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# PHENOTYPIC PLASTICITY FACILITATES MUTATIONAL VARIANCE, GENETIC VARIANCE, AND EVOLVABILITY ALONG THE MAJOR AXIS OF ENVIRONMENTAL VARIATION

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**Phenotypically plastic genotypes express different phenotypes in different environments, often in adaptive ways. The evolution of phenotypic plasticity creates developmental systems that are more flexible along the trait dimensions that are more plastic, and as a result, we hypothesize that such traits will express greater mutational variance, genetic variance, and evolvability. We develop an explicit gene network model with three components: some genes can receive environmental cues about the adult selective environment, some genes that interact repeatedly to determine each others' final state, and other factors that translate these final expression states into the phenotype. We show that the evolution of phenotypic plasticity is an important determinant of mutational patterns, genetic variance, and evolutionary potential of a population. Phenotypic plasticity tends to lead to populations with greater mutational variance, greater standing genetic variance, and, when the optimal phenotypes of two traits vary in concert, greater mutational and genetic correlations. However, plastic populations do not tend to respond much more rapidly to selection than do populations evolved in a static environment. We find that the quantitative genetic descriptions of traits created by explicit developmental network models are evolutionarily labile, with genetic correlations that change rapidly with shifts in the selection regime.**

**KEY WORDS:** **Evolutionary constraint, evolution of mutational covariance, evolvability, genetic covariance matrix, phenotypic plasticity.**

Most organisms have evolved some degree of phenotypic plasticity (West-Eberhard 2003). If this phenotypic plasticity is adaptive, the change in phenotype produced in that environment makes the organism more fit than it would have been with an average phenotype. For example, when plants are exposed to dry conditions, they may close stigmata or improve water-use efficiency, increase root-shoot ratios, and/or change leaf shape, etc. Such plasticity is predicted to have substantial effects on the evolutionary potential of a species. Theory suggests that plastic genotype-by-environment interactions may result in a release of heritable variation in a novel environment (Hermisson and Wagner 2004; Fierst 2011), and may ultimately shape the response to selection in the new environment (Price et al. 2003). Plasticity may also aid speciation and change ecological interactions (Agrawal 2001; Miner et al. 2005; Pfennig et al. 2010; Thibert-Plante and Hendry 2010). In computer models, nonadaptive (Espinosa-Soto et al. 2011) and adaptive plasticity (Fierst 2011) have each been shown to accelerate the evolution of a developmental network to a new environment. From the opposite perspective, the evolution of robustness to environmental changes has been shown to decrease mutational effects and slow evolutionary rates (Ancel and Fontana 2000). Plasticity can buffer the deleterious effects of novel environments, permitting organisms






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to survive, and later adapt (West-Eberhard 2003). An appropriate plastic response to a novel environment can increase the probability that an organism can persist in that environment, whereas an inappropriate response can reduce its chances of success (Price et al. 2003).

However, despite a number of theoretical studies, the role of plasticity in potentiating and shaping adaptation remains controversial (de Jong 2005). One explanation for this lingering controversy is that many theoretical efforts to understand the effects of plasticity on evolution use a statistical quantitative genetics approach (e.g., Via and Lande 1985; de Jong 2005; Lande 2009), rather than mechanistic models (Pigliucci et al. 2006). Key questions about evolved plastic responses, such as how much phenotypic diversity is revealed when a population encounters an environment outside the range of its recent history, cannot be adequately studied without a mechanistic model of how environmental inputs shape phenotypes. Although the interactions between plasticity and adaptation have been explored in several simple models of development (Ancel and Fontana 2000; Espinosa-Soto et al. 2011; Fierst 2011), these studies have yet to apply these mechanistic models to quantitative-genetics questions, such as the evolution of reaction norms, genetic variance–covariance matrices, and mutational correlations.

In this article, we explore the possibility that phenotypic plasticity may facilitate the emergence and maintenance of genetic variance, and that this genetic variation may be greatest along the dimensions most often favored in a heterogeneous environment with plasticity. Heterogeneous environments will often vary in their trait optima for multiple traits. If phenotypic plasticity evolves for these traits, then the developmental system must be flexible enough to allow variations in those trait combinations in response to the environment. As a result, we hypothesize that an adaptively plastic developmental system will vary more readily along dimensions for which trait optima vary, and we therefore expect that even random changes in genotypes will be more likely to have larger effects along those same dimensions. Therefore, in a population with adaptive developmental plasticity, the major axes of genetic variance and of the mutational covariance matrix are expected to be correlated with the major axes of correlated plastic divergence among environments. We therefore propose that the variances and covariances of the phenotypic effects of both new mutations and standing variation may evolve as an indirect effect of selection on the developmental system to promote adaptive plasticity. We test this hypothesis with an explicit developmental model of trait development and evolution.

Evaluating the effects of plasticity on well-studied measures of genetic variation allows us to apply quantitative-genetics theory to understand the evolvability of plastic populations. Over short periods, a powerful way of studying the evolutionary potential of a population is to investigate the magnitude and shape of the additive genetic variance–covariance matrix, **G**, whereas over longer periods, the properties of new mutations shape evolvability. The amount of genetic variance of each trait and the genetic covariance between traits has been increasingly studied over the last few decades. In the 1980s, Arnold, Lande, and Wade (Lande 1979; Lande and Arnold 1983, Arnold and Wade 1984a,b) laid the foundations for studying natural selection in the wild using partial regression models and genetic covariance matrices. These articles showed that the strength and multivariate pattern of selection on phenotypic traits could be measured in the wild, and many, many researchers have followed suit with such measures (Kingsolver et al. 2001; Kingsolver and Pfennig 2004). However, to predict the response to multivariate selection, it is also necessary to know the additive genetic variance of each trait, and importantly, the additive genetic covariance of pairs of traits. These additive genetic variances and covariances are collected into the so-called **G** matrix, with the variances on the diagonal and the covariances in the off-diagonal values. In the absence of perfect information about the frequencies and effects of all alleles in a population, prediction of response to selection requires **G**. More challengingly, it is necessary to know the value of **G** for each generation that selection may be applied. If **G** is relatively constant over time, then it suffices to measure it once, but if **G** evolves, a single measure of **G** may be increasingly misleading. Our knowledge of the behavior of **G** lags behind our understanding of selection, in part because **G** is more difficult to measure. Nevertheless, over recent years, much progress has been made in studying **G** both empirically and in theory (Steppan et al. 2002). We know that **G** can be changed by all the major evolutionary forces, such as correlational selection (Jones et al. 2003, 2004), drift (Lande 1980; Phillips et al. 2001), migration (Guillaume and Whitlock 2007), mutation (Jones et al. 2007), and recombination (because genetic covariances are often in part caused by linkage disequilibrium). When it has been measured, we know that **G** can change over time (Lofsvold 1986; Kohn and Atchley 1988; Paulsen 1996; Arnold and Phillips 1999; Roff et al. 1999; Roff and Mousseau 1999; Waldmann 2000; Begin and Roff 2001), but is sometimes relatively constant (Lofsvold 1986; Shaw and Billington 1991; Spitze et al. 1991; Platenkamp and Shaw 1992; Brodie 1993; Podolsky et al. 1997; Roff et al. 1999; Waldmann 2000; Begin and Roff 2001, 2003, 2004).

