RESEARCH PAPER

Phenotypic variability can promote the evolution of adaptive plasticity by reducing the stringency of natural selection

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Abstract

Adaptive phenotypic plasticity is a potent but not ubiquitous solution to environmental heterogeneity, driving interest in what factors promote and limit its evolution. Here, a novel computational model representing stochastic information flow in development is used to explore evolution from a constitutive phenotype to an adaptively plastic response. Results show that populations tend to evolve robustness to developmental stochasticity, but that this evolved robustness limits evolvability; specifically, robust genotypes have less ability to evolve adaptive plasticity when presented with a mix of both the ancestral environment and a new environment. Analytic calculations and computational experiments confirm that this constraint occurs when the initial mutational steps towards plasticity are pleiotropic, such that mutant fitnesses decline in the environment to which their parents are well-adapted. Greater phenotypic variability improves evolvability in the model by lessening this decline as well as by improving the fitness of partial adaptations to the new environment. By making initial plastic mutations more palatable to natural selection, phenotypic variability can increase the evolvability of an innovative, plastic response without improving evolvability to simpler challenges such as a shifted optimum in a single environment. Populations that evolved robustness by negative feedback between the trait and its rate of change show a particularly strong constraining effect on the evolvability of plasticity, revealing another mechanism by which evolutionary history can limit later innovation. These results document a novel mechanism by which weakening selection could actually stimulate the evolution of a major innovation.

KEYWORDS

constraint, developmental noise, evolvability, phenotypic plasticity

| INTRODUCTION 1

Phenotypic plasticity is an intuitive solution to the problems posed by environmental variation. Imagining the advantage possessed by an organism that could developmentally produce the optimal phenotype for any environment motivates inquiry into what barriers prevent species from too closely approaching this ideal. Following DeWitt, Sih, and Wilson (1998) and other reviews (Auld, Agrawal,

& Relyea, 2009; Murren et al., 2015), these barriers can be categorized into costs and limitations. A genotype that can produce a plastic phenotype may incur a cost when compared to another genotype that produces the same phenotype constitutively; these costs may stem from the burden of sensory organs, developmental mistakes or instability, or deficiencies of a hastily produced phenotype in comparison to a constitutive response. Given such costs, plastic generalists might be outcompeted by specialists that commit to a

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particular developmental trajectory. Further, the evolutionary success of plasticity can also be proscribed by constraints or limitations: inabilities to realize the full range of optimal phenotypes demanded by a complex, changing environment. For example, an animal might not be able to both produce an aggressive behaviour in response to one situation and behave passively in response to another because of the constraints imposed by the shared neurological and hormonal bases of the two responses. As the hypothesized costs of plasticity have typically been hard to observe (Auld et al., 2009; Van Buskirk & Steiner, 2009) and are empirically entangled with the adaptive benefits of plasticity in nature have tended to focus on understanding limitations. The focus of this study is to model how pleiotropic limitations or constraints can impede the initial evolution of an adaptive plastic response.

Plasticity has long been hypothesized as a catalyst for evolutionary change, driving empirical and theoretical approaches to mapping the limitations on its evolution. Plastic responses frequently vary among related species in slope and curvature (Murren et al., 2014), suggesting that evolution refines the shape of plasticity as closely related species diversify; plasticity may also catalyse speciation (Pfennig et al., 2010). Plastic responses can become fixed differences between species through genetic accommodation and permit persistence across a diverse niche (Schneider & Meyer 2017), and the factors allowing traits to vary with environmental cues can potentially be repurposed to build novelties (Moczek et al., 2011). These same factors make plasticity an attractive predictor of which species might be best able to tolerate stressors like climate change or adapt to them; for example, variation in plasticity explains differences in persistence in response to climate change among plant taxa in Thoreau's woods (Willis, Ruhfel, Primack, Miller-Rushing, & Davis, 2008). In plants, invasive species tend to be more plastic (Davidson, Jennions, & Nicotra, 2011), although questions remain about inferred causal connections between plasticity and invasion success.

