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INVITED REVIEW

Evolution and molecular mechanisms of adaptive developmental plasticity

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Abstract

Aside from its selective role in filtering inter-individual variation during evolution by natural selection, the environment also plays an instructive role in producing variation during development. External environmental cues can influence developmental rates and/or trajectories and lead to the production of distinct phenotypes from the same genotype. This can result in a better match between adult phenotype and selective environment and thus represents a potential solution to problems posed by environmental fluctuation. The phenomenon is called adaptive developmental plasticity. The study of developmental plasticity integrates different disciplines (notably ecology and developmental biology) and analyses at all levels of biological organization, from the molecular regulation of changes in organismal development to variation in phenotypes and fitness in natural populations. Here, we focus on recent advances and examples from morphological traits in animals to provide a broad overview covering (i) the evolution of developmental plasticity, as well as its relevance to adaptive evolution, (ii) the ecological significance of alternative environmentally induced phenotypes, and the way the external environment can affect development to produce them, (iii) the molecular mechanisms underlying developmental plasticity, with emphasis on the contribution of genetic, physiological and epigenetic factors, and (iv) current challenges and trends, including the relevance of the environmental sensitivity of development to studies in ecological developmental biology, biomedicine and conservation biology.

Keywords: eco-devo, environment, phenotypic plasticity, polyphenism, variation

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Introduction

It has become clear that the environment is more than just a filter of phenotypic variation during the transgenerational process of natural selection, as it also plays a key role in generating variation during organismal development. In fact, some degree of an effect of the external environment on phenotype seems pervasive in nature and is accounted for in classical evolutionary genetics in the environment and the genetic-by-environment components of phenotypic variation. However, until recently, environmentally induced variation, or variation altogether, was seen more as a nuisance in developmental biology. Research in that field typically focused on single (often inbred) laboratory strains of one of a handful of model organisms kept in constant (often very unnatural) laboratory environments. This situation is rapidly changing as new disciplines are emerging and growing. Evolutionary developmental biology (evo-devo) brought the focus to intra- and inter-specific (morphological) variation and its genetic basis (see Stern 2000). More recently, ecological developmental biology (eco-devo or eco-evo-devo) has started to bring the focus to how the external environment affects organismal development and how this impacts evolutionary change (see Gilbert & Epel 2009).

Phenotypic plasticity is the property whereby a single genotype produces distinct phenotypes in distinct environments. Organisms have different ways of adjusting to the environmental conditions they live in, including alterations in behaviour and/or physiology and/or

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morphology. Such phenotypic plasticity is not necessarily adaptive (Ghalambor *et al.* 2007) nor does it necessarily affect pre-adult development. We will use the term adaptive plasticity for those cases where its ecological relevance is established, for example by studies showing how environmentally induced variation leads to a better match between phenotype and selective environment (examples in Table 1 and Box 1). The term developmental plasticity will be used to refer to those cases where the environmentally induced variation is the product of changes in pre-adult development (e.g. coat colour variation in laboratory mice that depends on maternal diet; Waterland & Jirtle 2003). Cases where environmentally induced variation results from reversible changes directly in adult phenotypes (e.g. seasonal coat colour changes in the Arctic fox; Pocock 1912) will not be addressed here. This review will focus on adaptive plasticity linked to changes in development affecting morphological traits, with emphasis on the molecular mechanisms involved in the environmental regulation of development and in the evolution of this phenomenon.

Traditionally, studies of developmental plasticity have focused on the phenotypic responses to environmental variation and on its ecological role and underlying physiological mechanisms. Researchers have also explicitly addressed the evolution of plasticity and its contribution to adaptive evolution. A detailed analysis of those topics has been covered in a number of insightful books and reviews (e.g. Callahan *et al.* 1997; Schlichting & Pigliucci 1998; Pigliucci 2001; Nijhout 2003; West-Eberhard 2003). New technological and conceptual advances are now being recruited to unravel the molecular mechanisms of developmental plasticity (e.g. Aubin-Horth & Renn 2009; Gilbert & Epel 2009; Minelli & Fusco 2010). This has precipitated a tremendous expansion of information on these mechanisms and their relationship to evolution and justifies the importance of new synthetic efforts.

Table 1 Examples of developmental plasticity for selected animal systems

Biological system and plastic trait	Examples of inductive cues	Ecological relevance	References
Wings in female pea aphids	Crowding Nutrition Photoperiod Temperature	Dispersion	Braendle *et al.* (2006)
Wing polyphenism in locusts	Crowding	Solitary vs. gregarious and migratory morphs	Pener (1991); Simpson *et al.* (2001)
Horns in dung beetles	Nutrition	Mating strategies	Moczek & Emlen (2000)
Castes in social insects	Nutrition Pheromones	Division of labour	Korb & Hartfelder (2008); see Box 1
Teeth-like denticles in diplogastrid nematodes	Nutrition	Alternative diets	Bento *et al.* (2010)
Seasonal polyphenism in butterflies	Temperature Photoperiod Nutrition	Anti-predator strategy Thermoregulation	Beldade & Brakefield (2002); Nijhout (1999); see Box 1
Gender determination in vertebrates (e.g. reptiles, fishes, amphibians)	Temperature	Optimal sex ratio	Janzen & Paukstis (1991); Ospina-Álvarez & Piferrer (2008); Nakamura (2009)
Gender determination in invertebrates (e.g. *Daphnia magna*)	Photoperiod Crowding Temperature pH Nutrition Salinity	Optimal sex ratio	Hobæk & Larsson (1990); Cook (2002)
Morphological defences in planktonic crustaceans (*Daphnia* spp.)	Density of predators (assessed via kairomones)	Defence	Dodson (1974); Stabell *et al.* (2003); Stibor & Lampert (2000)
Head-size in spadefoot toad tadpoles	Density of conspecifics (assessed via food levels)	Food resources	Pfennig (1992); Pfennig *et al.* (2006)

Box 1. Two detailed examples of developmental plasticity

We describe two examples of adaptive developmental plasticity, each associated with a lineage-characteristic property of a different insect order: wing colour patterns in Lepidoptera and castes in social Hymenoptera. We illustrate different types of external cues inducing alternative developmental trajectories and phenotypes (abiotic in butterflies and biotic in Hymenoptera), their ecological significance (predator avoidance and division of labour), and our under-standing of the underlying mechanisms (including hormonal and epigenetic regulation).