Although **G** and the associated matrix **M** of mutational variances and covariances are powerful conceptual tools, they are ultimately only statistical summaries of data, and cannot explain the mechanisms behind covariances. A complete understanding of how plasticity might relate to evolvability requires a model of development as well as the quantitative-genetics model of evolution. The purpose of such a developmental model is not to depict accurately all aspects of biological development, but to provide a rich testing ground for evaluating how the

genotype–phenotype relationship interacts with selection (Wagner and Altenberg 1996). As a step toward synthesizing models of evolution with those of development, we adapt a model, previously used to study robustness and evolvability (Wagner 1996; Bergman and Siegal 2003; Draghi and Wagner 2009), to the question of how plasticity shapes and is shaped by evolution. Other studies have applied variants of this model to explore how plasticity shapes evolvability (Espinosa-Soto et al. 2011; Fierst 2011), but have not yet applied this approach to a quantitative-genetics framework. We extend the network model to incorporate two new features: explicit information from the environment and development of observable quantitative traits. The resulting model is allowed to evolve plasticity through the interactions of its "genes," without the contrivance of locithat modulate plasticity by fiat. As a result, the model is far less likely to encode a priori assumptions about the nature of plasticity, because the plastic behavior evolves from the interactions of a potentially large and complex developmental network. We therefore combine previously disparate approaches, using a developmental network model that can be described in quantitative genetic terms. This synthetic approach allows us to describe results in terms of empirically measurable parameters, whereas at the same time testing quantitative genetic assumptions about the stability of these evolutionary parameters.

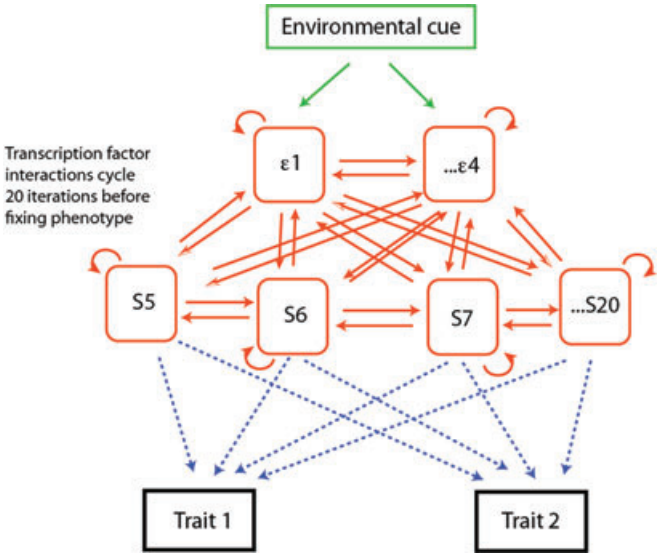


**Figure 1. A schemata of the developmental process. A total of 20 genes are potentially involved in an interactive network, where the expression of each gene product at each time point is determined by the sum of the effects of all interacting genes in the network, weighted by the specific pairwise effect of gene *i* on gene *j*. Four of these 20 genes (ε1 through ε2) may also receive information from the environment. After 20 iterations, each of the 16 genes that do not directly receive environmental cues (S5–S20) can affect the value of two traits, where the weight of the network gene on each trait is determined by a unique gene.**

# Methods

## GENE NETWORK MODEL

Our genotype–phenotype model is inspired by the idea of a network of transcription factors that regulate each others' expression levels through an iterative process (see Fig. 1 for a cartoon version of the developmental process). In short, a set of ε genes receive information from the environment. A total of $S$ genes, including the ε, then develop through a 20 time-step cycle, and each gene potentially influences the expression state of all $S$ genes, including itself. Each regulatory connection is defined by two separate values: a binary state that determines if the connection is active, and a real-valued weight that scales the gene's effects. After the iterative process, the steady-state expression levels of the $S - \varepsilon$ genes that did not directly receive environmental input are summed, weighted by an evolved trait-specific effect matrix, to determine the phenotypic value of two traits. Each trait is subject to stabilizing selection, with an optimum determined by the current environment. This model is loosely based on a model presented by Andreas Wagner (1996). However, in our variant, we make three changes: we use continuous, rather than discrete, expression levels; the steady-state expression levels do not themselves constitute the phenotype, but instead determine several quantitative traits; and an informative environmental cue helps determine the phenotype.

Each haploid genotype is characterized by four matrices. An $S \times S$ matrix of binary elements, $\mathbf{Y}$, determines if gene $j$ regulates gene $i$. (For all of the calculations we do here, $S = 20$.) $\mathbf{y}$ is an $S \times S$ matrix containing the signs and continuous-valued weights of these regulatory influences. Similarly, $\mathbf{Z}$ is a $2 \times (S - \varepsilon)$ matrix of binary elements determining if gene product $j$ contributes directly to trait $i$, and $\mathbf{z}$ is a matrix with the signs and continuous-valued weights of these contributions of the $j$th gene to trait $i$.

We considered three evolutionary scenarios, which we call *static*, *heterogeneous*, and *plastic*. In the static case, we model a scenario in which the trait optima, $(\phi_1, \phi_2)$, are fixed. In both the heterogeneous and plastic scenarios, the trait optima change each generation, as a result of a draw from a uniform distribution for the value of the selective environment. To model strong correlation between the two trait optima in a changing environment, we draw a value uniformly from the interval $[\frac{1}{2\sqrt{2}}, \frac{3}{2\sqrt{2}})$ and use this as the optimal trait value for both traits. Therefore, $\phi_1 = \phi_2$ in these evolutionary scenarios.

