Developmental plasticity: Re-conceiving the genotype

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Abstract

In recent decades, the phenotype of an organism (i.e, its traits and behavior) has been studied as the outcome of a developmental 'program' coded in its genotype. This deterministic view is implicit in the Modern Synthesis approach to adaptive evolution as a sorting process among genetic variants. Studies of developmental pathways have revealed that genotypes are in fact differently expressed depending on environmental conditions. Accordingly, the genotype can be understood as a repertoire of potential developmental outcomes or *norm of reaction.*

Re-conceiving the genotype as an environmental response repertoire rather than a fixed developmental program leads to three critical evolutionary insights. First, plastic responses to specific conditions often comprise functionally appropriate trait adjustments, resulting in an individual-level, developmental mode of adaptive variation. Second, because genotypes are differently expressed depending on the environment, the genetic diversity available to natural selection is itself environmentally contingent. Finally, environmental influences on development can extend across multiple generations via cytoplasmic and epigenetic factors transmitted to progeny individuals, altering their responses to their own, immediate environmental conditions, and in some cases leading to inherited but non-genetic adaptations. Together, these insights suggest a more nuanced understanding of the genotype and its evolutionary role, as well as a shift in research focus to investigating the complex developmental interactions among genotypes, environments, and previous environments.

Introduction

The concept of genotype is central to both biological and human sciences. New findings at the molecular level have established that it is gene expression as regulated by environmental and cellular factors, rather than DNA sequences *per se*, that shapes phenotypic variation. This recognition has led to a focus on individual developmental plasticity, a general property of organisms that was known but deemed marginal by mid-twentieth century evolutionists. This essay examines how insights to plasticity destabilize the concept of genotype on which the Modern Synthesis model of evolution was founded, and indicate ways to renew this central concept.

1. The genotype as a developmental program

For the past half-century, biology has been dominated by a gene-based approach in which an organism's DNA sequence is understood to comprise the instructions for that organism's development (see Keller 2000; West-Eberhard 2003; Griffith 2006). According to this view, an individual organism's set of genes (its *genotype*) determines that individual's physical traits and behaviors (its *phenotype*), so it is possible to know what the organism's features will be just by knowing its DNA sequence. Because gene expression itself is assumed to be under genetic control, the genotype is seen as a self-contained internal developmental 'program' that specifies a single, determinate phenotypic outcome (Sarkar 2006). The interpretive metaphor of the 'genetic program' has become a deeply imbedded construct for framing both developmental and evolutionary phenomena (West-Eberhard 2003; Newman and Müller 2006; Noble 2015).

This view of the genotype has led to three key evolutionary corollaries. First, if genes determine specific traits such as size, structure and behavior, *the organism's adaptation to its environment is set by its genotype*. Second, if traits of individuals depend on their genes, then the functional and fitness differences between individuals that cause natural selection are also specified by their genotypes-- in other words, *fitness differences originate in genetic differences*. Third, the *DNA sequence inscribed within the nucleus of each cell comprises the developmental information that is passed from one generation to the next*. Because this genetically encoded information is impervious to the environment as well as resistant to error, it is faithfully transmitted across a continuous evolutionary trajectory.

Together, these three points form the foundation of the elegantly simple and coherent Modern Synthesis model of adaptation as population-level change over time in the relative frequencies of alternative genetic alleles. It is a commitment to this causal model that lies at the heart of contemporary debate about whether this conceptual framework for adaptive evolution--and thus for contemporary research programs-- remains generally sound (Wray et al 2014) or requires revision (Laland et al. 2014). This tension reflects the fact that a no-longer tenable genetic program view of phenotypic and hence fitness variation is implicit in the Modern Synthesis approach (Newman and Müller 2006; Lynch and Wagner 2008; Noble 2015).

2. Conceptual models and empirical approaches

The idea of the genotype as a set of self-contained developmental specifications was given mechanistic solidity following the work of Watson and Crick in revealing the biochemical 'code' of nucleotides in the DNA molecule (Keller 2000). Following from this

foundational idea, and in marked contrast to the environmentally contextualized view of development that had characterized earlier work (Byrnes and Eckberg 2006), the goal of developmental studies has been to reveal this "sequestered" internal information (Gottlieb 2004). Similarly, mainstream evolutionary biologists have sought to identify the genetic basis of adaptive variation as if the process of development "did not exist" (West-Eberhard 2003 p. 18; see Amundsen 2001). This is done experimentally by raising genetically different individuals in a single, uniform 'control' or 'common garden' environment that is meant to be developmentally neutral, in the sense of permitting expression of the phenotype undistorted by environmental effects (Neumann-Held 2006 and references therein). Since the developmental environment is held constant in these studies, any trait differences among individuals is considered to result from differences in their genotypes[1]. As a result, a single-environment experimental design and a determinate view of gene-based variation serve to reinforce each other (Lewontin and Levins 1985).

Despite the ubiquity of this experimental approach, biologists are well aware that organisms develop not in 'neutral' environment-less conditions, but rather in particular environments--whether in nature or in the laboratory--that are characterized by specific physical factors, chemical compositions, resource levels, and the presence or absence of biotic interactors. They are equally aware that the exact states of such environmental factors influence the developmental process, and consequently the organism's functional and fitness traits. Indeed, it is precisely because of this influence that researchers employ the 'control environment' approach: they do so in order to exclude variability in environmental factors that would otherwise affect phenotypes. By rationalizing this approach, the idea of an

[1] In such "common garden" studies, inherited effects of previous environments are generally confounded with genotypic differences; see Section 6.

internally contained developmental program led to a neglect of environmental context in studies of gene expression (Griffiths 2006.