Seasonal polyphenism in Bicyclus anynana *butterflies*

Like many butterflies from highly seasonal environments (examples in Beldade & Brakefield 2002), *B. anynana* exhibits clear seasonal polyphenism in wing pattern and other traits (Brakefield *et al.* 2007). In sub-Saharan Africa, larvae that develop during the wet season produce adults with conspicuous wing patterns that include large marginal eyespots, while those that develop during the dry season produce adults with dull brown colours and very small eyespots (Fig. 1a). These alternative wing patterns correspond to alternative strategies to avoid predation. While the marginal large eyespots of the wet-season butterflies are thought to attract the predator's attention to the wing margin and away from the vulnerable body, the all-brown dry-season butterflies are cryptic against a background of dry leaves (Brakefield & Frankino 2009; Olofsson *et al.* 2010). Laboratory studies showed that the temperature during development, which predicts the natural seasonal fluctuations in precipitation, determines the production of the alternative wing pattern phenotypes (Brakefield & Frankino 2009).

Curiously, only the wing pattern on the ventral side of the wings (the surface exposed at rest) shows plasticity in relation to developmental temperature (Brakefield *et al.* 1998) and has been associated with predator avoidance. Despite correlations between wing surfaces (e.g. Beldade & Brakefield 2003), the patterns on the dorsal side (exposed only during flight or courtship) are not plastic and have been implicated in mate choice (Robertson & Monteiro 2005). Examination of this contrast in a phylogenetic context suggested that ventral patterns (shaped by natural selection) evolved at a lower rate than dorsal patterns (shaped by sexual selection) during *Bicyclus* diversification (Oliver *et al.* 2009).

B. anynana eyespots are used as models to explore the mechanisms regulating developmental plasticity. Artificial selection produced strains with wet or dry-like phenotypes across temperatures, changing the height of reaction norms but failing to significantly change their shape (Brakefield *et al.* 1996; Wijngaarden & Brakefield 2001; Wijngaarden *et al.* 2002). Rearing at different temperatures of butterflies from these lines, as well as from unselected laboratory populations, characterized the physiological and gene expression changes associated with developing alternative phenotypes. Like many polyphenisms, eyespot plasticity is related to the regulation of steroid hormones. Pupal titres of ecdysone and 20-hydroxyecdysone peak earlier at the higher temperatures that lead to the production of large eyespots (Fig. 1b). Furthermore, manipulation of hormone titres can affect ventral eyespot size (Brakefield *et al.* 1998). It is not known how ecdysteroid dynamics regulates eyespot development, but this probably involves the activated ecdysone receptor directly or indirectly regulating transcription of eyespot genes (Koch *et al.* 2003). The eyespot gene *Distal-less*, proposed to contribute to variation in dorsal eyespot size (Beldade *et al.* 2002), has a larger area of expression in larval wings of individuals that develop into the wet-season-like phenotype with larger eyespots (Brakefield *et al.* 1996). Further studies will be necessary to link hormone dynamics (including larval titres) to the regulation of genes and processes involved in eyespot formation (Beldade & Brakefield 2002), as well as to investigate the involvement of other regulatory and sensory mechanisms in environmentally sensitive wing pattern development.

Castes in social Hymenoptera

Social Hymenoptera (all ants and many bees and wasps) form essentially all-female colonies in which only one or a few individuals reproduce, while most engage in colony maintenance only (nursing, food procurement, nest building and defence) (Wilson 1971). With few exceptions, this division of labour is accompanied by caste-specific morphologies that can be as profoundly different as the development of wings in queens vs. their absence in ant workers (Fig. 1c). Whether a juvenile becomes a queen or a worker typically depends on nutrition during larval stages, but can also involve other cues (e.g. temperature and queen pheromones; Wheeler 1986) and switches at other development stages (including oogenesis, Passera & Suzzoni 1979), as well as different extents of genetic control (Schwander *et al.* 2010). The production of different castes can depend on specific ecological needs taking into account costs of producing each caste (Oster & Wilson 1978). For example, colonies of *Pheidole pallidula* ants produce large, nutritionally costly soldiers only when confronted with intraspecific competition (Passera *et al.* 1996), and

Box 1. *Continued*

colonies of *Myrmecina nipponica* produce smaller wingless queens in response to low food resources and patchy nest sites (Murakami *et al.* 2002).

While the variation in caste-specific morphologies tends to be discrete, intermediate adult phenotypes are sometimes produced as a result of developmental anomalies caused by parasitism, low temperatures or starvation (Wheeler 1937). In many ant species, however, female adults with intermediate phenotypes are not the result of disturbed development but, rather, are produced regularly and can replace normal queens (Peeters 1991). Both aberrant 'intercastes' and regularly produced 'ergatoid queens' show a mixture of discrete elements from winged queens and wingless workers, and provide an ideal opportunity to study the modular nature of caste-specific development (Miyazaki *et al.* 2010).

Studies of molecular mechanisms underpinning caste determination are starting to provide an integrated picture of how nutrition triggers the differentiation of alternative adult phenotypes, including through the effects of hormones and DNA methylation on gene expression. Early work established the existence of discrete developmental switches under endocrine control, with juvenile hormone (JH) playing a major role (reviewed in Wheeler 1986). The general model from hormonal studies posits that a rich larval diet results in elevated JH titres; above a certain threshold these cause individuals to develop into queens, and below into workers (Wheeler 1986; Hartfelder & Engels 1998). Analysis of gene expression in honeybees showed that JH influences caste differentiation by inducing different sets of JH-responsive genes (e.g. 'growth genes' in developing queens, Barchuk *et al.* 2007). Caste-specific gene expression is also responsible for wing development in ant queens and their absence in workers: the conserved insect wing development gene network is fully expressed in queen wing primordia and interrupted at different points in workers (Abouheif & Wray 2002). More recently, DNA methylation was implicated in linking hormonal and gene regulation control of caste differentiation (see Moczek & Snell-Rood 2008). For example, in honey bees, methylation is associated with caste-specific gene expression (Elango *et al.* 2009), and knock down of methylation in the JH-producing gland affected caste development (Kucharski *et al.* 2008) (Fig. 1d). These types of studies, powered by new genomic resources and analytical tools (e.g. Smith *et al.* 2010), will undoubtedly continue to shed light onto the proximal mechanisms of caste determination.