Additionally, only in the plastic scenario, the state of the environment is indicated by an environmental cue, represented by a real number $c$. Cues are directly proportional to the trait optima and are scaled to vary between $-\frac{1}{2}$ and $\frac{1}{2}$. Therefore, populations in both the heterogeneous and plastic scenarios experience frequent

environmental change, but only those in the plastic scenario have the potential to evolve adaptive plasticity.

Each of the $S$ genes in the network has a continuous-valued state $x_{i,t}$ for gene $i$ at time $t$, ranging from 0 to 1, which represents the transcriptional activity of that gene. Each gene is initially active; then, the states in each subsequent time steps are determined by summing the regulatory contributions of the $S$ genes (autoregulation is permitted) and environmental signals, and transforming this sum by a sigmoid function. If gene $j$ regulates gene $i$ (i.e., $Y_{ij} = 1$), then $x_{j,t}$ and $y_{ij}$ multiply to influence $x_{i,t+1}$:

$$x_{i,t+1} = \left(1 + \exp\left[-\sum_{j=1}^{S} Y_{ij} y_{ij} x_{i,t} + E_i c\right]\right)^{-1},$$

where $E_i$ is 1 if $i \leq \varepsilon$ and 0 otherwise.

Although some networks exhibit long transients or oscillations, in practice many networks quickly approach a steady-state expression pattern. After $\tau = 20$ time steps, we judge the stability of an expression pattern by comparing the root mean squared difference between the vectors $x_{\tau-1}$and $x_{\tau}$. If this error is less than a proscribed threshold (we used a threshold of 0.01), we consider the network to have reached a steady state and compute its phenotype; otherwise, that individual offspring is defined to be unfit and is killed, and a new individual is immediately created to take its place from randomly chosen parents.

The two traits comprising the phenotype are computed as the sums of positive and negative contributions from the set of all transcription factor gene products, excluding those that directly receive information from the environment. $Z_{ij}$ determines if gene $j$ contributes to trait $i$, and this contribution is the product of the steady-state expression of gene $j$ and the weighting factor $z_{ij}$:

$$t_i = \sum_{j=\varepsilon+1}^{S} Z_{ij}\, z_{ij}\, x_{j,\tau}.$$

## EVOLUTION SIMULATIONS

Evolution is based upon the Wright–Fisher model: populations of $N = 1000$ individuals reproduce in discrete generations with selection on both fertility and survival. When an organism is born, it acquires a number of mutations that are Poisson distributed with mean $U = 0.02$. With probability $\alpha = 0.2$, the mutation changes the architecture of a network—adding or removing interactions—by mutating $\mathbf{Y}$ or $\mathbf{Z}$. Such a mutation will remove an extant interaction or create an absent one; note that the corresponding value of $y_{ij}$ or $z_{ij}$ will be retained and continues to evolve. Interactions within the network ($\mathbf{Y}$) and from the network to traits ($\mathbf{Z}$) are equally likely, per capita, to be selected for mutation. With probability $1 - \alpha$, mutation changes the weight of a randomly chosen interaction by adding a perturbation from a Gaussian distribution with mean at zero and standard deviation of $\sigma_m$. By default we used a value of $\sigma_m = 0.5$.

Fitness is determined by first calculating the Euclidian distance, $d$, between the trait vector $\mathbf{t}$ and the vector of trait optima, $\boldsymbol{\phi}$. The factor $\omega$ scales the relationship between fitness $w$ and $d$ as:

$$w = \exp\left(-\frac{d^2}{2\omega}\right).$$

By default, we used $\omega = 0.2$, but in the supplemental material we show results for weaker selection at $\omega = 0.8$. To provide some intuition for these parameter values, we can calculate how fit an phenotype at the average of the range of optima would be if the current environmental optimum was at either extreme of that range. For $\omega = 0.2$, this phenotype would be about 29% as fit as a perfectly adapted organism, whereas for $\omega = 0.8$, the phenotype would be about 73% as fit as the optimum phenotype.

To produce a new individual, the first parent is chosen with probability $w/\overline{w}$, where $\overline{w}$ is the mean fitness in the current generation. The second parent is chosen in the same way, and is redrawn if the first parent is selected again. One haploid offspring is produced by recombining the parents' genotypes, followed by mutation and development in the environment appropriate for the offspring population. If an offspring's phenotype is unstable—that is, fails to reach an equilibrium within $\tau = 20$ time steps—then it is assumed to be lethal, and a new combinations of parents is selected. This procedure is repeated until $N$ stable offspring are produced, and combines fertility selection on the phenotype with viability selection against individuals with unstable networks.

The factors that determine how the expression of gene $j$ influences the expression of gene $i$ are imagined to be *cis*-regulatory elements. When recombination accompanies reproduction, these factors are therefore inherited in complete linkage. Each set of *cis*-regulatory elements is assumed not to be linked to any other set. Therefore, for each $i$, the rows of the $\mathbf{Y}$ and $\mathbf{y}$ matrices are inherited together from one parent, and a Bernoulli trial with probability 0.5 determines from which parent each pair of rows is inherited. The regulatory factors in the $\mathbf{Z}$ and $\mathbf{z}$ matrices are not assumed to be adjacent in the genome; therefore, each factor $Z_{ij}$ is inherited, along with it corresponding entry $z_{ij}$, from an independently chosen parent.

Simulations begin with a population of clones copied from a single individual. This individual is chosen randomly for each replicate, subject to two constraints: (1) the genotype must produce a stable phenotype in the initial, randomly chosen environment, and (2) the genotype's fitness in this environment must be above a threshold, set to 0.00005 in all simulations we present. The use of a threshold prevents unproductive simulations with miniscule fitness values, which would also be subject to numerical round-off errors.

Several default parameters, including the minimal starting fitness and the distance of the optimal phenotypes from the coordinate origin, were chosen by experimentation. To maximize our power to detect influences on **G** and **M** while avoiding bias, we selected the parameter combination that produced distributions of angles of **G** and **M** that were closest to uniform in the static and heterogeneous scenarios, without regard to these distributions in the plastic scenario.

### MEASURING THE M AND G MATRICES

The mutational variance–covariance matrix **M** was measured by introducing single mutations to an individual genotype and measuring the change in each trait relative to the unmutated genotype. The mean of the squared differences for trait 1, averaged across various mutations assayed in all of the individuals in a single population, is the variance in trait 1; the mean of the product of a mutation's effect on trait 1 and on trait 2, averaged across the individuals in one population, is the covariance between trait 1 and trait 2. **M** was measured in multiple environments, each characterized by a value of the environmental cue, $c$, when appropriate.