Unexpectedly, it is the intense focus of contemporary biologists on molecular, presumably internal pathways of developmental regulation that has newly underscored the environment's critical role by providing a mechanistic basis for it. Thanks to a flood of recent observations, it is now clear that genes are differently expressed depending on environmental context, leading to tremendous regulatory diversity and complexity (references in Carroll et al. 2005; Lemos et al. 2008; Sultan 2015). In light of these findings, genes can more accurately be viewed as "potential resources" for developmental pathways (Sarkar 2006) than as fixed pieces of information. Even biologists who seek to preserve the Modern Synthesis conceptual framework acknowledge that "technological advances in the past decade have revealed an incredible degree of plasticity in gene expression in response to diverse environmental conditions" (Wray et al. 2014). These molecular data make clear that phenotypes are not scripted in advance from the nucleus, but instead emerge from regulatory interactions in which environmental factors participate in specific ways. The organism's environment as well as its genotype provides the kind of precise developmental information that guides the cellular and nuclear processes that shape phenotypes, including dynamic traits such as physiology and behavior (Gottlieb 2004; Gilbert 2012).

This powerful insight requires that biologists replace the 'genetic program' model of internal developmental control with one in which each genotype may express different phenotypes depending on its environment-- in other words, with a focus on developmental plasticity as expressed in response to specific conditions (Figure 1). More broadly, the general term *ecological development* or *eco-devo* (Gilbert 2001; Gilbert and Bolker 2003)

114 situates the normal developmental process in its environmental context by emphasizing how
115 regulatory pathways integrate environmental signals at the cellular and molecular levels
116 (references in Sultan 2007, 2010, 2015; Gilbert and Epel 2009, 2015). Under this unified
117 concept, *plasticity* describes those cases in which outcomes differ appreciably among
118 environments, as distinct from environmentally insensitive or *canalized* trait expression
119 patterns.

120 An 'eco-devo' approach can be implemented by means of a key experimental
121 change: by inverting the design so as to bring in rather than exclude environmental variation.
122 To do this, a researcher generates replicate individuals of each experimental genotype (via
123 cloning or inbreeding), and grows these genetic replicates in each of several distinct
124 environments. The resulting phenotypes can be plotted to visually characterize each
125 genotype's range of environment-specific developmental outcomes, known as its *norm of*
126 *reaction* (Woltereck 1909; Gupta and Lewontin 1982; Stearns 1989; Sultan and Stearns
127 2005). The norm of reaction for any trait in an organism reflects both the particular genotype
128 and the precise set of environmental states in which it is measured.

129 Note that the idea of characterizing a genotype by its pattern of environmental
130 responses (rather than by the trait it expresses in a single 'control' environment) predates the
131 Modern Synthesis, with its emphasis on inborn, genetic determination of phenotypes (Sarkar
132 2004). Instead, the norm of reaction makes explicit the environmental context-dependency of
133 the phenotypes that a given genotype produces. Once this context-dependency is recognized,
134 the researcher's choice of environmental conditions becomes critically important (Miner et
135 al. 2005). Indeed, subtle differences among laboratories in animal handling and rearing
136 techniques may be one reason why bioemedical researchers have often been unable to

137 replicate one another's results, leading to a 'reproducibility crisis' that is mistakenly
138 attributed to sloppiness or chance (Voelkl and Würbel 2016). To the extent that experimental
139 environments reflect naturally-occurring conditions, norm of reaction studies can provide
140 information about trait expression in real populations. As discussed below, empirically
141 determined norms of reaction illuminate two key evolutionary issues: adaptation and genetic
142 variation.
143

144 **3. Developmental plasticity as adaptive variation**

145 Based on knowledge of a species' ecology, it is possible to evaluate whether the
146 phenotypes expressed by a given genotype are functionally adaptive to the alternative
147 environments in which they occur (e.g. Dudley and Schmitt 1996; Schmitt et al. 2003; Sassi
148 et al. 2007; Chapman et al. 2008). The norm of reaction for any developmental, physiological
149 or behavioral trait of interest may be relatively constant across environments or change from
150 one environment to another. Such changes may constitute adaptive adjustments (as indicated
151 by positive ecophysiological or fitness effects in the inducing environment), or may simply
152 reflect inevitable environmental effects on development such as reduced growth in resource-
153 poor conditions. In the many plants, fungi, lichens, invertebrates, amphibians, reptiles, fish,
154 mammals, and birds in which norms of reaction have been found to comprise adaptive
155 responses to specific conditions, plasticity provides for an individual, developmental mode of
156 adaptation (Schmalhausen 1949; Bradshaw 1965; Lively 1986; Schlichting 1986; Stearns
157 1989; Scheiner 1993; Sultan 1995, 2000; 2003b, 2015; Pigliucci 2001; DeWitt and Scheiner
158 2004; Gilbert and Epel 2009; 2015; and references therein).

159 For example, individual plants of the widespread colonizing species *Polygonum*
160 *persicaria* grown at reduced light produce far greater photosynthetic leaf surface area relative
161 to their mass than do cloned plants of the same genotypes grown in full sun (Sultan and
162 Bazzaz 1993a; Sultan 2003; Griffith and Sultan 2005). This increase in the plant's ability to
163 catch scarce photons (and hence maintain growth and reproduction) results from two
164 developmental changes expressed in moderate and low light compared with full sun:
165 increased relative allocation of plant tissue to leaves (Figure 2), and broader, thinner leaf size
166 and structure (Figure 3). Similarly, *Polygonum* plants raised in dry or nutrient-poor soil
167 invest a higher proportion of their body mass into root tissues, and make the roots themselves
168 longer and thinner, compared with genetically identical individuals grown in moist or rich
169 soil. These plastic responses result in much more extensive root systems that can more
170 effectively collect soil resources that are present in low concentrations (Sultan and Bazzaz
171 1993b,c; Bell and Sultan 1999; Heschel et al. 2004).
172 These findings from cloned *Polygonum* plants grown in contrasting light and soil
173 conditions exemplify three key points that characterize developmental plasticity across
174 biological systems. First, these plastic responses are not trivial tweaks to a pre-determined
175 developmental program, but substantial changes in the expression of functionally important
176 traits. Second, the very different phenotypes produced by *Polygonum* genotypes in different
177 conditions constitute environment-specific adjustments, in this case ones that enhance
178 function by increasing the availability of the most limited resource. Viewed in another way,
179 such functionally adaptive developmental adjustments improve the environment that the
180 plant experiences: plants in low light that increase their surface area experience an
181 environment in which more photons are available, and plants with very high root surface area