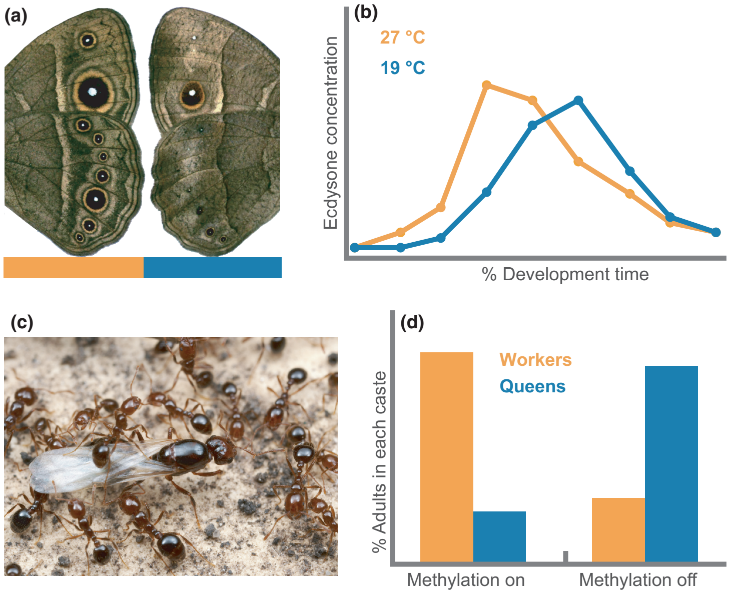

Fig. 1 Examples of developmental plasticity and underlying molecular mechanisms. (a) *Bicyclus anynana* wet- (left) and dry-season-like (right) phenotypes obtained by rearing larvae at different temperatures. Note that the larger eyespot on the forewing is typically hidden behind the hindwing in resting butterflies (the posture relevant for the anti-predatory strategies described). Also, note that wing size (typically larger in dry-season phenotypes) was adjusted to emphasize comparison of colour patterns. (b) Differences in hormone titre dynamics (adapted from Brakefield *et al.* 1998; Oostra *et al.* 2011) during pupal development, when patterning and pigment biosynthesis (cf. Wittkopp & Beldade 2009) genes are expressed. (c) Large-winged queen and small wingless workers of the fire ant *Solenopsis invicta* (photo © Alex Wild). (d) RNAi-based knockdown of methylation enzymes in newly hatched honeybee larvae causes most of them, which typically develop into workers, to develop into queens (adapted from Kucharski *et al.* 2008).

Here, we provide an overview of adaptive developmental plasticity, covering studies that span from the evolution and ecological relevance of plasticity to the environmentally induced changes in development and their underlying molecular mechanisms.

Our contribution was thought out so as to include both breadth of conceptual coverage and emphasis on current advances. We provide a wide and integrative overview of adaptive developmental plasticity, a topic that is the subject of much classical and intense current research and one that involves different disciplines of biological research. Each one of the main sections in the paper could be, and has been in some cases, the topic of detailed review elsewhere. In trying to bring different aspects together in a way that best complements those previous synthetic efforts, we will refer to such efforts where a more in-depth analysis of specific topics can be found. At the same time, we will also use multiple research examples from animal systems to illustrate key findings and concepts.

Evolution of and via developmental plasticity

Natural selection acting on genetic variation has led to differences between species (e.g. Scheiner 1993) and between populations of the same species (e.g. Crispo & Chapman 2010) in the degree and types of plastic responses. Analyses of those populations/species provide insights into the ecological conditions and biological properties that favour plastic vs. nonplastic development and into the mechanisms underlying evolutionary transitions between the two. In this section, we briefly discuss both the evolution of plasticity and the contribution of plasticity to adaptive evolution.

Evolutionary transitions to and from plastic development

Recent theoretical models have advanced our understanding of factors that favour the evolution of plasticity, including the predictability of environmental fluctuations (e.g. Leimar *et al.* 2006; Reed *et al.* 2010) and the costs of plasticity (see Snell-Rood *et al.* 2010). Here, we focus on empirical studies. Transitions between plastic and robust development, as well as between environmentally and genetically determined alternative phenotypes (i.e. polyphenism and polymorphism, respectively; see Box 2), have been documented at different phylogenetic levels. For example, post-colonization erosion of plasticity of head-size was reported for snakes (Aubret & Shine 2009), the evolution of different degrees of genetic caste determination for ants (reviewed in Schwander *et al.* 2010), and back-and-forth transitions between genetic and environmental sex determination for vertebrates (see Stelkens & Wedekind 2010). Environmental sensitivity of developmental processes is probably the ancestral condition in most cases, with selection then working for the ability to buffer environmental effects (see Newman & Müller 2000; Nijhout 2003). This has been suggested, for example, for caste determination in ants (Anderson *et al.* 2006) and sex determination in reptiles (Janzen & Paukstis 1991).

Beside studies of natural populations such as those mentioned previously, there are also revealing studies where changes in plasticity resulted from artificial selection in laboratory populations. Temperature-dependent coloration in butterflies and moths offers some of the most compelling examples of these studies. Artificial selection on adult wing patterns in *Bicyclus anynana* butterflies (Box 1) and on larval coloration in *Manduca sexta* moths (Suzuki & Nijhout 2006) produced changes in the height and/or shape of the reaction norms that describe the relationship between environmental and phenotypic change (see Box 2). In both cases, these changes were associated with changes in hormone titre dynamics and were of polygenic nature. In contrast, the importance of single genes has also been documented; for instance, by analyses of mutants that lose or gain environmental sensitivity. Examples include loss of sensitivity to the hormone that mediates diet-associated mouth morphology in *daf-12* mutants of *Pristionchus pacificus* nematodes (Bento *et al.* 2010) and exposure of hidden temperature sensitivity for larval coloration in *black* mutants of *Manduca sexta* (Suzuki & Nijhout 2006). The relevance of particular genes, as well as of a species' gene content, for environmental sensitivity and plasticity will be addressed further below.

In recent years, sophisticated analyses have started to highlight specific developmental and genetic mechanisms that presumably confer robustness or plasticity to development. Robustness may be enhanced by redundancy in cell precursors (e.g. Braendle & Felix 2008), in gene enhancers (e.g. Frankel *et al.* 2010), and in regulatory microRNAs (e.g. Brenner *et al.* 2010), as well as the action of particular gene families such as heat shock proteins (e.g. Takahashi *et al.* 2010). Modularity in developmental genetic networks, in turn, has been proposed to have an important role in enabling phenotypic plasticity, as decreased pleiotropy between networks may facilitate the induction of different modules under different environmental conditions (Snell-Rood *et al.* 2010). By acting on all those types of mechanisms, natural selection can presumably adaptively adjust the likelihood and/or the extent of plasticity in trait development. Through a process that has been referred to as genetic accommodation (see Box 2), natural selection can also fine-tune this plasticity, including its degree (e.g. Lind & Johansson 2007), the identity of the

Box 2. Some key concepts in developmental plasticity

Developmental plasticity refers to the property by which the same genotype can produce different phenotypes through environmental regulation of development (see main text). At the other end of the spectrum (Braendle & Felix 2009), *canalization* (or *robustness*) is used to describe those situations where development produces the same phenotype despite environmental (and/or genetic) perturbation (e.g. blue solid line in Fig. 2; Flatt 2005). Both plasticity and canalization are not absolute properties of a developmental program: the development of a particular trait might show environmental sensitivity during a specific time window and be highly robust outside that. Reversible changes in adult phenotypes, often in behaviour or physiology, correspond to a form of phenotypic plasticity sometimes referred to as *acclimation* (e.g. Wilson & Franklin 2002; Brakefield *et al.* 2007) to distinguish from effects on development.