**G** was measured as the covariances between the trait 1 in offspring and trait 2 in parents. To minimize biases due to selection and unequal family sizes, we generated one offspring from each of the $N(N-1)/2$ possible parental combinations and compare the trait values of the offspring to the average trait value of its two parents. Because $N = 1000$ in all presented data, **G** was well estimated by this procedure. The additive genetic covariance of traits 1 and 2 is calculated from the average covariance of trait 1 in offspring and 2 in parents and vice versa. We also do not allow mutation during these reproductive events, and discard parent and offspring combinations if any of the three are unstable in the test environment. Like **M**, **G** was measured separately in each relevant environment.

### EVOLVABILITY ASSAYS

We measure evolvability by the mean change, of either the phenotype or fitness, of a population in response to a selective pressure. We assay evolvability with selective gradients oriented in seven directions in trait space. Rather than define optimal phenotypes, we redefine fitness in these assays to promote continual adaptive change in both traits. Fitness in these assays is determined by two additional parameters, a measure of selective strength $s$, and a measure of the orientation of the gradient, $\theta$, as follows:

$$fitness = (1+s)^d,$$

where

$$d = \left(x - \frac{1}{\sqrt{2}}\right)\sin\theta + \left(y - \frac{1}{\sqrt{2}}\right)\cos\theta.$$

**Table 1. Mean genetic and mutational variances and correlations for the parameter values in Figure 2.**

| | Mean genetic variance | Mean genetic correlation | Mean mutational variance | Mean mutational correlation |
|---|---|---|---|---|
| Static | 0.00045 | 0.03 | 0.0024 | 0.01 |
| Heterogeneous | 0.00051 | 0.04 | 0.0025 | 0.01 |
| Plastic | 0.00098 | 0.61 | 0.0034 | 0.30 |

In each simulation, a population evolved under the conditions described above is generated, then copied for each replicate simulation. Simulations are performed for $\theta = 45^\circ$, $30^\circ$, $15^\circ$, $0^\circ$, $-15^\circ$, $-30^\circ$, $-45^\circ$, which range from selection along the axis of plasticity when $\theta = 45^\circ$, to selection orthogonal to that axis when $\theta = -45^\circ$. For example, the $\theta = 45^\circ$ scenario selects for unlimited but proportional increases in both traits, whereas the $\theta = 0^\circ$ scenario selects for stasis in trait 1 and an unlimited increase in trait 2. Each of these seven scenarios is replicated 30 times for each evolved population, and each population evolved for 100 generations.

## Results

The populations were able to evolve to relatively high fitness in nearly all cases. When the organisms were allowed meaningful environmental cues in a heterogeneous environment over sufficiently long time, they usually evolved adaptive phenotypic plasticity (Fig. S1), by which they tended to match the environmental optimum fairly well for environments intermediate to the observed range and not quite as well for less common extreme environments. Outside of the range of environments in which they evolved, the plastic responses to environmental cues tended to correlate with the direction of plasticity within the evolved range, although these plastic responses were smaller and more variable than the evolved response to previously experienced cues.

The patterns of genetic variance and covariance depended on whether the selective optima changed and on whether the organism received cues about the optima. In populations that evolved phenotypic plasticity, the amount of genetic variation for each trait was in average increased by about a factor of two for these parameters and for those in the examples in the Supporting Information (Fig. 2 and Table 1). Figure 3 shows the genetic correlations of the **G** matrix for each case. **G** for static cases has some variation in magnitude and shape, but on average the **G** matrices for the static cases tend to have genetic correlations between the two traits near to zero. With environmental heterogeneity (but without plasticity), the correlational patterns of **G** are similar to the static case. Heterogeneity in selection is not enough, in this model, to

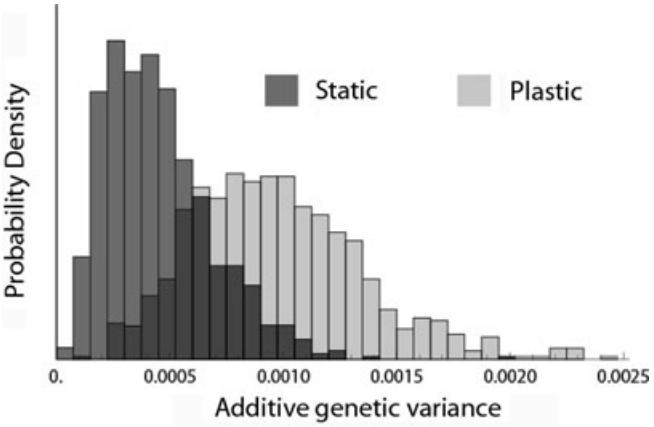


**Figure 2.** Distribution of $V_A$ for populations evolved to a single optimum (static) and those with evolved with constantly changing optima and informative cues (plastic). Populations evolved for 50,000 generations before measurement. Population size was $N = 1000$, genomic mutation rate was $U = 0.02$, and the strength of selection, ω, was 0.2; see Methods for details. Over 800 replicates were performed for each condition.

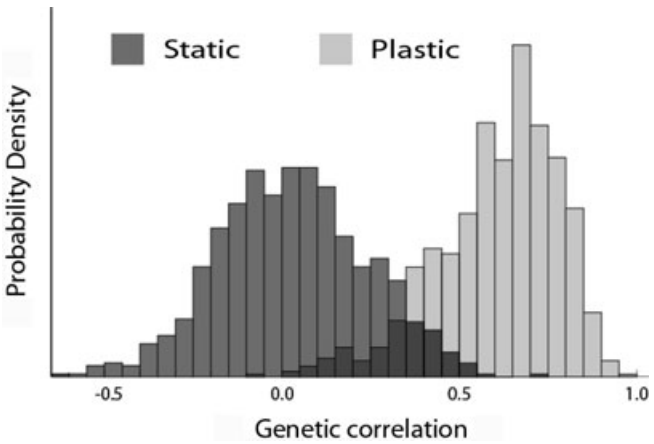


**Figure 3.** Distribution of genetic correlations for populations evolved to a single optimum (static) and those evolved with constantly changing optima and informative cues (plastic). Parameters are the same as in Figure 2.

strongly structure **G**. However, if the organisms receive useful environmental information, such that they evolve plasticity for the pair of traits, the **G** matrix tends to be exaggerated along the same dimension that the optima vary, with an average genetic correlation for these parameters of approximately 0.6. Plasticity does change the structure of **G**, making the major axis of **G** most likely to occur along the lines of plastic response. These differences between populations evolved with plasticity in heterogeneous environments and those evolved in static environments were also seen when populations evolved for longer (250,000 generations) under both strong ($\omega = 0.2$) and weaker ($\omega = 0.8$) selection (Figs. S2 and S3).

