at such an equilibrium any change in phenotypic state (e.g., where individuals are, what alleles they express) is likely to be a change away from matching the selective environment (i.e., maladaptive) as most individuals will already be in conditions to which they are suited [21]. It can be shown that the conditions under which the MR operates are equivalent to those specified by the RP [21]; therefore, the genetic cue approach is also likely to provide insight into the evolution of a wide range of population genetic phenomena including modifier loci, linkage disequilibrium, recombination, evolvability, and dispersal or migration (reviewed in [21]). Thus, we might expect lower mutation or recombination rates to evolve when fitness landscapes are rugged and do not vary much between generations as this makes it likely that any phenotypic change would be maladaptive [10,21].

Applying the ‘genetic cue’ perspective
Phenomena involving cue integration are taxonomically widespread. To further illustrate the value of the genetic cue perspective, we discuss two examples where predation or herbivory intensity varies and individuals can invest in costly defences based on information from various sources. For instance, defences in both crustaceans and plants can be induced by individual experience and maternal cues. Here we show that genetic cues are also likely to play a role.

Many species of *Daphnia* develop distinct defensive morphologies against predators, usually in response to waterborne chemical cues of predator presence (e.g., predatory phantom midge larvae kairomones). For *Daphnia pulex* these defences include dorsal ‘neck teeth’ and their induction has been studied in considerable detail [25–30]. Phantom midge larvae are gape-limited predators and it is mainly juvenile daphnids (up to the fourth instar) that are vulnerable to them. Correspondingly, the neck teeth are present during instars one to four and tend to be most strongly expressed in the third instar [27]. The development of neck teeth in response to kairomones can be viewed as cue integration. If mothers experience kairomones, but not their offspring, offspring express neck teeth mainly in the second instar [27]. Furthermore, offspring have a developmental window for induction of neck teeth, during the late embryonic stage [29] while in maternal brood chambers. Without exposure to kairomones then, neck teeth are not expressed. If offspring experience kairomones in time, the degree of neck tooth expression depends on the strength and duration of kairomone exposure [27,29]. Thus, from a developmental cue integration perspective, there should be an early indication that defence is needed, through maternal or embryonic experience, and, given this, the strength of defence investment depends on continued evidence that it is needed. We can extend this to include genetic cues as follows.

There is substantial variation in how readily individuals induce defences, even among clones collected from the same ponds [26,28]. Given that daphnids go through bouts of asexual reproduction interspersed with episodes of sex, there is ample opportunity for locally adapted genetic variation to accumulate at different times and in different microhabitats. Thus, prevailing genotypes are likely to cue (correlate with) local conditions (e.g., local abundance of predators) in a similar way as maternal cues [5]. For instance, *D. pulex* clones taken when phantom midge larval densities were at their highest frequently induced defensive morphologies at very low kairomone concentrations, while clones taken when phantom midge larvae were rare and fish predators predominated showed weaker responses (few individuals induced defences, and only at higher kairomone concentrations) [26]. The informational interpretation is that the former clones had high inherited (genetic) expectations of predation risk by phantom midge larvae and therefore did not need much corroboration from environmental cues to develop defences, while the latter clones had very low phantom midge predation risk expectations and therefore required stronger environmental evidence to induce defences. To date there have been no empirical tests of this explanation for variation in the inducibility of defences in daphnids. In the field, clones could be sampled across their spatiotemporal niches (different places and different seasons) to ascertain whether they show reaction norms that on average are favourable for the conditions encountered. Laboratory manipulations of the requisite spatial and temporal variation in predation risk would also be feasible.

Plants often induce biochemical defences in response to insect herbivory [31]. In addition, it has been suggested that antiherbivore defences might commonly be induced transgenerationally [32,33]. One reason to expect adaptive maternal effects to evolve in plants is that pollen dispersal often occurs over much greater distances than seed dispersal, possibly inhibiting local genetic adaptation and favouring epigenetic signalling from mother plants to seeds [9,34,35]. There are numerous molecular mechanisms of the induction of plant defences involving the jasmonate signalling pathway that are being actively explored. These include direct responses to plant tissue wounding [31] and transgenerational induction involving small-RNA signalling from mother plant to seeds [32,33] as well as genetic (ecotypic) variation in defence [36]. Box 1 illustrates how integration of these different effects can evolve, if they are explicitly regarded as potentially informative cues during development. See [5,9] for other examples of similar evolutionary models.