for water uptake have greater access to moisture. Third, whether adaptive or inevitable, phenotypic changes due to developmental plasticity alter external conditions for that individual as well as for co-occurring plants, animals and microbes in its habitat. For instance, plants in darker microsites produce larger leaves that cast more shade, reducing temperature, light quantity and red: far red spectral quality at the soil surface; these thinner leaves also decompose more rapidly, which increases mineral cycling rates in the soil. Because the particular phenotypes that organisms express will differently influence their experienced and external environments, plastic developmental responses partially shape the selective pressures under which they evolve (Sultan 2015; see also Laland et al. 2008), an evolutionary feedback termed *niche construction* (Odling-Smee et al 2003, 2013; Laland et al. 2016).

Norm of reaction (eco-devo) studies thus reveal the genotype as a repertoire of possible developmental responses expressed by the organism in specific conditions, rather than as a self-contained set of fixed developmental instructions with a single outcome. As in the case of *Polygonum* plants, these environmental responses often comprise an immediate, developmental mode of adaptation to contrasting conditions. This mode of adaptation takes place at the level of the individual organism, as distinct from adaptive phenotypes produced by natural selection via population-level allele frequency change. An important evolutionary consequence is that, unlike the random and rare occurrence of favorable new genetic variants, plasticity can provide adaptive variation when it is needed (i.e., in response to a particular environmental challenge or change) and in numerous individuals in a population at once. As noted by Sewall Wright (1931), this may buffer selective change by allowing existing genotypes to maintain fitness in altered or diverse conditions (recent models

205 demonstrating this effect include Chevin et al. 2010; Draghi and Whitlock 2012; Gomez-
206 Mestre and Jovani 2013).
207
208 **4. A norm of reaction view of genetic diversity**
209 When genotypes are viewed as determinative, self-contained developmental
210 programs, they are assumed to be consistently associated with particular outcomes.
211 Accordingly, in this model the functional and fitness trait differences that fuel natural
212 selection directly reflect the genotypic diversity that is present. Just as conceptualizing the
213 genotype as a repertoire of environmentally contingent outcomes reveals new sources of
214 adaptive variation, this conceptual step also leads to a more nuanced view of the genetic
215 diversity necessary for selective evolution.
216 Due to sequence differences along pathways of environmental perception and
217 phenotypic response, distinct genotypes exposed to the same range of conditions will express
218 different norms of reaction, for various traits (Stearns and Sultan 2005; Moczek et al. 2011).
219 In a classic paper on 'nature and nurture,' J.B.S. Haldane (1946) observed that, in naturally
220 evolved systems, these differing norms of reaction are very rarely parallel. Instead, as
221 numerous quantitative-genetic studies have since confirmed, genotypes are generally
222 characterized by plastic adjustments that differ in magnitude and/or direction in response to a
223 given set of environments (Barton and Turelli 1989; Kruuk et al. 2008; Des Marais et al.
224 2013; *genotype by environment interaction*, the statistical term for such non-parallel response
225 patterns, results in 874,000 publication hits on *Google Scholar*). As a result of non-parallel
226 norms of reaction, the trait differences among a given group of genotypes will depend not
227 only on those genotypes but also on the environments they encounter.

228 Two evolutionary points follow from this insight, as illustrated by *Polygonum* norms
229 of reaction for leaf allocational plasticity (Figure 2). First, the size of trait differences among
230 genotypes varies from one environment to another: the same set of genotypes may produce
231 phenotypes that are similar or identical in some conditions but quite different in others. For
232 example, the ten *Polygonum* genotypes shown (which were originally drawn from a natural
233 population) invested similarly in leaf tissue when they were grown at High and Moderate
234 light, but differed considerably at Low light, since some genotypes increased leaf allocation
235 more sharply in this more extreme environment than did others. In general, existing genetic
236 variation may be exposed to natural selection only in certain conditions, and hidden from
237 selection or 'cryptic' in environments where genotypic norms converge (Wilson et al. 2006;
238 Snell-Rood et al. 2010; evolutionary consequences discussed by Van Dyken and Wade 2010;
239 Ledón-Rettig et al. 2014; Paaby and Rockman 2014; and references therein). Consequently,
240 a population's potential for selective evolution depends jointly on its genotypic diversity and
241 on the environment(s) that occur (additional references in Sultan 2015).
242 Second, the rank order of phenotypes produced by a given set of genotypes can vary
243 from one environment to another, if non-parallel norms of reaction happen to cross. In the
244 *Polygonum* data, for example, the genotype with the highest leaf allocation at High light has
245 the second lowest allocation at Low light, the two highest-allocation genotypes in Low light
246 are the two lowest in both Moderate and High light, and the lowest-allocating genotype at
247 Low light is the highest at Moderate light (Figure 2). If environments vary, such 'crossing
248 over' of reaction norms can prevent consistent selective change (in this case, for example,
249 selection for genotypes that allocate more to leaf tissue) and instead maintain multiple
250 genotypes in a population (Via and Lande 1985; Gillespie and Turelli 1989). Norm of

reaction data thus reveal that both the amount and the particular patterns of genetic diversity are environmentally contingent and not intrinsic properties of a population's genotypes. In other words, the surprising answer to two basic questions regarding the potential selective evolution of a functional or fitness trait --how much genetic variation for the trait is present, and which genotype produces the highest trait value--must both be answered, 'it depends on the environment(s)'. One practical consequence is that evolutionary studies require precise information about environmental as well as genetic variation within natural or experimental populations.