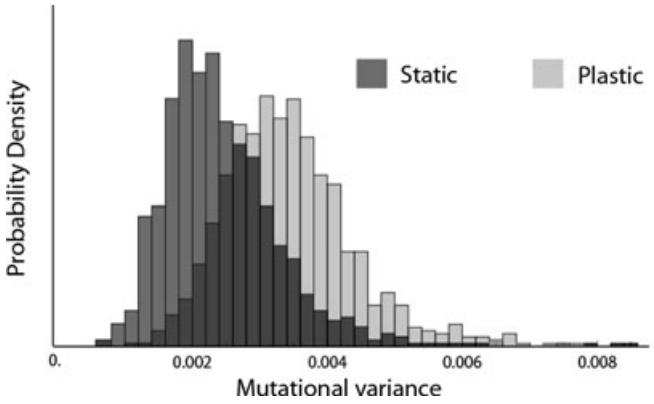


**Figure 4.** Distribution of mutational variance for populations evolved to a single optimum (static) and those evolved with constantly changing optima and informative cues (plastic). Parameters are the same as in Figure 2.

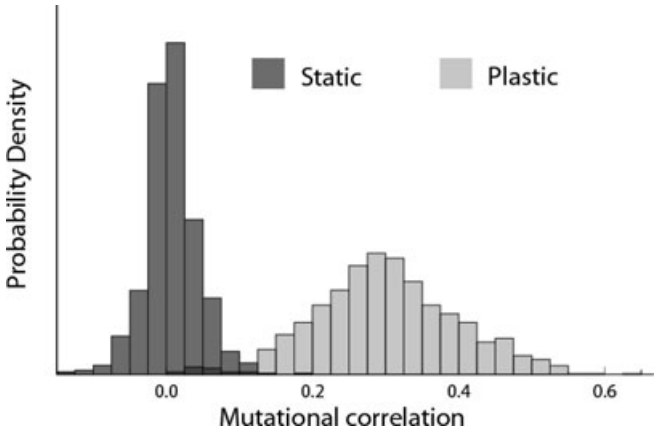


**Figure 5.** Distribution of mutational correlations for populations evolved to a single optimum (static) and those evolved with constantly changing optima and informative cues (plastic). Parameters are the same as in Figure 2.

The pattern of mutational effects is similar: the amount of mutational variance is greater for populations with plastic developmental systems compared to those with stable environments or even those with heterogeneous selection without reliable environmental cues (Table 1). These increases in mutational variance are larger earlier in the evolutionary history of the plastic species (compare Figs. 4 and S2). Moreover, evolution of plasticity is correlated with evolution of developmental systems in which mutation effects tend to be greatest along the dimension of that plasticity (see Fig. 5). Although the mutational covariance of populations evolving in the static environment tends to be close to zero under these conditions, in plastic populations the mutational correlations are typically high (on average $P_M = 0.3$) (Fig. 5), and the mutation covariance matrices have greatest variation in the direction of plasticity. Mutational correlations of the starting populations are indistinguishable from zero (static:

$t = 0.77$, df $= 399$, $P = 0.44$; plastic: $t = -0.50$, df $= 399$, $P = 0.62$). These patterns in mutational correlations are also found in populations that evolved for longer (250,000 generations) under both strong ($\omega = 0.2$) and weaker ($\omega = 0.8$) selection (Figs. S2 and S3). Thus, as we hypothesized, the developmental system evolves under plasticity to vary most in the direction that is adaptive via plastic response to changing optima.

To understand the effects of these changes to the developmental system on the future evolutionary potential of the populations, we investigated the change in mean fitness over 100 generations in various directions in trait space. Figure S4 shows the change in phenotype caused by plasticity immediately upon introduction to a new environment, where the traits undergo directional selection, in some cases for different trait combinations from those that were previously favored. If the new optimum diverges from the old optimum along the major axis of previous environmental variation, then the population gets a preadaptive shift due to plasticity that tends to be in the right direction (see Fig. S4).

In a complex model such as this, the genetic underpinnings of variability evolve along with the phenotype, such that evolvability changes during the duration of the experiment. We therefore examined the mean change in fitness over durations ranging from a single generation to 100 generations. In all cases, we average the log mean population fitness at the focal time with the log mean fitness at $t = 0$, to avoid counting plastic responses to the cues as evolved changes.

After one generation, plastic populations evolve significantly more than static or heterogeneous populations at all angles except $-30^\circ$ and $-45^\circ$. At later generations, plastic populations have a small advantage when evolved under strong selection for shorter times (Fig. 6), but not under weaker selection for 250,000 generations (Fig. S5). In addition, all populations adapt better when the fitness landscape favors an increase in one trait alone (angles near $0^\circ$). These results confirm that the greater variability of plastic populations translates into increased evolvability in a range of directions, particularly when the trait combination selected for corresponds to the axis of plastic variability. Additionally, the results suggest that not all variation is pleiotropic. Figure S6 confirms that even in plastic networks with a major axis of pleiotropic variability, mutants with strong effects on a single trait alone are still common. It is likely that the presence of these single-trait mutations in all networks contributes to the boost in evolvability at $0^\circ$.

The greater variability in plastic populations can be parsed into two components: the probability that a mutation changes the phenotype at all, and the mean size of the perturbation of mutants that do have an effect. Although the former is often used as a proxy for mutational robustness, both measures capture different aspects of a genotype's sensitivity to mutation. Here, the mean proportions of mutations with phenotypic effects were very similar among one hundred populations evolving in static, heterogeneous, or plastic conditions (averaged over the cues for the seven evolvability scenarios): 0.604 in plastic populations versus 0.597 ($P = 0.009$) in static and 0.596 ($P = 0.004$) in heterogeneous for populations under strong selection ($\omega = 0.2$). In contrast, the mean phenotypic effect of consequential mutations was 0.047 phenotypic units, much higher than the averages for static (0.032, $P < 3 \times 10^{-16}$) and heterogeneous (0.032, $P < 3 \times 10^{-16}$). This result suggests that plastic networks do not necessarily have more essential connections, but that the organization of those connections differ from static and heterogeneous environment networks. Intriguingly, we also found that mutations were no more likely to affect both traits simultaneously in plastic populations, suggesting that the observed mutational correlations in these populations are caused by the magnitude of pleiotropic mutations, and not their frequency (92.6% of mutations affecting one trait affected both in plastic populations, vs. 92.5% [$P = 0.15$] for static and 92.4% [$P = 0.07$] for heterogeneous).