Reaction norms are graphical representations of the environmental dependence of the phenotype. Developmental plasticity can manifest itself in the form of graded variation in phenotype or in discrete switches between alternative developmental trajectories. A reaction norm displays phenotypic variation across an environmental gradient (see Schlichting & Pigliucci 1998). It is often used for situations where this environmental gradient corresponds to a more or less linear grading in phenotype (e.g. yellow line in Fig. 2), but it can also describe situations of (nearly) discrete alternative phenotypes (e.g. nonlinear relationship as in the orange line in Fig. 2). Importantly, reaction norms can be obtained for different 'end phenotypes' (morphology, life history, behaviour) but also for 'intermediate phenotypes' such as hormone titres, methylation patterns and levels of gene expression during development (e.g. Aubin-Horth & Renn 2009). The reaction norms for such different phases do not necessarily need to have the same shape (dotted vs. solid lines in Fig. 2). In fact, even invariant phenotypes (i.e. flat reaction norm represented by the solid blue line in Fig. 2) can result from cellular and molecular processes that are plastic (e.g. dotted blue line in Fig. 2) (see Braendle & Felix 2008). Reaction norms drawn for different genetic backgrounds allow an assessment of genotype-by-environment interactions (e.g. Ostrowski *et al.* 2000; Sarkar & Fuller 2003; Debat *et al.* 2009). The genetic-by-environment component of phenotypic variation translates into reaction norms of different shapes for different genotypes, while the environment component corresponds to nonflat reaction norms.

Polyphenism describes a situation where inter-individual variation in phenotype does not result from differences in genotype, but rather from differences in the environment (e.g. wing development in pea aphid females influenced by different environmental cues; Braendle *et al.* 2006). The term polyphenism is used for situations where alternative phenotypes are discrete (e.g. orange line in Fig. 2) – even if, in some cases, intermediate phenotypes can be produced (e.g. intercastes in ants; see Box 1). To contrast with polyphenism, the term *polymorphism* is used for those cases where inter-individual variation in phenotype is caused by differences in genotype, often single or few alleles of large effect (e.g. wing development in pea aphid males influenced by allelic variation at the *aphicarus* locus; Braendle *et al.* 2006).

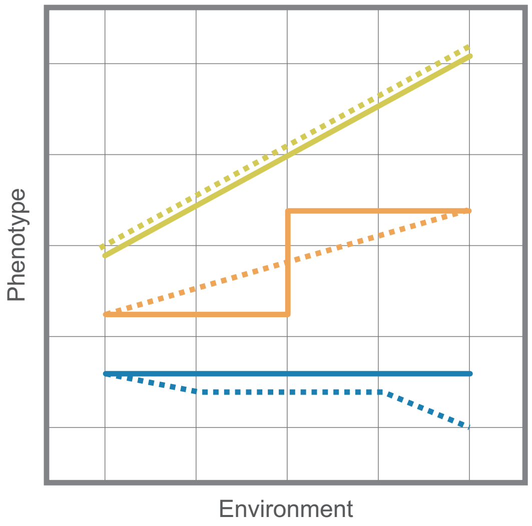

Fig. 2 Different shapes of reaction norms describing the environmental dependence of phenotypes produced from the same genotype. The lines can represent either end phenotype (solid) or some intermediate steps such as gene expression (dotted), with different colours corresponding to different types of developmental sensitivity to the environment. The blue example illustrates robust development, where even despite variation in underlying gene expression (nonflat dotted line), development always results in the same end phenotype across environments (flat solid line). Both the orange and yellow examples correspond to plastic development, where the same genotype will produce different phenotypes in different environments. The yellow is an example of a linear relationship between environmental and phenotypic gradient, and the orange to a nonlinear relationship with discrete alternative phenotypes (i.e. polyphenism). Note that we intended to illustrate qualitatively different types of shapes of reaction norms; the heights and quantitative values being irrelevant here.

Box 2. *Continued*

Genetic assimilation describes an evolutionary process by which an environmentally induced phenotype becomes genetically fixed, so that the environmental cue is no longer necessary for the expression of that phenotype (see Pigliucci *et al.* 2006). The term *genetic accommodation*, on the other hand, is a broad term referring to evolutionary mechanisms whereby selection acting on quantitative genetic variation moulds a novel phenotype, environmentally induced (but also one arising by mutation), into an adaptive phenotype (e.g. Suzuki & Nijhout 2006). The concept of genetic accommodation describes trans-generational mechanisms of (quantitative) genetic change that can both fine-tune developmental plasticity or canalize development. In contrast, the term *phenotypic accommodation* has been used to refer to intra-generational adjustment between developmental variables that does not depend on genetic change (see West-Eberhard 2003).

environmental cue that triggers it (e.g. Edgell & Neufeld 2008) and the sensitivity thresholds for that cue (e.g. Moczek & Nijhout 2003).

Impact of developmental plasticity on adaptive evolution

The relevance of developmental plasticity to adaptive evolution is receiving increasing attention, despite the fact that developmental plasticity is characterized by phenotypic changes without changes in gene sequence, while adaptive evolution is specifically characterized by changes in allele frequencies. Phenotypic plasticity was often seen as being irrelevant or even a hindrance to adaptive evolution (see discussion in Pfennig *et al.* 2010): (i) irrelevant because the raw material for evolution by natural selection is heritable phenotypic variation, and not environmentally induced phenotypes not transmitted from parents to progeny; and (ii) a hindrance because plasticity can shield genetic variation from natural selection, either because alternative genotypes can end up producing the same phenotype or because environment-specific genes (i.e. those expressed only in one environment) will be under relaxed selection in the noninducing environment. However, this view has changed and increasing attention is now being given to the contribution of developmental plasticity to adaptive evolution and the mechanisms whereby this contribution can occur. Studies on different systems illustrate the impact of plasticity on phenotypic diversification (e.g. West-Eberhard 2003), including the origin of novel traits (e.g. Moczek 2010), and on speciation, including adaptive radiations (e.g. Wund *et al.* 2008). The arguments and empirical evidence for these effects were reviewed recently by Pfennig *et al.* (2010).