Several modelling approaches have suggested that populations that have evolved to produce a plastic response are more evolvable in response to environmental change (Ancel & Fontana 2000; Espinosa-Soto, Martin, & Wagner, 2011; Fierst, 2011), and experiments have found some support for this correlation empirically (Schaum & Collins 2014; Noble et al. 2019). Plasticity also mediates evolution by hiding genetic variation from natural selection. For example, selection against a plastic response-favouring, for example, uniform size across a temperature gradient-can lead to hidden genetic divergence across space (Conover & Schultz, 1995) or a cryptic adaptive response to environmental change (Merilä, Kruuk, & Sheldon, 2001). Variation in the shapes of reaction norms constitutes a form of hidden or cryptic genetic variation which can be revealed when a population encounters a novel environment (Schlichting, 2008), and understanding local variation in plastic responses is a requirement for accurate prediction of range shifts due to climate change (Valladares et al., 2014). That plasticity can both cause phenotypic variation and also hide it has led to an ongoing debate over the circumstances that link plasticity to higher evolvability

(Ghalambor, McKay, Carroll, & Reznick, 2007; Schaum & Collins 2014). It is clear that understanding which traits and organisms are likely to display plasticity is vital to making accurate predictions about how populations adapt to novel circumstances.

Models of limitations on the evolution of plasticity vary in both the treatment of populations and in the nature of the links between genotypes, environments and phenotypes. Approaches to modelling the evolving populations include quantitative genetics (Via & Lande. 1985; De Jong, 1990; Van Tienderen et al. 1991; Gomulkiewicz & Kirkpatrick, 1992; Gavrilets & Scheiner, 1993; Lande, 2009), adaptive dynamics (Ernande & Dieckmann, 2004) and population genetics (Draghi & Whitlock, 2012; Gomez-Mestre & Jovani, 2013; Leimar, Hammerstein, & Dooren, 2006; Scheiner & Holt, 2012; Svanbäck, Pineda-Krch, & Doebeli, 2009). Models also differ in whether the plastic trait arises from the interactions of explicit loci (e.g. Scheiner & Holt, 2012) or is allowed to vary without genetic constraints (e.g. Ernande & Dieckmann, 2004). Each approach has confirmed some intuitive expectations (Ghalambor et al., 2007; Hendry, 2015) but also revealed surprises; for example, a lack of predictability of the selective environment can impede the evolution of plasticity (Gavrilets & Scheiner, 1993) but also, when environmental change is sufficiently unpredictable, select for plasticity as a mechanism of diversifying bet-hedging (Scheiner & Holt, 2012).

A major cause of this diversity in approaches is the complex role of pleiotropy in models of plasticity. The traits produced by a single genotype across multiple environments can be considered as separate traits correlated by pleiotropy in their underlying genes (Falconer, 1952), or as the expression of a functional relationship between continuous environmental variables and quantitative traits (Gomulkiewicz & Kirkpatrick, 1992). The insights gained from a modelling approach also depend on which features are allowed to evolve and which are held constant. Quantitative genetics is an ideal modelling framework for predicting the effects of pleiotropy on traits under selection, but provides no path towards understanding how mutational pleiotropy can itself evolve to modify or break constraints. Models with explicit genetics and genotype-phenotype relationships solve this problem by allowing these correlations to evolve, though at the cost of relying on simplistic or toy models that may be difficult to generalize. For example, Scheiner and Holt (2012) studied a model with both plastic and nonplastic loci and tuned the number of each to control pleiotropy among new mutations; Draghi and Whitlock (2012) used a developmental model that computed phenotypes from environmental inputs and genetically encoded connections between nodes in a computational network.