5. Transgenerational plasticity: developmental effects of previous environments

A fully contextualized picture of the genotype includes the recognition that an organism's development may be influenced by its parents' conditions as well as by its own immediate environment (e.g. Falconer 1981; see Salinas et al. 2013 and references therein for examples across 32 biological orders, from *Archaea* to *Mammalia*). Effects of parental environment on progeny development are generally considered as a transgenerational form of developmental plasticity, mediated by several distinct and often interacting mechanisms of inheritance (reviewed by Badyaev and Uller 2009; Herman and Sultan 2011).

In both animals and plants, maternal individuals can directly transmit environmental influences on progeny development (for instance, due to resource stress or predation) to eggs or seeds, via changes in the amount and composition of cytoplasmic factors including nutrient reserves, hormones, defensive chemicals, and small RNA's (Roach and Wulff 1987; Kirkpatrick and Lande 1989). Molecular epigenetic effects such as DNA methylation and histone modifications can be transmitted to progeny by either paternal or maternal

274 individuals (Jablonka and Raz 2009; Soubry et al. 2014). These inherited epigenetic 'marks'
275 alter gene expression via effects on DNA transcriptional activity and hence modify
276 developmental outcomes (Duncan et al. 2014; Gugger et al. 2016; Kawaakatsu et al. 2016;
277 and references). Although few data are available as yet, epigenetic variants may comprise a
278 substantial portion of heritable fitness-related differences among individuals in natural
279 populations (e.g., Cortijo et al. 2014). Once induced--often by specific environmental
280 stresses--epigenetic modifications in plants and animals may be stably transmitted across
281 several or many generations (e.g. Remy 2010; Schmitz et al. 2011; additional references in
282 Jaenisch and Bird 2003; Jablonka and Raz 2009; Gapp et al. 2014; Sultan 2015).
283 Like immediate plastic responses, transgenerational environmental effects on
284 development may comprise either inevitable limits (such as reduced offspring mass due to
285 maternal nutrient stress) or specifically adaptive adjustments (Uller 2008). Studies in diverse
286 systems have shown that adaptive transgenerational plasticity may be surprisingly common,
287 and may contribute substantially to individual fitness (Mousseau and Fox 1998; Herman and
288 Sultan 2011; Salinas et al. 2013). For instance, when *Polygonum* plants suffered drought
289 stress, their offspring developed more extensive root systems and consequently survived
290 better in dry soil, compared with progeny of isogenic parents that had instead been given
291 ample moisture (Herman et al. 2012). In anemonefish (*Amphiprion melanopis)*, juveniles
292 raised in water with a high concentration of carbon dioxide did not exhibit the predicted
293 decrease in growth and survival if their parents had been exposed to the same elevated
294 carbon dioxide conditions (Miller et al. 2012). This developmental resilience was evidently
295 mediated by parentally transmitted carbon dioxide-induced epigenetic changes to enzymes
296 that affect acid-base metabolism (Miller et al.). Epigenetic mechanisms also mediate adaptive

297 parent-environment effects in *Mimulus* (monkeyflower) plants: when parent individuals
298 experienced simulated insect attack, their progeny produced leaves with altered gene
299 expression patterns that resulted in an increased density of defensive hairs (Scoville et al.
300 2011; Colicchio et al. 2015). Interestingly, both maternal and paternal *Mimulus* plants
301 evidently contribute to this progeny response, via distinct epigenetic mechanisms (Akkerman
302 et al. 2016).
303
304 **6. The multi-generational norm of reaction**
305 Together, cytoplasmic and epigenetic factors provide for a non-genetic source of
306 heritable phenotypic variation that may originate in parental, grandparental, or possibly more
307 remote generations (Bonduriansky 2012; English et al. 2015). These inborn environmental
308 effects show clearly that distinguishing internal from external developmental information is
309 deeply problematic (Bateson and Gluckman 2011; Sultan 2015). They also add a further
310 layer of complexity to the relationship between an organism's genotype and its realized
311 functional and fitness traits. A given genotype will be to some extent differently expressed in
312 alternative environments, resulting in a specific norm of reaction. Yet this response pattern
313 itself will be influenced by previous conditions due to environmentally induced, inherited
314 regulatory elements.
315 An example from a transgenerational plasticity experiment in *Polygonum* serves to
316 illustrate this point (for an animal example, see Plaistow et al. 2015). Each of the three
317 panels in Figure 4 presents the norm of reaction for a single genotype, showing the different
318 sizes of leaves produced by replicate seedlings of that genotype grown in shade versus full
319 sun. However, not one but two norms are shown for each genotype: for seedlings of a given

genotype, their plastic response to alternative light conditions was very different depending on whether their parent plant had grown in sun or in shade (Figure 4; compare orange and green lines in each panel). Notice too that the effect of parental shade on progeny responses was not consistent across the three genotypes (compare the difference between orange and green lines across panels). Rather, the transgenerational effect of shade versus sun was genotype-specific, presumably due to DNA sequence effects on the induction and transmission to offspring of particular cytoplasmic and/or epigenetic factors.

These data make clear that the norm of reaction is not a determinate property of the genotype, but is itself conditioned by inherited environmental information. Just as a genotype does not specify a single, determinate phenotype, neither does it give rise to one determinate plasticity pattern in response to a given environmental range. Moreover, just as genotypes differ in patterns of immediate environmental response, they also differ in transgenerational environmental effects on development (Vu et al. 2015; Herman and Sultan 2016), because DNA sequence influences the production of heritable regulatory molecules and the dynamics of epigenetic mechanisms (for example, via differences in potential methylation sites; Meaney and Ferguson-Smith 2010; Kawakatsu et al. 2016). Consequently, an organism's realized phenotype represents not only an active interaction between its evolved genotype and its environment, but a higher-order interaction between genotype, environment, and a sequence of previous environments whose developmental effects may themselves interact--an "immensely complex web of interactions" or "entanglement" between genotype and environment over several generations (Keller 2010, p. 7).