The novel interpretation we argue for in both cases above – that an individual’s genotype can serve as a cue of the risk of predation or herbivory in the near future – has so far not been tested empirically. Such tests would be important, because they can increase our understanding of the circumstances that favour genetic versus environmental determination of phenotypes and, more generally, the integration of information during development. In contrast to traditional approaches to the study of phenotypic plasticity and genetic polymorphism, our approach allows these phenomena to be conceptualised within a common framework, thereby facilitating predictions of the use and integration of cues.
**Box 1. Plant defence induction against herbivory**

Figure 1 illustrates a simulation model of the induction of plant resistance against herbivory as motivated in the main text, which follows the general scheme outlined by Holeski et al. [33]. Local patches vary spatially and temporally in the expected intensity of herbivore attack, which can be either low or high. The defence phenotype expressed in the mature plant $u$ protects the plant by changing herbivore consumption by a factor $1 – u$ but has the cost of changing the reproductive output of the unconsumed parts of the plant by $1 – u/2$. In the model, herbivore attack acts both as an environmental cue that induces defence and as a selective factor (Figure IA). A maternal cue can also be produced by the plant, priming the seeds for defence induction, and it is possible for herbivory intensity-correlated genetic variation in $u$ (‘genetic cues’) to accumulate under certain conditions (see below). Performing evolutionary simulations under various conditions, we explore the extent to which $u$ is influenced by genetic, maternal, and direct environmental cues (see the supplementary material online for modelling details). We show that defences can be induced as a response to a combination of maternal and environmental cues (Figure IB), a combination of genetic and environmental cues (Figure IC), or just environmental cues (Figure ID). These outcomes depend on which influences can convey information about the likely herbivory intensity, given temporal and spatial variation in conditions and gene flow, and on the availability of mechanisms of cue transmission. ‘Genetic cue use’ (genetically polymorphic antiherbivore defences) is predicted when there is substantial genetic variation among patches at evolutionary equilibrium (e.g., Figure IC: very high patch temporal stability and very limited seed and pollen dispersal) and therefore cue locus allele frequencies better predict the risk of herbivory than noisy maternal cues.

![Figure 1](image_url)

**Figure 1.** Evolution of inducible defences against herbivory in diploid hermaphrodite plants. See the supplementary material online for further details. (A) Sketch of the life history and information flow to the mature plant. Ovules are fertilised by dispersing pollen, and seeds receive genetic cues (alleles at a cue locus) from each parent as well as small RNA-mediated epigenetic cues from the mother plant. After seed dispersal the growing plant might be fed upon, which influences the level of jasmonate signalling and is a cue of the risk of herbivory for the mature plant. (B-D) Evolutionary equilibria in defence levels. (B) High temporal stability of herbivory, very limited seed dispersal, and free among-patch pollen dispersal. The grey curve shows the average induced defence as a function of the maternal epigenetic cue. The points show induced defences of individual plants in low (blue) and high (red) expected herbivory patches. The deviation of the points from the grey line is a response to the intensity of herbivory on the growing plant. There is little genetic variation in defence. (C) Very high temporal stability and very limited seed and pollen dispersal, together with very noisy transmission of the maternal cue, results in an equilibrium with substantial genetic variation at the cue locus, which approximately corresponds to the three genotypes of an additive two-allele locus. Deviations from the grey line are responses to the intensity of herbivory on the growing plant. There is little maternal influence on the level of defence. (D) High temporal instability with low and high herbivory intensity varying randomly across generations, in which case only the direct environmental cue (herbivory on the growing plant) influences induced defences.
New perspectives on dominance, epistasis, and genetic conflict
For genes that encode developmental systems, the genotype at a genetic cue locus can play a similar role as environmental cues, in the sense of providing information to the organism about selectively relevant circumstances. Based on this view of genes as cues of the selective environment, we should expect systems that fine-tune development to genetic variation to evolve [7,22]. This can occur via selection for genetic modifiers that adjust developmental trajectories [12,15]. For instance, if the different homozygotes at a two-allele locus are adapted to markedly different environmental conditions and there is substantial gene flow in the population, the phenotype of the heterozygote is likely to evolve to match one of the homozygotes (e.g., the most commonly adaptive one). This will occur through the invasion of modifier loci that change the phenotype of the heterozygote [37]. Thus dominance can be viewed as evolving via the fine-tuning of the developmental influence of genetic cues of the selective environment [22].