Although these theoretical studies have shed light on the ecological circumstances that allow plasticity to render a benefit, less theoretical attention has been paid to the factors that might specifically stall or block the early stages of the evolution of a plastic adaptation. Here I focus on the scenario of how plasticity might evolve in a population that is well-adapted to one environment and then encounters patches of a second environment requiring a different optimal phenotype, and distinguishable from the ancestral environment via an informative cue. This general scenario might describe a number of possible circumstances such as range expansion across a heterogeneous landscape, the evolutionary emergence of heterogeneity in a resource or host, or migration of competitors into some portion of a range. Two additional stipulations make this scenario more specific: first, I model the case in which the environmental cue that serves to signal the appropriate response differs only in degree, not in presence, between the two environments. Therefore, a mutation that causes the developmental process to become sensitive to this cue will show pleiotropy-affecting the trait in both environments-and therefore reduce fitness in the environment for which the phenotype was already optimal. A second premise of the model is the assumption that the initial mechanisms for sensing signals and producing responses are likely to have limited acuity and precision, leading to stochastic expression of the phenotype. This principle is embodied by the metaphor of genotypes as computer programs that stochastically execute instructions; the model is a simplified programming language using fuzzy logic in a representation of the inherently stochastic biology of sensing and responding to signals. This approach follows in a tradition of using algorithms for information processing inspired by computer science to stand in for the unknown complexities of genotype-phenotype maps, including gene network models using the framework of neural networks (starting with Wagner, 1996) and the AVIDA system, in which computer programs compete for space in virtual ecosystems (Ofria & Wilke, 2005). The promise of this kind of approach is that such models capture high-level, abstract features of genotype-phenotype relationships like epistasis and degeneracy (many genotypes coding for each distinguishable phenotype). Validating this potential, such approaches have yielded general insight into evolutionary topics like mutational robustness (Bergman & Siegal, 2003), evolvability (Draghi & Wagner, 2009), complexity (Adami, Ofria, & Collier, 2000) and plasticity (Fierst, 2011).

Using this simulation model along with analytic formula for mean fitness, I investigate how robustness to intrinsic noise evolves and limits the evolution of a plastic response. I find that the evolution of robustness to this development stochasticity sharpens the focus of natural selection, consequently limiting the success of early mutational steps towards an adaptive plastic response. After demonstrating the generality of this effect in an analytic framework, I test if phenotypic variability predicts evolvability for plasticity in my computational simulations, and if the cause of this correlation is specific to the effects of phenotypic noise on selection. After a preliminary finding that the evolution of increased robustness to noise does impede the evolution of plasticity, I derived six secondary predictions that would specifically support my hypothesized mechanism for this link. These are: (1) robustness to phenotypic variability should be correlated with low ability to evolve plasticity, (2) genotypes must be able to produce plastic mutations regardless of phenotypic variability, (3) plastic mutations should generally show pleiotropy, (4) weaker selection should improve evolvability for plasticity, (5) low phenotypic variability should not be generally associated with low evolvability in other contexts and (6) deleterious mutations should not be required intermediaries in the evolution

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of plasticity. The second prediction stems from the hypothesis that the primary effect underlying the observations is not merely a developmental constraint that limits plastic mutations to more variable genotypes; the third prediction follows from the premise that pleiotropy constrains the fitness of plastic mutations. The fourth expectation-that weaker selection will improve evolvability for plasticity-is based on the idea that increasing phenotypic variation is mathematically similar to increasing the width of the Gaussian fitness function, whereas the fifth and six hypotheses delimit my specific hypothesis for how stochastic variability reshapes selection on plastic mutants. My results confirm each of these hypotheses within the scope of this computational model. Together, these results highlight a potentially generic and novel pathway by which random phenotypic variability can stimulate innovation and show that this hypothesis explains constraint in a complex model of developmental information processing.

2 | MODEL & METHODS

Below I first derive an analytic simplification of fitness in a heterogeneous environment and analyse the effects of phenotypic variability on mutations conferring plasticity. In the subsequent section, I motivate the design of a computational model designed to explore phenotypic variability and the evolution of plasticity, then proceed to a detailed description of its methods.