As a result of this complexity, developmental plasticity cannot simply be accommodated into a deterministic model of adaptive evolution as a genotype's 'extended

phenotype'-- that is, as a unique, genotype-specified response norm. Note that theoretical models that use this simplification have provided valuable insights regarding the environmental heterogeneity, accurate cues and other conditions expected to favor the evolution of plastic versus fixed reaction norms (e.g., Via and Lande 1985; Scheiner 1993, 2013; Moran 1992; Tufto 2000; Sultan and Spencer 2002; Berrigan and Scheiner 2004; Scheiner and Holt 2012). The effects of inherited non-genetic factors on selective dynamics have also been investigated in a number of sophisticated models (e.g. Kirkpatrick and Lande 1989; Danchin et al. 2011; Day and Bonduriansky 2011; Bonduriansky et al. 2012; Danchin 2013; Geoghegan and Spencer 2013; reviewed in Van Dooren et al. 2016). A further modeling challenge will be to fully integrate multi-generational influences on adaptive variation and selection. For example, a simulation model by Leimar and McNamara (2015) showed that developmental systems can evolve so as to adaptively utilize genetic, environmental, and prior-environmental developmental information. Models that address this complexity may help to frame key questions about the potential impact on selective trajectories of these variably persistent modes of developmental information. Resolving these questions will ultimately depend on empirical studies to illuminate the causal 'entanglement' that shapes adaptive variation.

7. Implications for research

The developmental program view of the genotype has dictated an exclusive focus on heritable genetic information as the basis of phenotypes and hence of selective evolution. As a result of this simplified causal framework, evolutionary biologists have aimed to isolate the *genetic* component of phenotypic variation in order to track the *genetic* basis of

366 adaptation, completing an internally sequestered causal circle. Even studies of plasticity and
367 epigenetics have been circumscribed by this view: epigenetic changes are considered to be
368 evolutionarily relevant only if they persist stably across hundreds of generations as
369 'epimutations' (e.g., Haig 2007; Cortijo et al. 2014), while a predominant evolutionary
370 question regarding plastically expressed phenotypes is whether they can become constitutive
371 (*genetically assimilated* sensu West-Eberhard 2003; Ehrenreich and Pfennig 2015).
372 Reconceiving the genotype in light of developmental plasticity calls for a shift in
373 focus and in research approaches. An essential first step is to recognize the evolutionary
374 relevance of short-term environmental and epigenetic factors. As a result of immediate and
375 inherited effects on gene expression, these transient influences substantially shape the
376 phenotypic variation expressed in each generation, and consequently selective trajectories
377 (see Barton and Turelli 1989; Stearns 1989; Wade and Kalisz 1990; Sultan 1992, 2003, 2015;
378 Nager 2000; Kingsolver et al. 2012; Anderson et al. 2014). Because genotypes respond
379 differently to these influences, developmental response systems are themselves subject to
380 selection, but as 'entangled' evolutionary entities; the impact of selection on genotypes is
381 attenuated by highly complex environmental interactions.
382 To understand the causes and consequences of natural selection requires focusing
383 directly on this mechanistic and evolutionary complexity. The empirical study of interacting
384 influences on phenotypes (for instance, interactions between sequence variation and
385 epigenetic dynamics) is just beginning (Kawakatsu et al. 2016). As West-Eberhard has
386 noted, ascribing phenotypic and fitness determination to the genotype has 'deflected'
387 attention from the central biological question of how 'condition-sensitive regulation is
388 organized and evolves' (2003, p. 17); the time has come to take on this compelling question.

First, evolutionary biologists must devote serious attention to the environments of organisms, not only in terms of putative selective pressures, but with respect to both cues and direct influences on development. This requires identifying such factors and characterizing their patterns of spatial and temporal variation, including environmental auto-correlation across generations. Such studies are particularly demanding because developmental cues and influences may involve multiple, covarying aspects of natural environments (Miner et al. 2005; Chevin and Lande 2015).

A related point pertains to empirical research more broadly. Because environmental state affects the expression of phenotypes and of genetic diversity, experimental decisions regarding growth conditions can matter enormously to the results and to their utility for understanding natural systems. Ideally, the design of uniform growth environments, as well as the choice of alternative environmental states in norm of reaction experiments, should reflect conditions that are relevant to the organism in real populations; to the extent that this is not feasible, interpretation of experimental findings should include this point of reference.

Incorporating epigenetics into evolutionary biology will require intensive research activity to illuminate several key issues, including (i) epigenetic effects on functional and fitness variation in natural systems; (ii) induction and persistence dynamics in response to specific environmental cues or stresses; and (iii) genetic variation for induced epigenetic changes and their transmission. Data on these questions will inform experimental and theoretical investigations into the possible role of epigenetic systems as a distinct mode of adaptive variation, longer-term than immediate plasticity yet more labile than selective change (Herman et al. 2014; Noble 2015; Gugger et al. 2016; e.g. Houri-Ze'evi et al. 2016). For technical reasons, initial work has focused on methylation, but it is equally important to

412 investigate the various other epigenetic regulatory mechanisms that have recently come to
413 light.

414 A developmental plasticity viewpoint can also inform approaches to studying human
415 evolution. Just as genotype and environment cannot meaningfully be isolated from each other
416 as causes of adaptive evolution, nature and culture can be seen as 'entangled' causes in the
417 evolution of key human traits: like ecologically meaningful features of other organisms, the
418 traits that characterize human beings take shape only in cultural--i.e., environmental--context
419 (Laland and O'Brien 2011).