Another consequence of viewing developmental systems as potentially using genetic cues is that genetic conflict [38] is likely to play a significant role in the evolution of these systems [7]. To see why this is so, consider two habitats with different phenotypes being optimal in each habitat and, for simplicity, haploid individuals that reproduce sexually. If there is a two-allele locus with alleles producing phenotypes that are suitable for each habitat, depending on the intensities of selection and gene flow allele frequencies will differ between habitats. Potential modifiers that are fully linked to an allele that is common in one habitat and rare in the other will mainly experience one of the habitats, so their evolutionary ‘interest’ will be to produce a phenotype that is successful in that habitat. For unlinked modifiers, however, the situation can be radically different. A modifier allele at an unlinked locus might be present at similar frequencies in both habitats and its evolutionary interest will be to produce phenotypes that do well overall. Therefore, unlinked modifiers that produce less extreme phenotypes will be favoured. It is even possible that unlinked modifiers favour genetically monomorphic generalist phenotypes whereas fully linked modifiers favour genetic polymorphisms. Such differences in the evolutionary interests of modifier genes with contrasting linkage to a genetic cue locus represent genetic conflict [38]; evolutionary change favoured by linked modifiers (increased phenotypic divergence between morphs) selects for unlinked modifiers to reverse this change. As well as less phenotypic differentiation, unlinked modifiers can favour development that is sensitive to environmental cues [7], in effect favouring phenotypic plasticity over genetic polymorphism. The evolutionary outcomes of such ecologically driven genetic conflicts will depend on the mechanisms of regulation of development and gene expression. In general, the genetic cue approach highlights the need for further work on ecologically driven genetic conflicts, having the potential to predict patterns of linkage and epistasis in phenotype determination from Darwinian first principles.

A Darwinian framework for development: evoeolutionary feedback is key
Since the informational interpretation of genotypes was introduced in the literature [6,7], it has attracted the interest of researchers exploring a range of phenomena, including phenotypic polymorphisms (polyphenisms [39]), transgenerational epigenetic influences on development [9,40], mechanisms of ageing [17], sex-determination systems [20,41], early-life influences on health and disease [18], genetic variation in stress sensitivity [19], and ecological responses to anthropogenic environmental change [42]. To encourage wider application, we encapsulate its basic logic in a general informational (Bayesian) framework [23] for development in Figure 2. Such approaches embody fundamental Darwinian logic since fitness is maximised by phenotypes that maximise their fit to current conditions by utilising any sources of information available when it is cost-effective to do so [43].

A crucial feature of an ecologically consistent [44,45] informational framework for development is that it must incorporate various evoeolutionary feedbacks. Two are illustrated in Figure 2.

- If an environment varies spatially, the distribution across habitats of individuals can be regarded as a Bayesian prior distribution for the developmental system they possess. Local cues during development provide further information on local conditions. However, the manner in which such cues modify development affects how the survival and reproduction of individuals depend on local conditions, determining the spatial distribution of individuals and hence the prior distribution itself.

![Figure 2. A Darwinian framework for integrating genetic and epigenetic information during development. We envisage environments comprising local habitats linked by dispersal. Conditions can vary among habitats and over time. The local habit, parental states, and genes all provide cues that are integrated by the developmental system to determine the mature phenotype. The developmental system is under selection to match phenotypes to environments. The distribution of individuals across habitat types is determined by the demographic processes of survival, reproduction, and dispersal. It is thus influenced by the developmental system itself, through the phenotypes that develop in different conditions. At phenotypic determination (during development), this distribution acts as a Bayesian prior distribution on habitat type. Given a cue of local conditions during development, the posterior probability that the local habitat is of a given type depends on the developmental system. Thus, selection on the developmental system to change its responses to environmental cues depends on its existing configuration.](image-url)
Box 2. Promising areas for future applications of the ‘genetic cue’ perspective

- Bacteria often combine activities of genetic elements (e.g., plasmids) with social cues (e.g., quorum sensing) in their responses to local environments [48]. Because these responses often involve producing some sort of public good (e.g., iron-sequestering siderophores [49,50]), cues of the local social environment can be crucial for controlling such investment [50,51]. It is likely that frequencies of public good alleles will vary according to the historical social structure of populations (particularly if they assort independently of the bacterial genome; e.g., on plasmids); therefore, patterns of bacterial ‘cooperation’ might be best understood in terms of adaptive integration of environmental and genetic cues. Such logic will be readily testable using experimental evolution. For instance, bacterial cultures could be maintained that differ in the degree to which social structure (e.g., clonal diversity within a culture) varies across generations. Our ‘genetic cue’ perspective would predict quorum-sensing strains to predominate in ‘socially unstable’ cultures.