Different types of non mutually exclusive mechanisms account for the potential positive impact of plasticity on adaptive evolution. Clearly, by providing the means by which organisms can cope with new environmental challenges (Yeh & Price 2004), plasticity can play an important role for the immediate survival of populations exposed to change in the external environment. Then, exactly because phenotypic plasticity can shield genetic variation from natural selection, it can presumably promote the accumulation of cryptic variation (i.e. genetic variation that does not result in phenotypic variation). When released, this heritable variation can provide raw material for adaptive evolution and be important for phenotypic diversification (reviewed in Schlichting 2008). Under some circumstances, environmentally induced phenotypes can become fixed through a process called genetic assimilation (see Box 2). It has been argued that plasticity can, in fact, accelerate adaptive evolution. For example, studies of melanogenesis in *Daphnia* have suggested that the developmental mechanism underlying ancestral plasticity was repeatedly co-opted to facilitate rapid adaptation (Scoville & Pfrender 2010).

Insights into the evolutionary transitions between environmentally sensitive and environmentally insensitive development, and into the contribution of plasticity to evolutionary diversification, require an understanding of both the ecological relevance of plasticity and the mechanisms by which the environment regulates development.

Ecology and development in phenotypic plasticity

Development translates genotypes into phenotypes in a process that is influenced by the external environment. Aside providing some basic building blocks, particular variables of the external environment, in some cases, function as cues that trigger switches in development and lead to the production of alternative phenotypes to face different types of ecological challenges (examples in Table 1 and Box 1). This section focuses on the ecological significance of developmental plasticity, and on the types of effects that external environmental cues can have on organismal development.

Ecological significance of environmentally induced phenotypic variation

Developmental plasticity is adaptive when the environmentally induced changes result in a better match between the adult phenotype and its selective environment. The induced alternative phenotypes typically correspond to different ecological tactics, such as alternative tactics to achieve copulation in horned (guarding of nest) vs. hornless (sneaky copulations) males of *Onthophagus taurus* dung beetles (Moczek & Emlen 2000); alternative tactics to escape predation in cryptic vs. conspicuous *B. anynana* butterflies (Box 1); and presumably alternative foraging tactics in 'toothless' (bacteriovorous) vs. 'toothed' (predatory) *Pristionchus pacificus* nematodes (Bento *et al.* 2010).

A good match between phenotype and ecological conditions is achieved when the environmental cue that triggers changes in development is a reliable predictor of the future selective environment (but not necessarily the same). Such external cues can be of different types, both abiotic (e.g. temperature and photoperiod) and biotic (e.g. presence of other species and density of conspecifics), and they typically reflect environmental heterogeneity in time and/or space. For example, temperature fluctuations predict alternating seasons relating to many cases of seasonal polyphenisms, including coloration in butterflies; fish kairomone concentration reflects high predation environments that leads *Daphnia* crustaceans to develop morphological defences; and leg rubbing in locusts reflects high population densities that result in the production of the winged migratory morph (see Table 1 and Box 1 for references). The environment can also be manipulated by conspecific individuals. In most ants, for example, the high-nutrition diet that determines that a juvenile will develop into a queen is the result of feeding by adult workers (Box 1). In this case, there is microenvironmental heterogeneity within which the different morphs co-occur and can carry out the division of labour within the colony.

Environmental cues and developmental sensitivity

The environmentally induced phenotypic variation can be more or less continuous (e.g. larger or smaller wings in *Drosophila*; Powell *et al.* 2010) or discrete (e.g. presence or absence of wings in queens vs. workers in some social insects; Box 1). Both gradual or 'switch-like' changes in development can be triggered by different types of environmental cues, often in combination (e.g. Braendle *et al.* 2006), and result in simultaneous changes in different traits.

There is rarely, if ever, a 'one cue to one trait' relationship. Plasticity often involves changes in multiple traits in the same organism. For example, environmentally induced wing development in ants, locusts and pea aphids (references in Table 1) is associated with changes in other morphological traits (e.g. body mass and ovary development in ants, body pigmentation in locusts, antennae and eye development in aphids) and with changes in life history traits (e.g. longevity and fertility in ants, gregarious vs. solitary lifestyles in locusts, mode of reproduction in aphids). On the other hand, there is also a substantial degree of cue specificity in determining how the development of particular traits is altered. For example, different species of predators induce different types of anti-predator morphologies in *Daphnia* (e.g. Laforsch & Tollrian 2004; Beckerman *et al.* 2010) as well as in frogs (Vonesh & Warkentin 2006). The same cue can affect different developmental switches at different developmental stages (e.g. low food availability determines formation of teeth and production of dauer larvae in some nematodes; Bento *et al.* 2010). Also, different cues can induce developmental switches at multiple stages. In ants with strong caste dimorphism, for example, queen–worker determination depends on hormones deposited by the queen during oogenesis (Passera & Suzzoni 1979), and the differentiation of subcastes (such as minor and major workers or soldiers) depends on nutrition during larval development (Wheeler & Nijhout 1983). These multiple environmentally sensitive switch points along the developmental trajectory allow diversification of adult morphs specialized for different roles.

The effect of change in a particular environmental cue on phenotype, characteristically represented as a reaction norm (see Box 2), is highly dependent on developmental sensitivities. These sensitivities exist in relation to thresholds of the values of the inductive environmental cue beyond which there is change in development and phenotype (Ostrowski *et al.* 2000). They also exist in relation to restricted time windows of the development during which the external environment can influence the outcome (Ostrowski *et al.* 2002), development being quite robust outside these sensitive periods (Braendle & Felix 2008). Both sensitivity thresholds and sensitivity periods can evolve and might differ between populations.

Effects of the external environment on developmental timing and trajectories

The effects of the environment on developmental timing can be of different types, with the environmental cue more or less uniformly extending or reducing the total duration of development, affecting specifically particular developmental stages or leading to arrested development altogether. For example, temperature (e.g. Bochdanovits *et al.* 2003), nutrition (e.g. Brian 1975) and presence of predators (e.g. Beckerman *et al.* 2010) often affect development time and lead to differences in body size and correlated life history traits. In some arthropods, the duration but also the actual number of instars can vary across environments (e.g. Esperk *et al.* 2007; Beckerman *et al.* 2010). Furthermore, some organisms, typically in unfavourable environments, have environmentally induced arrested development at different stages: embryonic diapause (Moriyama & Numata 2008), larval diapause (Golden & Riddle 1984), and pupal diapause (Belozerov *et al.* 2002). While it is clear that diapause represents an adaptive plastic response, the same is probably not true for many cases where developmental rates (and correlated body size) are affected by availability of energy resources (such as temperature or food) (see examples in Gotthard & Nylin 1995).