420

421 Beyond a more inclusive framework for understanding adaptive evolution, a focus on
422 developmental plasticity may offer new insights to related research areas. One pressing issue
423 is biodiversity conservation. Human activities are increasingly altering natural habitats, from
424 the spread of agrochemicals and other contaminants to the terrestrial and aquatic effects of
425 global change. The near- and long-term prospects of organisms to adaptively withstand these
426 changes will depend critically on existing developmental response norms, since novel
427 conditions will affect the expression of functional phenotypes and of the genetic potential for
428 further selective evolution (Nussey et al. 2005; Ghalambor et al. 2007; Sultan 2007; Visser
429 2008; Carroll et al. 2014). To date, some of this information has proved encouraging. In
430 studies with fish, for instance, parental exposure to both higher water temperatures and
431 elevated carbon dioxide levels caused offspring to express phenotypes that were adaptive to
432 these novel stresses. In these cases, transgenerational plasticity provided for a rapid and
433 substantial increase in offspring tolerance to predicted future conditions (Miller et al. 2012;
434 Salinas and Munch 2012).

In medicine, a shift is partly underway from seeking genetic determinants of disease as such, to a more nuanced focus on the role of genetic factors in modulating the effects of physical, nutritional and social environments (Gluckman and Hanson 2005). For instance, researchers studying the impact of a particular genetic variant on the incidence of depression explicitly described this as differential genetic modulation of stressful life experiences-- that is, as an interaction between an individual's environment and his or her genotype (Caspi et al. 2005). This framework has shaped a productive and important program of research, leading to the recent identification of epigenetic mechanisms that mediate this interaction (Wankerl et al. 2014). Several of the most prevalent human diseases in modern societies are currently being investigated using a plasticity (i.e., genotype x environment interaction) framework in place of a simple "gene for" hypothesis; these include several cancers (reviewed by Ghazarian et al. 2013), diabetes and cardiovascular disease (reviewed by Lee et al. 2011), and Parkinson's disease (e.g., Ritz et al. 2016). Such studies may lead to new therapeutic approaches focused on changing environmental factors to improve health outcomes for individuals or communities (see Gluckman et al. 2009; Lock 2015).

8. Conclusions: The evolving genotype

The phenotype emerges from multi-generation interactions between genotype and environment. This complicated picture is concordant with an explosion of recent discoveries regarding extra-genetic inherited factors that transmit environmental information across generations and the regulatory flexibility of gene expression in general. These data make clear the need to replace a twentieth-century understanding of the genotype as a self-

457 contained, deterministic developmental ‘program’ with a contemporary model that reflects
458 the environmental context-dependency of phenotypic outcomes.

459 Along with a changed view of the genotype itself, the evolutionary corollaries of the
460 developmental program model must be revised. To begin with, the notion that an individual’s
461 genotype dictates its adaptedness to its environment must be amended. Phenotypes are
462 produced actively through the process of individual development, as shaped by the
463 genotype’s interactions with regulatory information that is conditioned by past and present
464 environments. Depending on the organism and trait in question, the environments
465 encountered, and the particular genotype, the plasticity inherent in the developmental process
466 may provide for considerable adaptive adjustment, or alternatively it may lead to inevitable
467 fitness limits; both adaptive and inevitable aspects of plasticity shape phenotypic outcomes at
468 the individual level (Sultan 2003). As a result, genotypes do not specify trait or fitness
469 differences among individuals. Rather, the differences that fuel natural selection reflect not
470 genotypic diversity alone, but interacting developmental factors including the immediate
471 environment and inherited cytoplasmic and epigenetic elements. Importantly, the
472 developmental impact of these extra-genetic factors, as well as their precise patterns of
473 perception, transduction, and transmission, are genotype-specific rather than entirely
474 independent of DNA sequence.

475 In view of these complex regulatory interactions, an organism’s DNA cannot be
476 considered to contain its developmental norm of reaction, much less the complete
477 instructions to specify a particular phenotype. What, then, is the status of the genotype as an
478 evolutionary unit? One way to approach this question is to distinguish between genetic
479 information as evolutionary record and as evolutionary cause (Sultan 2015). Unquestionably,

genotypes evolve: they contain the biochemical material that resulted from a history of transmission and mutation over time, as conditioned by phylogenetic context, selection, random drift and gene flow. The genotype can thus be seen as the product of evolution, as it comprises a uniquely stable repository of these historical events across time. Yet the genotypes in a population do not in themselves determine the adaptive diversity that shapes selective change, because they contain only partial developmental information, and hence only partial information regarding fitness variation. The causes of adaptive evolution include the genotype-specific dynamics of immediate and trasngenerational developmental response in the context of environmental distributions. Studying these causes requires changing experimental design and approach so as to directly interrogate these complex interacting sources of variation. This research program offers a revised and renewed understanding of the genotype that will allow development to be fully integrated into the evolutionary process.

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Figure Captions

Figure One. Alternative views of the genotype

Inherent to the Modern Synthesis is a deterministic model of phenotypic expression (above) in which the genotype is seen as a self-contained, internal developmental program. In contrast, a model that recognizes developmental plasticity (below) views the genotype as a developmental repertoire of varying, environmentally context-dependent outcomes.

Modified from Sultan SE. 2009 Evolutionary implications of individual plasticity. In *Transformations of Lamarckism* (eds Jablonka E, Gissis S), pp. 193-203. Vienna Series in Theoretical Biology, Cambridge, MA: MIT Press.

Figure Two. Developmental plasticity for the proportion of total biomass allocated to leaf tissue by *Polygonum persicaria* plants in response to contrasting light levels

Each line represents the reaction norm of a single plant genotype, based on the mean of 6 clonal replicates in each of three greenhouse light treaments (Low (8%), Moderate (37%) and high (100%) levels of incident midsummer sun). Across genotypes, trait change due to plasticity (the effect of light environment) is highly significant ($P < 0.001$). Genotypes differ in their specific patterns of plastic response, resulting in changes in among-genotype variance and rank order from one environment to another (Genotype x Environment interaction effect $P < 0.001$). Because their norms of reaction cross, there is no consistent effect of genotype on phenotype (the main effect of Genotype is non-significant; $P > 0.05$).