Comparisons of the structures of networks from populations evolved under static, heterogeneous, and heterogeneous with cues (plastic) conditions reveal very few differences. We measured network features of the most fit individual at generation 50,000 in 100 replicate populations for each of the three treatments, and distinguished between the computation layer of a network—the $S$ interacting genes whose steady state determine the traits—and the output connections that link the computation layer genes to the traits. For each portion of the network, we measured the number of active connections and the mean absolute value of the weight of active connections.

These results show that the computation layers of plastic networks are very slightly more strongly interconnected than those of networks evolved in static or heterogeneous conditions, but the output layers have virtually identical connectivities. All $P$-values are calculated with the Wilcoxon rank-sum test with continuity correction, and no comparisons between static and heterogeneous networks were significant. On average, 50.2% of the connections between $S$ genes were active in plastic networks, which was significantly greater than the 49.4% ($P = 0.018$) in static networks and 49.45% ($P = 0.034$) in heterogeneous networks. Similarly, the mean weight of connections in plastic networks, 0.597, was slightly but significantly greater than the mean in static (0.578, $P = 0.0007$) and heterogeneous (0.583, $P = 0.014$) networks. However, the number of active connections from the computational layer to the traits and their mean weights was not significantly different between any of the three scenarios.

Aside from these very minor structural differences, analysis of the effects of mutations on the steady-state behavior of the networks suggests an explanation for the greater phenotypic variability of populations of plastic networks. We measured the number of genes whose steady-state expression level was altered

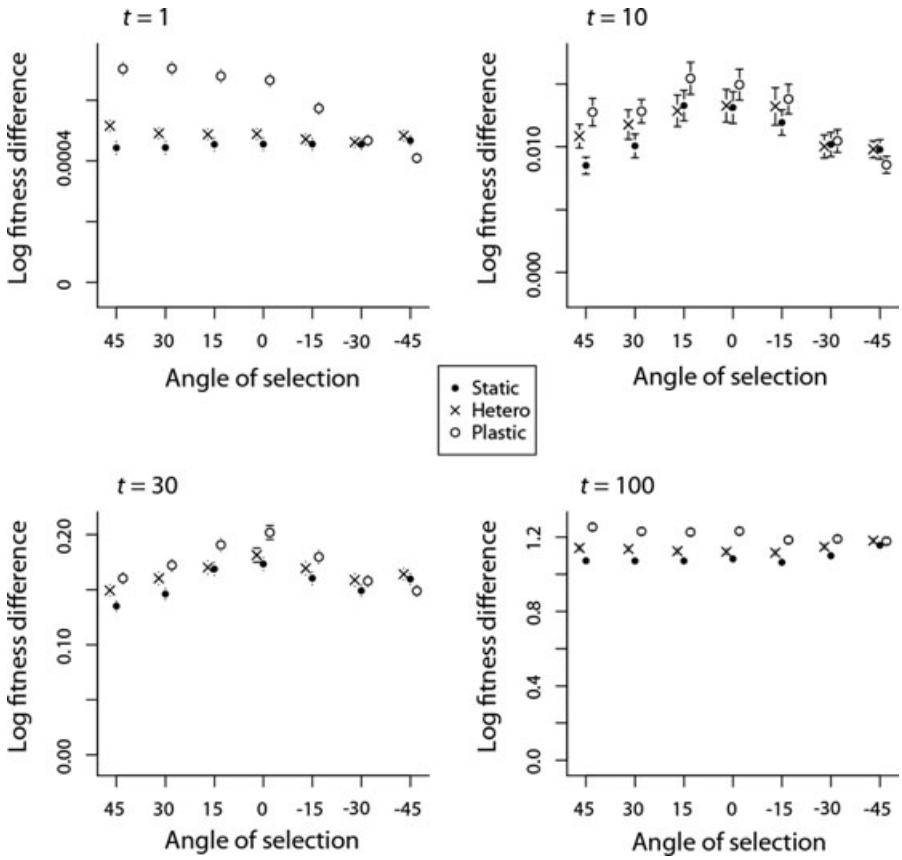


**Figure 6.** **Evolvability depends on the direction of selection and the evolutionary history of the population. Log differences between the mean fitness at generations $t$ = 1, 10, 30, and 100 and the mean fitness at $t$ = 0 (at the beginning of the evolvability assay) are averaged for 250 replicate populations, such that any plastic responses to the new environments are not counted as evolution. Prior to these evolvability assays, each of the replicate populations evolved for 50,000 generations in the static, heterogeneous (fluctuating without cues), and plastic (fluctuating with cues) with standard parameters. Angle increases clockwise from the *y*-axis, such that 45° represents an environment selecting for an equal increase in both traits, and −45° selects for an increase in trait 1 and an equivalent decrease in trait 2. Bars depict 95% confidence intervals.**

by mutation, as well as the sum of the absolute value of those perturbations in expression level. Although the average number of genes perturbed by a mutation is only slightly greater in plastic networks (9.65 vs. 9.54 for static [$P = 0.0176$] and 9.51 for heterogeneous [$P = 0.018$]), the mean effect of these perturbations is twofold greater in plastic networks (summed absolute deviation is 0.095 vs. 0.047 for static [$P < 3 \times 10^{-16}$] and 0.045 for heterogeneous [$P < 3 \times 10^{-16}$]).

Taken together, these results suggest that plastic networks are more phenotypically variable because the steady states of their computational networks are much more sensitive to mutation. Because each mutation may affect the steady-state expression of many genes, each of which may contribute to either or both traits, this sensitivity creates mutational variability both along the 45° axis and at adjacent angles. However, because there is little signature of this sensitivity in the connectivity of the networks, this sensitivity must result from the detailed wiring of the network. Finally, we note that in these evolved plastic networks, the steady-state expression levels of all of the $S-E$ genes that may contribute to phenotype change over the range of evolved cues (−0.5 to 0.5). This confirms that, in our model, plasticity evolves not as a single pathway within a fixed network but as a global feature distributed over the dynamics of the entire network.