The environmental control of developmental rates can also affect body structure and result in the production of not just larger or smaller but distinct adult morphologies. For example, if the rates of development of different traits are not affected in the same manner, environmental sensitivity can modify the correlation between traits and generate novel trait combinations. A role for this type of heterochrony has been proposed in relation to differences between castes and body parts in ants (Miyazaki *et al.* 2010). Differential rates in association with different body structures have also been suggested to explain changes in allometry (i.e. characteristic patterns of relative organ size; see Stern & Emlen 1999) in environmentally dependent omnivore vs. carnivore morphs of spadefoot toad tadpoles (Storz & Travis 2007).

Aside from the global or local effects on developmental timing, the environmental cue can also trigger a switch between alternative developmental trajectories that result in drastically different morphologies. Studies of the actual process of development of different organisms are adding to a detailed characterization of the formation of alternative environmentally induced morphologies. These include some classic examples of adaptive developmental plasticity such as *Daphnia* anti-predator morphologies (Laforsch & Tollrian 2004; Miyakawa *et al.* 2010), beetle horns (Moczek & Nijhout 2002; Moczek 2007; Tomkins & Moczek 2009), pea aphid wings (Braendle *et al.* 2006; Brisson 2010; Legeai *et al.* 2010), and social insect castes (Abouheif & Wray 2002; Miura 2005; Box 1). The way by which external environmental cues control patterns of gene expression that result in alternative phenotypes is now being elucidated for these and other examples of plastic development and is discussed in more detail below.

Molecular mechanisms of developmental plasticity

Current research in adaptive developmental plasticity is characterizing the molecular mechanisms that link variation in external environmental cues to the changes in organismal development that result in the production of different phenotypes. For a long time, the external environment and plasticity were disregarded in studies of developmental biology. This is despite the fact that organismal development itself, with its characteristic tissue-by-stage-specific gene expression, is perhaps the most compelling example of cellular plasticity. During organismal development, cell differentiation and pattern formation are the result of intrinsic signals that provide cells of developing organisms with information about their position. In developmental plasticity, the choice of alternative developmental trajectories is also fixed genetically, while the decision between those paths depends on different mechanisms that control gene expression. These different mechanisms are the topic of this section.

Gene content and gene expression

Despite the fact that phenotypic plasticity is defined as environmentally induced phenotypic variation produced from single genotype (thus leaving out consideration of genetic variation), there are many revealing examples of a clear correlation between genetic composition and plasticity. This can be seen in terms of both allelic variation at specific loci and the extent of plasticity in different populations, as well as in the gene content on the genomes of species characterized by very plastic development.

Above, we referred to single mutations identified in laboratory populations, which lead to loss (*daf-12* mutant of *Pristionchus pacificus*, Bento *et al.* 2010) or gain (*black* mutant of *Manduca sexta*; Suzuki & Nijhout 2006) of environmental sensitivity. Studies in developmental genetics are, in fact, rich in examples of mutants with condition-dependent phenotypes (i.e. whose effect can only be seen in particular environments; e.g. Gibert *et al.* 2007). For example, null mutations of the *she-1* gene, a regulator of hermaphrodite development in *Ceanorhabditis briggsae*, are temperature sensitive, and this observation has lead to suggestions that this organism might have once been a facultative hermaphrodite (Guo *et al.* 2009). Naturally segregating alleles have also been identified, which correlate with plasticity. One of the most remarkable examples is, perhaps, that of the alternative wing morphs of pea aphids where an allele responsible for male wing polymorphism is associated with female wing polyphenism (Braendle *et al.* 2006).

The pea aphid system also provides a powerful illustration of the correlation between genomic content and developmental plasticity. Specifically, this has been highlighted in relation to expansions in the pea aphid genome of genes involved in regulating gene expression through DNA methylation, chromatin modifications and microRNAs (The International Aphid Genomics C 2010).

Whatever the allelic or gene composition of an organism is, it is clear that environmentally induced changes in development ultimately result from environmentally induced changes in gene expression. The latter can have an effect on which, and to what level, particular genes are expressed, and probably also particular alternative transcripts or alleles. An emblematic example of genes whose expression, and thus effect, depends on the environment is that of heat shock protein (Hsp)-encoding genes. Their expression is characteristically influenced by temperature or other types of environmental stress to buffer perturbations to development and ensure the production of predictable phenotypes (e.g. Takahashi *et al.* 2010).

Analysis of plasticity in gene expression has also been carried out for groups of candidate genes or pathways involved in particular environmentally sensitive developmental switches. Examples include analysis of wing development genes in queen vs. worker ants (Abouheif & Wray 2002), of key body plan and hormone-related genes in *Daphnia*'s induced defences (Miyakawa *et al.* 2010), and of sex-determining genes in species with environmental sex determination (Shoemaker *et al.* 2007). New analytical tools such as microarrays and RNA-Seq now make it possible to move from (necessarily biased) candidate gene approaches to less biased (but of more challenging interpretation) whole-transcriptome scans. Approaches for high-throughput analysis of gene expression now available for multiple systems are making possible the characterization of transcriptomic reaction norms (see Aubin-Horth & Renn 2009). Expression profiling studies are documenting differences in gene expression during development between environments and between alternative phenotypes; for example, differences in larval gene expression that correlate with changes in adult body weight for *Drosophila melanogaster* reared at different temperatures (Bochdanovits *et al.* 2003) and comparison of gene expression between castes and intermediary developmental stages of the termite *Reticulitermes flavipes* (Scharf *et al.* 2003). Such types of studies have shown that, in some cases, up to 50% of the genome may vary in expression between environments (reviewed in Snell-Rood *et al.* 2010).

Below, we highlight two key points that we think will be critical for future studies of the genetic underpinnings of plastic development. First, a detailed assessment of environmentally induced variation in gene expression can greatly benefit from expression profiling of particular tissues (rather than whole bodies where tissue-specific signals might escape detection) and across a series of developmental stages (not only because of the intrinsically dynamic nature of development but also because environmental effects on developmental rates might preclude identification of equivalent 'physiological' stages in different environments). Second, the growing data on gene sequence, expression and function in the context of environmentally induced variation highlight the value of developing a more ecologically mindful annotation for genes and genomes (see Landry & Aubin-Horth 2007), adding to the existing, more biochemically centred gene ontologies.