(Figure reprinted from S. E. Sultan (2003) Phenotypic plasticity in plants: A case study in ecological development. *Evolution and Development* 5, 25-33.)

Figure 3. Developmental plasticity expressed by genotypes of the common annual plant *Polygonum persicaria*

Significantly broader and structurally thinner leaves are produced by replicate plants of the same *Polygonum* genotype when grown in moderate shade (left) compared with full summer sun (right). Photo courtesy of Dan B. Sloan and S. E. Sultan.

Figure Four. The effect of parental environment on progeny norms of reaction

Data plots show the size of individual leaves that were produced by seedlings growing in either full sun or simulated shade, for 3 *Polyonum persicaria* genotypes. **Green** = norm of reaction showing seedling developmental responses to the two environments when their parent plant had been grown in shade; **orange** = norm of reaction showing developmental responses of seedlings of the same genotype when their parent plant had been grown in full sun. Norms of reaction are based on mean leaf size for 10 replicate seedlings of each genotype and parental environment in each progeny growth treatment. B.H. Baker, L. Berg, and S. E. Sultan, unpublished data.

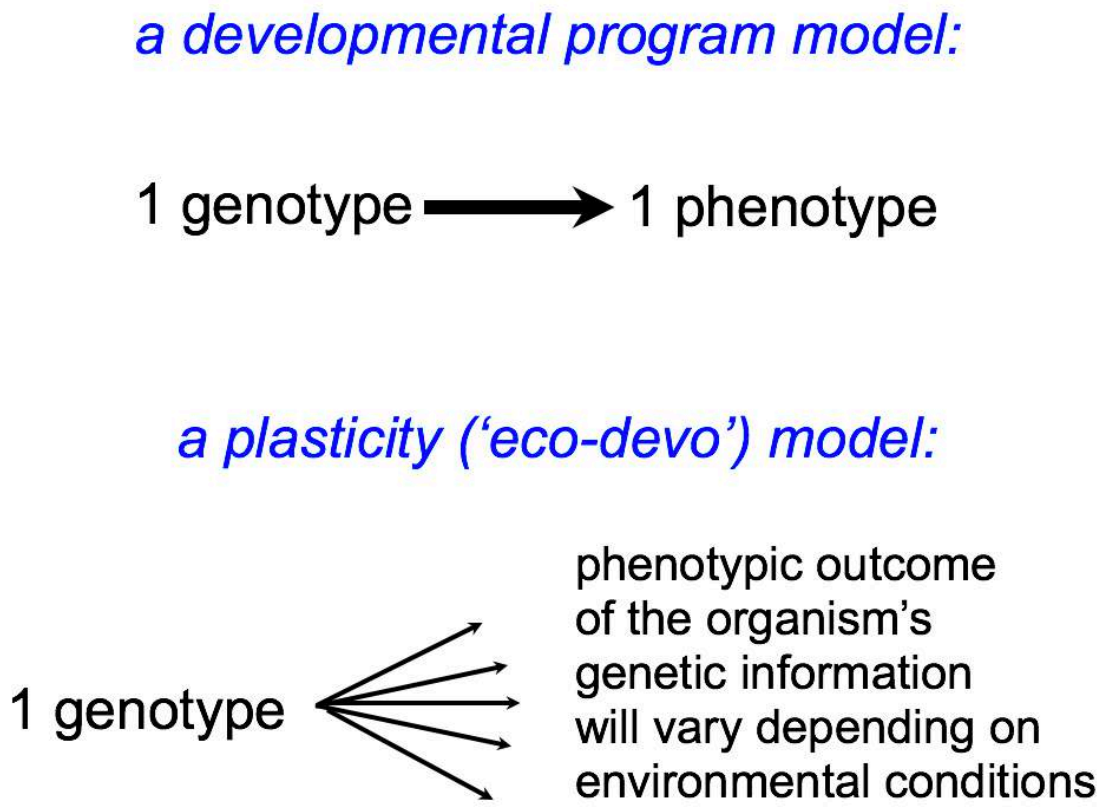
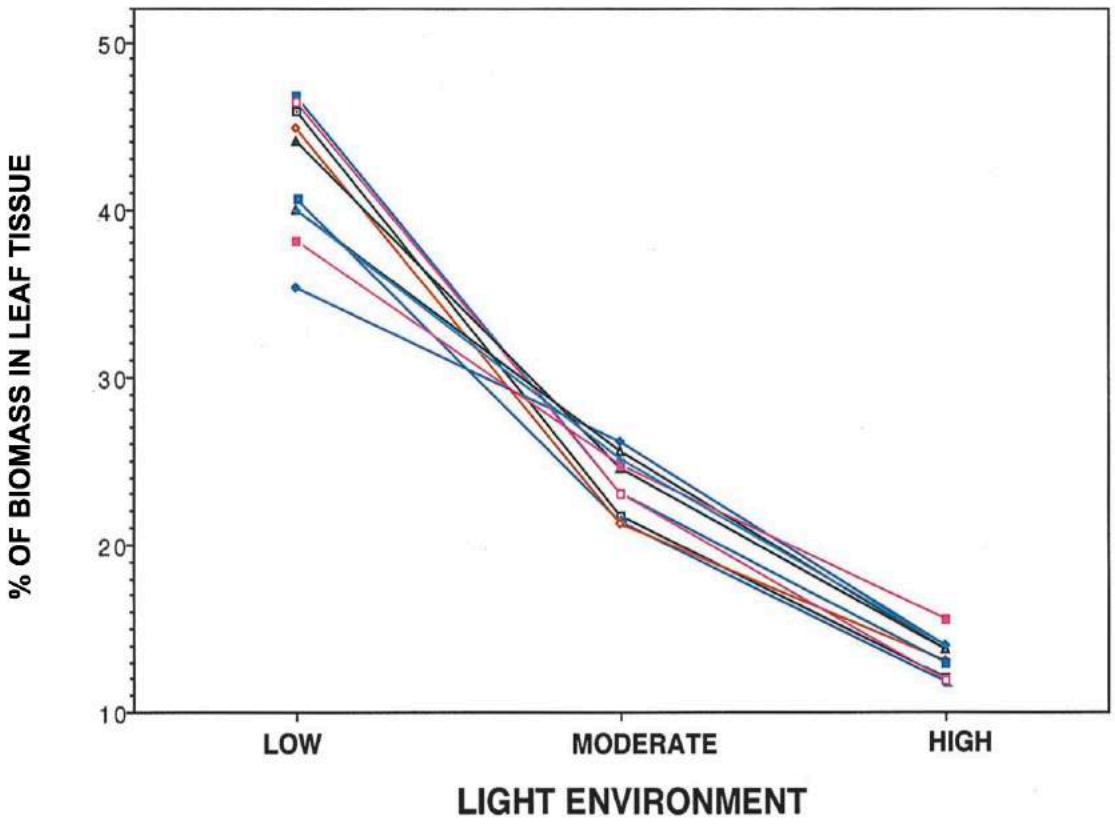
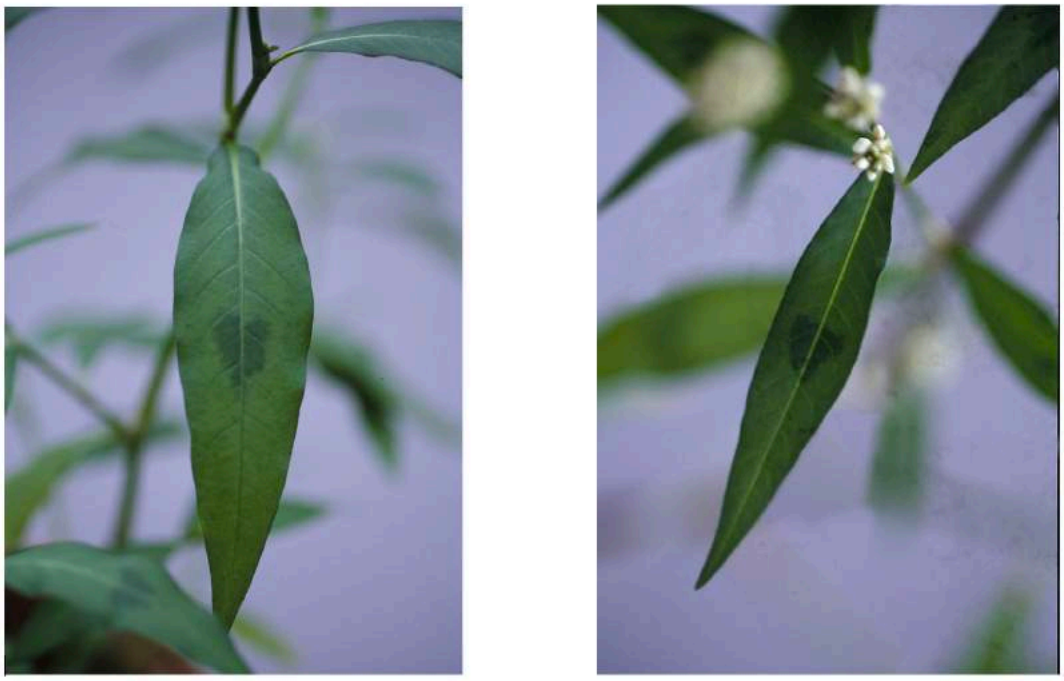