## Discussion

Finding the reasons for the maintenance of biodiversity is one of the key goals of evolutionary biology. Organisms vary because they have different genotypes, because they are exposed to different environments, and because their different genotypes often have different responses to various environments. Genetic variance ultimately derives from new mutations, but the effects of these mutations depend on the details of the developmental systems of the organisms that carry them. In this article, we have shown that the evolution of phenotypic plasticity in response to environmental heterogeneity may in turn affect the nature of

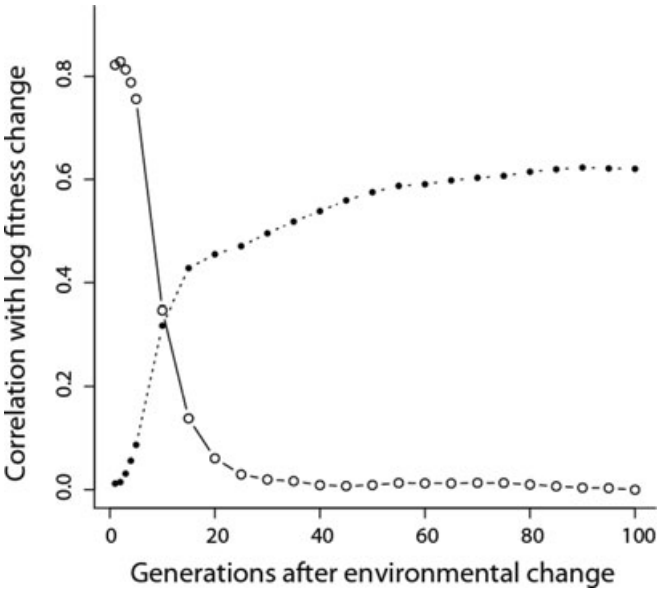


**Figure 7.** **Total additive genetic variance (open circles) predicts evolvability at short time scales, whereas total mutational variance (filled circles) predicts evolvability over longer periods. For each of 250 populations at each of the seven test environments, we calculated the average genetic variance and mutational variance and calculated the Spearman-rank correlations of these measures with the mean net log fitness improvement for various time points after the population was challenged with a new environment. Each point integrates the total change in fitness up to that time. Data shown are for plastic populations; data for static and heterogeneous conditions qualitatively similar (see Fig. S7).**

subsequent mutations, heritable standing variation, and future evolution in the population. We suggest that a phenotypically plastic response to multivariate selection will predispose the developmental system to make it easier to vary genetically for traits affected by plasticity. As a result, the effects of mutation and the genetic variance–covariance patterns of a population can be skewed toward the axis of greatest plasticity. Populations that have evolved plasticity may also respond initially to future selection in new directions more rapidly than do populations that are more static. However, the **G** matrix does not predict the relative response to selection for more than a very few generations (Figs. 7 and S7). Developmental network models connect the effects of new mutations intimately to the evolutionary context of those mutations, such that the effects of alleles can vary substantially with the continued evolution of the developmental system. As a result, the specific details of genetic covariance encoded in **G** need not be very predictive of medium to long-term evolutionary trajectories.

Quantitative genetic theory (Lande 1976; Schluter 1996) predicts that the response to selection will be biased toward the direction that has the greatest genetic variance. From a **G** matrix perspective, the direction in trait space with the greatest genetic variance is the leading eigenvalue of the **G** matrix. This eigenvalue of **G** has been called $g_{max}$ by Schluter (1996), who also showed that over five known cases, the evolutionary divergence of species or populations was usually more pronounced along the direction predicted by $g_{max}$ than expected by chance, as also found by McGuigan et al. (2005) and Renaud et al. (2006). This is the expected result if selection is constrained by genetic variance.

However, as Schluter (1996) points out, it is also the pattern that we might expect if the evolution of **G** itself is changed through the process of selection. At least two alternative processes have been suggested to explain why $g_{max}$ and divergence may coalign. First, migration between diverging populations may create genetic variation in the direction of divergence (Schluter 1996; Guillaume and Whitlock 2007). Second, correlational selection within a population may favor a developmental system that covaries along the pattern of fit genotypes (Schluter 1996). Jones et al. (2007) investigated this second hypothesis, and showed that the mutational covariance (and therefore the **G** matrix) can evolve to give greater variation in the direction of ridges in the pattern of correlational selection.

In this article, we have suggested a special case of this second alternative, where selection is heterogeneous over time but the optima of two traits are correlated. Phenotypic plasticity focuses genetic variation along the line of selective correlation to a much greater extent than the correlations between changing trait optima experienced by the populations without predictive cues (see Table 1). Thus, $g_{max}$ may correlate with divergence not only because of the faster response to selection in that direction, but because the functional relationship between the phenotype and environment causes the genetic variation in a phenotypically plastic population to align with the most likely direction of selection in a new environment. However, we have found that these correlations in standing genetic variation do not predict faster evolution along major axes after about 20 generations.

Under most circumstances, we have found that the mutational variance and the standing additive genetic variance for the traits increases with plasticity relative to populations in heterogeneous environments, but without plasticity. What might be the cause of this extra variance? We believe that the increased variance is a consequence of less effective stabilizing selection acting against genotypes that deviate from the optimum in any given environment, so that selection is less effective in removing extreme phenotypes. We think there are three, nonexclusive possibilities for why this selection is less effective with plasticity. First, selection in any given environment is less strong when that environment only appears infrequently. If the selective effects of alleles are not perfectly positively correlated in all environments, then selection is weaker against any given allele on average than it would be in a static environment (Kawecki 1994; Fry 1996; Holt 1996;

Whitlock 1996; Snell-Rood et al. 2010). Second, if the fitness effects of alleles are negatively correlated among environment, then the average response to selection would be weaker than in a static environment. (These first two hypotheses basically correspond to the main hypotheses for the evolution of senescence; Holt 1996.) These two hypotheses seem unlikely to be the full explanation, however, because we observe no corresponding increase in variance in the populations that are exposed to heterogeneous environments without environmental cues.