Environmental regulation of gene expression

Different mechanisms are known that act interactively to regulate gene expression, keeping it in tune with physiological adjustments to the environment. Among these, the role of endocrine hormones and DNA methylation has received, and is receiving, special attention in the context of developmental plasticity (see Gilbert & Epel 2009).

The sensitivity of hormones to the environment, together with their widespread role as regulators of post-embryonic development, underscores their role as intermediaries in linking external environmental information with developmental switches (Nijhout 1998). In fact, a hormonal regulation has been characterized for most, if not all, well-described examples of developmental plasticity (see Nijhout 2003; Gilbert & Epel 2009). Insect juvenile hormone and ecdysteroids, in particular, have been implicated in many cases of plastic development, including that of seasonal polyphenism in butterfly wing patterns and of castes in social hymenoptera (Box 1). In many cases, the same hormone influences multiple developmental decisions and different traits during the development of one same organism; often associated with different sensitivity thresholds (Bento *et al.* 2010) and/or different sensitivity periods (Moczek & Nijhout 2002; Oostra *et al.* 2011). The environmental cues can induce changes in titres and/or dynamics of hormone production, and the hormones can then affect gene expression. This can happen, for example, via their nuclear receptor proteins which, when activated by the hormone signal, have transcription regulator activity (Baniahmad & Tsai 1993) or possibly also via hormone-related changes in chromatin (Lu *et al.* 1998).

DNA methylation is one of the mechanisms, sometimes collectively called 'genetic bookmarking', that leads to changes in gene expression independently of changes in nucleotide sequence. Genetic bookmarking includes different types of modifications to DNA and nucleosomal histone proteins, which can affect the accessibility of gene regulatory regions to the gene expression machinery. For example, the methylation of CpG dinucleotides in DNA reduces gene expression by preventing binding of transcription factors, while changes to nucleosomal histones, such as acetylation and methylation, can affect chromatin structure and transcriptional state (Siegfried & Simon 2010). Genetic bookmarks are characteristically reversible but they can be inherited through cell division and also through organismal reproduction, a process broadly referred to as epigenetics. During normal development, each cell lineage exhibits a distinct epigenetic signature that can be reversibly modified to regulate gene expression. Epigenetics is receiving considerable attention in research on developmental biology and on biomedicine, and also in the context of phenotypic plasticity, natural variation and evolutionary biology at large (Bossdorf *et al.* 2008; Richards 2008; Gilbert & Epel 2009; Jablonka & Raz 2009). It has been demonstrated that DNA methylation plays a key role in mediating many cases of environmentally induced phenotypic variation (Angers *et al.* 2010), including caste determination in honeybees (reviewed in Moczek & Snell-Rood 2008; see Box 1). In fact, DNA methylation seems to be widespread across social Hymenoptera (Kronforst *et al.* 2008) with a highly conserved and complex methylation system present in some groups (Wang *et al.* 2006). Recently, comparisons among different ants have characterized genome-wide levels of methylation that are higher in species where queen–worker dimorphism is stronger, leading to the suggestion of an association between methylation and morphological specialization (Bonasio *et al.* 2010).

Challenges and trends

In the section above, we provided a broad overview of some of the best-studied molecular mechanisms underlying developmental plasticity: changes in gene expression and its regulation by both hormones and epigenetic processes such as DNA methylation. These mechanisms interact in complex ways whereby they regulate and are regulated reciprocally. For example, steroid hormones can influence gene expression by affecting chromatin states (Lu *et al.* 1998), and, conversely, their biosynthesis and action can itself be under epigenetic regulation (e.g. Martinez-Arguelles & Papadopoulos 2010). There are also other relevant mechanisms that we have not addressed. These include other regulatory mechanisms, involving players such as regulatory microRNAs and post-translation modification of regulatory proteins (Weake & Workman 2010), as well as mechanisms of signal reception and signal transduction (see discussions in Aubin-Horth & Renn 2009; Fusco & Minelli 2010). The very initial stage of how environmental cues are sensed can involve direct biochemical effects (e.g. temperature effects on reaction kinetics and on protein conformation) and/or be mediated by the neuroendocrine system, capable of transducing environmental information into a physiological response. Studies of adaptive developmental plasticity will clearly gain from also addressing the molecular underpinnings of signal detection and transduction in relation to the environmental cues, and their relationship to different regulatory mechanisms that alter organismal development.

A complete understanding of adaptive developmental plasticity will require knowing the different sensory and regulatory mechanisms, but also how these, in turn, affect development to produce changes in phenotype that result in differences in individual fitness in natural populations. In nature, the integration of all levels of information is complicated by the fact that the developmental environment is more complex than single changing cue, the phenotype is more than one particular trait, and the selective environment presents more than one ecological challenge. Also, typically, there is extensive genetic variation in natural populations, and different genotypes do not necessarily respond to environmental variation in the same manner. Current studies are starting to specifically address variation in nature also at the molecular level, including for gene expression (e.g. Scott *et al.* 2009), hormone dynamics (e.g. Zera 2007) and epigenetics (see Bossdorf *et al.* 2008 and Richards 2008). The integration of these different studies of the proximal mechanisms of the environmental sensitivity of development will need to be made within an evolutionary framework, including the evolutionary history of the regulating mechanisms and their interactions (Johnson & Tricker 2010), as well as the origin and diversification of (plastic) developmental networks (Minelli & Fusco 2010). It is clear that environmentally induced variation will need to continue to be studied in multiple systems (representing different types of cues, developmental and phenotypic changes, and ecological situations), at different levels of biological organization (changes in molecular processes, organismal development, and impact in natural populations) and bringing together different disciplines (genetics, developmental biology, ecology and evolutionary biology).

Environmentally induced variation is at the heart of new trends in biological and biomedical research. The new discipline of eco-(evo-)devo is perhaps the most emblematic example of this. It unites fields such as epigenetics and evo-devo (see Gilbert & Epel 2009) around the study of developmental plasticity. It takes explicit account of the environment in generating inter-

Box 3 Coping with climate change

In recent years, researchers and the general public alike have become increasingly aware of environmental changes (notably, global changes in temperature) that are going on and of their effects on biodiversity. Despite some discussion about the causes, the trend for a globally warmer planet and for locally more extreme fluctuating conditions is undisputed, as are the effects on natural populations (Walther *et al.* 2002). Numerous documented examples of these effects include changes in species abundances (e.g. Blaustein *et al.* 2001), range (e.g. Battisti *et al.* 2005), migration patterns (e.g. Cotton 2003), phenology (e.g. Forister & Shapiro 2003), physiology (e.g. Pörtner & Knust 2007), genetic composition (e.g. Levitan & Etges 2005) and also local and/or global extinction (e.g. Thomas *et al.* 2004).