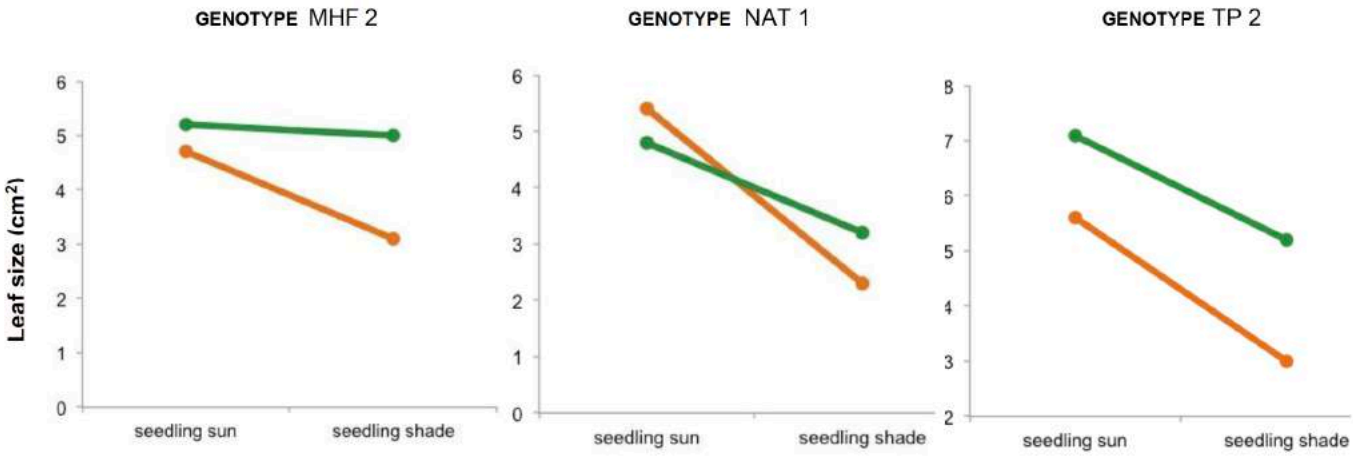
Figure 1



1019 Figure 2



1020 Figure 3



1021 Figure 4