The third hypothesis is that the evolution of plasticity under strong selection allows evolution of weaker deleterious pleiotropic effects. The same alleles that may affect plasticity also have the potential to affect the traits themselves. As a result, an allele with strong favorable effects on plasticity may increase in frequency, but that allele may also by chance decrease the mutational canalization of the trait. If selection on plasticity is strong, the net selective effect of the allele may be positive, even if it also somewhat reduces the fitness of the individual by increasing variance around the optimal trait. These effects need not be universal, in the sense that it may be possible to evolve a genotype that responds adaptively to environmental cues but without an increase in mutational variation, and this genotype may be most fit. It may be difficult for the evolving population to find such a genotype initially. We observe that the relative increase in mutational variance is greater early in the evolutionary trajectories of these populations and also greater when selection is strongest; both of these observations are consistent with the hypothesis of a transient period of low robustness caused by the pleiotropic effects of mutations selected for plasticity.

Genetic correlations between traits that respond to similar environmental challenges may facilitate evolution to new environments. Consider Figure 8, where we plot the hypothetical optima for two plant traits—water-use efficiency and root-shoot ratio—that vary in their fitness across a moisture gradient. A plant population that evolves over a range of environments that vary in moisture will have trait optima for these two traits that vary predictably, with greater water-use efficiency and larger root-shoot ratios favored in the less wet environment. However, if genotypes from this population are transferred to an even dryer environment, the optimum will shift in a predictable way, toward even larger water-use efficiency and greater root-shoot ratios. Given that the trait optima in a given environment are determined by the functional relationship between the phenotype and environmental factors, it seems likely that in many cases the optimal phenotype in a new environment will often (although certainly not always) be roughly predictable from the variation in the optimum for a previously experienced set of environments. If this is the case, then the correlation between $g_{max}$, mutational variance, and phenotypic plasticity that we have shown lead us to predict that phenotypically plastic populations may harbor genetic variation—and the mutational patterns to create new variation—most greatly in the direction in which that variation is likely to be required.

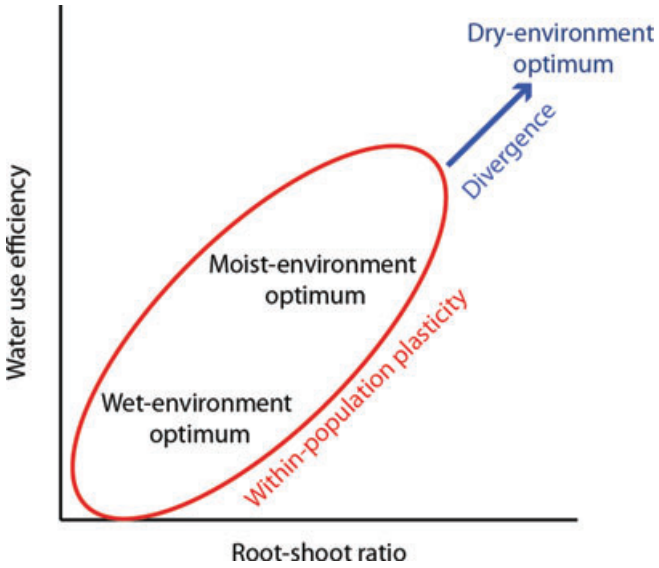


**Figure 8. Patterns of variation in optima among environments may predict future paths of evolutionary divergence. For example, the optimal phenotypes for water-use efficiency and root-shoot ratio are monotonically related to water availability in an environment, so the range of optima within a species' experience can be partially predictive of the optimum in a novel moisture environment.**

Although these correlations are in the right direction, and they can be very strong in the ancestral environment, our tests of evolvability show that such effects are short lived and only affect the response to selection over a few generations. Such short-term effects can be important, however, especially in a population that has recently switched to a new environment. The persistence of a species in a new or changing environment may depend on its rate of adaptation, which is often limited by the amount of genetic variance available (Bürger and Lynch 1995; Gomulkiewicz and Holt 1995; Lande and Shannon 1996). Such persistence may also depend on the ability of an organism to keep pace with its evolving biotic environment; the outcome of competition or other antagonistic ecological interactions may depend on the evolvability of the participants (Yoshida et al. 2003; Carroll et al. 2007; Gilchrist and Lee 2007).

Our model of plasticity differs from previous quantitative genetic treatments of the topic in that plasticity and the traits themselves are allowed to evolve as a consequence of the outcome of an explicit and evolving developmental network. Although we make no claim that this model matches biological reality, in this model the traits, their correlations, and their responses to the environment evolve as a natural part of an interacting network, rather than being determined by fiat. As a result, we were less likely to build subconscious bias in to the model, and it can

also show richer, and more biological, behavior. The conclusions therefore vary from the usual outcomes of quantitative genetic models in several ways. For example, we find that each naturally defined trait is more likely to evolve useful genetic variation than is an arbitrarily defined linear combination of traits, which is not true with the artificially defined bivariate normal distribution assumed in typical quantitative genetic models. In our models, the distribution of mutational effects on phenotypes evolves as a consequence of the developmental model, rather than by top-down assumption. Therefore, the observed distributions of mutational effects may better reflect how developmental mechanisms evolve to shape pleiotropy, and therefore make more realistic predictions.

These developmental models show great promise for the study of phenotypic plasticity itself. It will be straightforward to add realistic cost functions, feedback between the traits and development, and feedback between the match between phenotype and environment with development.

Our models make several predictions that should be amenable to empirical study. We predict that populations that have evolved plastic responses to the same environmental gradients for two or more traits should show genetic and mutational correlations among those traits in the same direction as their plastic responses. In particular, this genetic correlation should be stronger than in populations or species without the correlated plasticity. We predict that divergence among populations will often correlate with plastic responses to similar environments within populations.

## ACKNOWLEDGMENTS

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## *Supporting Information*

The following supporting information is available for this article:

**Table S1.** Mean genetic and mutational variances and correlations for the parameter values in Table 1 and four variants sets.

**Figure S1.** Plasticity evolves over long periods of selection in a fluctuating environment.

**Figure S2.** Distributions of genetic and mutational variances and correlations after 250,000 generations.

**Figure S3.** Distributions of genetic and mutational variances and correlations after 250,000 generations of weak selection.

**Figure S4.** Plasticity increases the initial mean fitness in environments with selective gradients near 45°.

**Figures S5.** Evolvability for weak selection ($\omega = 0.8$) after 250,00 generations.

**Figure S6.** Example mutant distributions for replicates of the static (left column) and the plastic (right column) populations.

**Figure S7.** Correlations between additive genetic variance (open symbols) and mutational variance (black symbols) with the net increase in log fitness, as a function of time because the selective environmental switch.

Supporting Information may be found in the online version of this article.

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