The impact of climate change on a population will depend both on the magnitude and pattern of that change and on the environmental sensitivity of the organisms in question (Tewksbury *et al.* 2008). Organisms are expected to have some intrinsic capacity to cope with changing environmental conditions (e.g. Davis *et al.* 2005; Parmesan 2006) mainly in three different ways, illustrated in Fig. 3: (a) dispersal to suitable habitats elsewhere, also known as 'habitat tracking' (e.g. Hitch & Leberg 2006); (b) evolutionary adaptation through natural selection acting on segregating genetic variation (e.g. Rodríguez-Trelles & Rodríguez 1998); and (c) adjustment by means of phenotypic plasticity without a change in genotypes (e.g. Przybylo *et al.* 2000; Charmantier *et al.* 2008). The relative contribution of these mechanisms depends on different factors, including species' biology, extent of environmental change and availability of alternative habitats (Gienapp *et al.* 2008). It is important to explicitly address each of the coping mechanisms. The role of environmentally induced changes in phenotype has mainly focused on reversible changes such as adjustment of behaviour or physiology (acclimation; see Box 2). A role for developmental plasticity has been included in theoretical models exploring its significance to how natural populations deal with environmental change (e.g. Chevin *et al.* 2010), but there is still relatively few experimental data on this.

Still, the most worrying situation is that of the many species that may fall outside these categories, lacking both the plasticity that could allow them to better cope with environmental change (e.g. Nussey *et al.* 2007) and the genetic variation that would allow them to evolve in response to climate change (e.g. Barrett *et al.* 2011). Unless the impact of climate change can be mitigated, many of these species may face extinction (see Chevin *et al.* 2010).

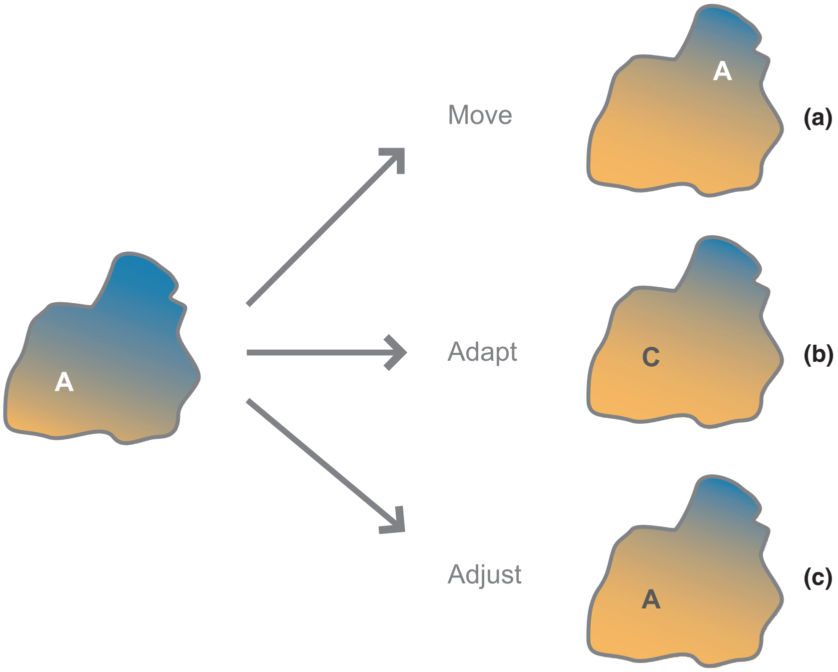

Fig. 3 Coping with changing environments. In nature, populations can deal with climate change in different ways: (a) through habitat tracking, individuals move to different places and this can result in changes in species distributions, (b) through natural selection on segregating genetic variation, allele frequencies change across generations as populations adapt to novel environmental situations, and (c) through phenotypic plasticity, individuals can adjust without changes in genetic composition. Background colour shading represents an environmental gradient (e.g. temperature), and characters represent populations with letters (A or C) corresponding to different genotypes and colours (white or grey) to different phenotypes.

individual variation in phenotype through changes in development, and in contributing to evolutionary diversification (see also West-Eberhard 2003). In fact, plasticity has been highlighted as one of the major themes for an extended evolutionary synthesis (Müller 2007; Pigliucci 2007). Aside its obvious place at the centre of an effort to unite ecology and developmental biology and its contribution to evolutionary biology, the influence of the developmental environment on phenotype can also have important implications for biomedicine and biodiversity. First, both the *in utero* environment (including maternal stress and nutrition; e.g. Burdge & Lillycrop 2010), and trans-generational environmental effects carried in parental gamete epigenomes (including in the sperm; Puri *et al.* 2010) have been implicated in the developmental origin of adult disease (examples in Gilbert & Epel 2009; Gluckman *et al.* 2009). Second, the study of developmental plasticity can also be of relevance for appropriately assessing the biodiversity consequences of anthropogenic environmental change. Natural populations have different mechanisms for dealing with environmental change, including global change in climate (see Box 3). While demographic and genetic mechanisms have received considerable attention in this context, the role of developmental mechanisms (Chevin *et al.* 2010; Reed *et al.* 2010) is lagging behind. Clearly, plasticity can help organisms exploit novel environments (e.g. Yeh & Price 2004; Ghalambor *et al.* 2007) and provides a means of rapidly adjusting to external change, but it might also pose problems. For example, in organisms with temperature-dependent sex determination, dramatic climate change can potentially lead to extremely biased sex ratios with serious demographic consequences (Janzen 1994; Miller *et al.* 2004). It might also pose a problem if the triggering cue and selective environment change independently, and the former is no longer a good predictor of the latter.

It is clear that developmental plasticity will continue to be an active area of research and will greatly profit from the availability of sophisticated methods of molecular analysis (which traditionally were a privilege of only a handful of classical laboratory models) for multiple systems with interesting ecology and/or unique biological properties (see Milinkovitch & Tzika 2007; Abzhanov *et al.* 2008; Aubin-Horth & Renn 2009). It is also clear that a complete understanding of natural variation will gain from including the study of development, and it will continue to bring genetic models out of the laboratory, and ecological systems into the laboratory. These are certainly exciting times when different disciplines are joining efforts to understand what is arguably one of the most fascinating, and until recently largely ignored, properties of biological systems; that of variation.

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