2.1 | Analytical formula for selection on plastic mutants

Consider an organism that produces a focal trait *z*, which takes on continuous, nonnegative values depending on the genotype, environment and random factors. Assume that the distribution of phenotypes can be modelled as Gaussian with a mean μ and a variance σ^2 . The environment imposes selection which is also modelled as a Gaussian function; specify the width of the selection function with the variance parameter σ^2_{opt} , the optimal phenotype in environment 1 as $z_{opt}(1)$ and the optimum in environment 2 as $z_{opt}(2)$. The mean fitness of a Gaussian distribution of phenotypes under Gaussian selection is the solution of the following integral:

$$\bar{\omega}\left(\mu,\sigma^{2}\right) = \frac{1}{\sigma\sqrt{2\pi}}\int_{-\infty}^{\infty} \exp\left(-\frac{\left(z-z_{opt}\left(1\right)\right)^{2}}{\sigma_{opt}^{2}}\right) \exp\left(-\frac{\left(z-\mu\right)^{2}}{\sigma^{2}}\right) dz \quad (1)$$

The solution of Eq. (1) yields a useful, classical result (e.g. Lande, 1976; Bull 1987) for mean fitness in a single environment:

$$\bar{\omega}\left(\mu,\sigma^{2}\right) = \exp\left(-\frac{\left(\mu_{\text{opt}}-\mu\right)^{2}}{2\left(\sigma_{\text{opt}}^{2}+\sigma^{2}\right)}\right)\frac{\sigma_{\text{opt}}}{\sqrt{\sigma_{\text{opt}}^{2}+\sigma^{2}}}$$
(2)

To extend this model to a heterogeneous environment, consider that within a generation individuals have a probability p to live and experience selection in environment 2 and a probability

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(1 - p) to experience environment 1. Offspring from each environment enter a common pool, then disperse randomly among environments to form the next generation of adults; this population model corresponds to the hard selection model considered in Via and Lande (1985). The mean fitness of a genotype with mean phenotypes $\mu(1)$ in environment 1 and $\mu(2)$ in environment 2 and phenotypic variances $\sigma^2(1)$ in environment 1 and $\sigma^2(2)$ in environment 2, is therefore the weighted arithmetic average of its mean fitness in each environment:

$$\bar{\omega} = p \exp\left(-\frac{\left(\mu_{opt} - \mu\left(1\right)\right)^{2}}{2\left(\sigma_{opt}^{2} + \sigma\left(1\right)^{2}\right)}\right) \frac{\sigma_{opt}}{\sqrt{\sigma_{opt}^{2} + \sigma\left(1\right)^{2}}} + (1-p) \exp\left(-\frac{\left(\mu_{opt} - \mu\left(2\right)\right)^{2}}{2\left(\sigma_{opt}^{2} + \sigma\left(2\right)^{2}\right)}\right) \frac{\sigma_{opt}}{\sqrt{\sigma_{opt}^{2} + \sigma\left(2\right)^{2}}}$$
(3)

To understand the link between phenotypic variability and the evolution of plasticity, consider the competitive fitness of mutants arising in a population of organisms that meet two criteria: they are well-adapted to a single environment (environment 1) and express no latent plasticity if exposed to other environments. I then analyse the effects of two other determinants of mutant fitness: pleiotropic effects that link a mutant's effects in environments 1 and 2, and the phenotypic variability expressed by both the resident and mutant genotypes. Figure 1 illustrates a hypothesis that mutations conferring some initial quantity of plasticity face two issues in competing with resident types well-adapted to a single environment: mutants may have reduced fitness in environment 1 through pleiotropic effects, and they may fail to gain much fitness by producing a phenotype in environment 2 that falls short of $z_{out}(2)$. Greater intrinsic variability in the resident and mutant phenotypic distributions would serve to mitigate both problems by effectively broadening the fitness function around each optima, which is illustrated as follows. The landscape plot of mutant fitnesses in Figure 1(d), drawn from comparisons of mutant and resident mean fitnesses computed with Equation 3, show that low-variability genotypes depend on mutations with both a high degree of accuracy to the optimum phenotype in environment 2, and a low pleiotropic side effect on the trait in environment 1. Figure 1(d) shows that both restrictions are relaxed as the variability of the resident genotype increases. One implicit assumption of this analysis is that the mutant and resident have the same degree of phenotypic variability; increased variability in the mutant might still improve its fitness in the novel environment, but would introduce a new cost in the ancestral environment due to the relative imprecision of the mutant compared to the resident.