- Males of many fish species express various mating tactics within populations, from simple differences in mating behaviour to the development of alternative morphs [52]. Such variation can be underpinned by genetic differences and/or environmental (including social) influences in different species [52–56], which have traditionally been thought of as representing distinct evolutionary outcomes (e.g., status/condition-dependent versus mixed evolutionarily stable strategies [52]). By contrast, our cue integration perspective facilitates explicit analysis of the ecological conditions favouring different forms of cue use (or combinations thereof), as well as likely evolutionary transitions among systems [56]. This lends itself naturally to empirical comparative analysis. For instance, species in the genus *Xiphophorus* (swordtails) show a range of different alternative male morph-determining systems, from genetic polymorphisms (e.g., *X. nigrensis*, *X. maculatus*, *X. multilineatus* [54,55]) to social determination (e.g., *X. variatus* [53]). Given the well-resolved phylogenies for this genus [57,58], we would expect closely related species that determine male morphs differently to also differ in how stable their population densities (and therefore operational sex ratios) are.

- Understanding the evolution of cooperative breeding in vertebrates has typically focussed on explaining patterns of dispersal within and among species [59]. A key driver of delayed dispersal (and therefore helping by non-breeders) has been suggested to be the existence of substantial spatial variation in breeding habitat quality that is likely to persist across generations [59]. This is reminiscent of the conditions under which an inherited state is likely to reliably cue the best fit to local conditions (i.e., the ME operates [10]), suggesting that the genetic cue perspective is likely to be useful in elucidating the complex interplay between ecological and genetic factors underpinning vertebrate societies. Formal cue integration models would identify key socioecological drivers of patterns of helping in facultative cooperative breeders (e.g., stronger habitat quality differences favouring delayed dispersal [10]). These would specify a priori statistical models for existing long-term field datasets, as well as suggest bespoke manipulations of the key factors in established field-study systems.

At evolutionary stability the developmental system will integrate prior information and developmental cues in an optimal way given the prior distribution resulting from its particular mechanism for phenotype determination.

- The correlation between cue genes and the local selective environment imposes selection on the cue genes themselves and how they are integrated by the developmental system. The correlation depends on the developmental process itself; it will typically be low when developmental systems ignore genetic cues, since cue genes are then under weak selection, and higher when phenotypes depend more on such cues. Thus the information content of genetic cues, and hence the selection pressure on developmental systems to integrate these cues, depends on the developmental system itself. Again, at evolutionary stability the developmental system should be optimal given the selection pressures it generates.

Such feedback raises the possibility that there might be more than one evolutionarily stable developmental system in any given environment.

Concluding remarks: empirical and philosophical prospects

Substantial empirical effort remains to fully understand any developmental process underpinning phenotypic variation from an adaptive perspective. Our framework (Figure 2) lends itself naturally to generating hypotheses that are testable using the ‘modern toolkit’ of approaches for studying adaptation in evolutionary biology. To illustrate how it could be applied we give a few examples of promising areas of inquiry in Box 2.

A major challenge in modern biology remains to fully understand how genetic variation maps to phenotypic variation. We offer our developmental cue integration framework (Figure 2) as a powerful basis for theorising about the links between genotype and phenotype in Darwinian systems. There are important philosophical implications of this perspective [8,46,47]. The idea that both genetic and environmental cues are ‘read’ by the mechanisms of development to maximise phenotypic ‘fit’ to the environment demonstrates that thinking of inheritance systems such as the genome as representing (biased subsets of) environments has considerable explanatory utility in biology [47]. We are confident that explicitly informational approaches to understanding biological systems, centred on phenotypes as evolved information-processing systems, can offer profound new insights.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tree.2015.04.002.

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