Pleiotropy is a common feature of models of plasticity that consider a linear reaction norm where the mean phenotype is determined by the addition of an intercept parameter and the product of a slope parameter and an environment cue value. Under this



FIGURE 1 An illustration of the fitness effects of correlated mutations in genetic backgrounds with different degrees of phenotypic variability. (a) Fitness landscapes in environments 1 and 2. (b) A pleiotropic mutant in a low-variability genotype (σ = 75) that produces a plastic response of ($z(1) = z_{opt}(1) + 150$, $z(2) = z_{opt}(1) + 750$; there is a pleiotropic response in z(1) to the plastic response in z(2). Dashed lines illustrate the distribution of the mutant phenotypes in both environments in comparison to the resident type, shown in solid lines, which is well-adapted to environment 1. This mutant gains little fitness in environment 2 and loses more fitness through its effects in environment 1; the combination of a small benefit in environment 2 and a large cost in environment 1 make this mutation deleterious. (c) The same mutant as in (b), in a genetic background with higher variability (σ = 150). (d) Fitness of mutants with the change in z(2) indicated on the x-axis, and a correlated proportional increase in z(1) as indicated on the y-axis, for three different variability backgrounds. The example mutation shown in panels (b) and (c) is marked with a cross. Resident and mutant types are assumed to have the same values of σ for these calculations, which are made using Eq. 3 for p = 0.5. Deleterious mutants are defined as having selection coefficients s < -0.001; nearly neutral have $-0.001 \le s < 0.001$, moderately beneficial have $0.001 \le s < 0.1$, and highly beneficial have $s \ge 0.1$. Note that 'ideal plastic mutations'—those with no pleiotropy and exactly the correct change in z(2) – are always beneficial; it is those mutations that fall short of the ideal in either size or pleiotropy that can be flipped from deleterious to beneficial with higher variability

parameterization, a change to either the slope or intercept term affects the trait across all environments (excepting that the trait value when the cue equals zero is not affected by changes in slope). This kind of model has been used frequently in studies of the evolution of plasticity (e.g. De Jong & Gavrilets, 2000; Lande, 2009; Leimar et al., 2006; Scheiner, 2013), though critics note that other parameterizations can produce different results (Ergon & Ergon, 2017). Although a change to either the slope or intercept term is pleiotropic, such models should not be taken as a statement that distinct sets of genes control the slope or intercept (de Jong, 1990); rather, such models reflect the idea that genes may affect both trait means and their sensitivities to environmental cues, causing pleiotropy among trait values in different environments. Because only two environments are considered here, the degree of pleiotropy can be captured by a single parameter without invoking this assumption of a linear reaction norm.

This analysis shows a general argument connecting phenotypic variability with the evolution of plasticity in a scenario mimicking niche expansion: a population without a history of plasticity encounters a new, distinct environment. Using the computational model below, I applied this idea to understand simulations of this same scenario with a much more complicated genotype-phenotype mapping and the full complexities of an individual-based population simulation.

2.2 | COMPUTATIONAL MODEL OF DEVELOPMENT WITH NOISE

2.2.1 | Motivation & design considerations

My computational model was designed to represent the flow of information from the detection of a stimulus through to gene regulation and ultimately the production of a trait across developmental time. This information flow is simulated as the execution of a virtual computer program in a highly simplified language; an individual's genotype determines this program, and its phenotype is produced by executing that program. This representation of development is clearly quite abstracted from the biology of gene regulation and expression, and its value depends on how well it captures relevant and generic features of biological information processing. This model was designed to represent three features that might generally characterize the early evolution of an adaptive plastic response. These are: that the evolution of plasticity involves increased sensitivity to some environmental cue, that some degree of noise or randomness affects each stage in the detection and processing of a cue and the organism's response and that the complexity of the plastic response should be allowed to vary via mutation.

This first feature–sensitivity to a cue–is represented in the model by an external cue: a positive real number that is tightly correlated with the optimal trait value in a given environment. The relevance of this modelling choice becomes clear when we imagine the evolution of plasticity unfolding in two stages. First, a population is challenged to adapt to a single, constant environment, in which the cue has a non-zero value but is not informative. Then, the population RNAL OF EVOlutionary Biology 🟑

is exposed to a mix of this older environment and a novel habitat in which both the cue and the optimal phenotype are significantly larger. If the expression of a mutation that causes the organism to become sensitive to the cue is pleiotropic—affecting the phenotype in both environments—then that pleiotropy could constrain or complicate the evolution of plasticity by creating maladaptation in the environment to which the organism is already well-adapted.

The second major feature of the model's design is noise. As detailed below, the fuzzy logic encoded in the mechanics of the virtual programs introduces randomness in both the ascertainment of a cue and the realized response. The degree of this noise, and its consequences for phenotypic variability, can mutate and be tuned by natural selection. A previous publication explored how noise can mutate and evolve in a complex and more realistic model of gene expression (Draghi & Whitlock, 2015); here I simplify that approach to focus on the general phenomenon of random variability in biological systems and its potential effects on the evolution of plasticity.

The third desired feature is that a plastic response should not be constrained to a prespecified function, such as a linear reaction norm, but allowed to evolve along a spectrum from simple to complex. The model attains this goal by allowing the complexity of the underlying virtual program to mutate and evolve by rough equivalents to insertion and deletion mutations. Each program is made up of a series of instructions, and an instruction may be tweaked by mutation, deleted, or added *de novo* from a space of random instructions. This variety of mutation effects allows genotypes and the corresponding reaction norms to change in complexity when such changes are beneficial.

2.2.2 | Genotype-phenotype model

Each genotype contains instructions that direct a developmental process to produce a single trait, *z*; every genotype has the potential to use a cue, *y*, from the environment in this developmental process. At the beginning of development, *z* was set to zero or, in specific simulations, to a random value from a Gaussian distribution; *y* was set by the environmental condition of the organism's development and did not change over the course of that development. The development of the trait *z* was determined by executing the program contained in that organism's genotype. To simulate random influences in development, several aspects of the behaviour of these programs are determined stochastically in accordance with mutable noise parameters.

A genotype consists of an ordered list of instructions of three possible types, each illustrated in Figure 2. Addition instructions add (or subtract) a Poisson-distributed random number to the current value of z. An addition instruction is defined by its sign (positive or negative), the mean of the Poisson and a coefficient which multiplies the result of the Poisson, as well as by its location in the program. The second type of instruction is a *goto* statement; when executed, these statements cause the execution of the program to jump to another line. *Goto* statements are defined by their location in the code, the location to which they direct execution, and a third parameter defining a chance of success; in the case of failure,



FIGURE 2 Examples of evolved genotypes (programs) and phenotypes (trait distributions). Top: An ancestor (program A; dark grey distribution) and evolved descendant (program B: light grey distribution) subject to stabilizing selection in one environment (the black line represents the fitness function). The numbers in brackets after conditional statements measure their specificity; the range shows values of the variable that cause the statement to evaluate as true with 10% and 90% probability, respectively. Bottom: An ancestor (C; dark grey) and evolved descendant (D; light grey) subject to stabilizing selection with distinct optima in two environments

execution of the program instead moves to the next line. The final type of instruction is a *conditional* statement. These statements execute the next line of code if a condition is met; otherwise, program execution skips the following line and continues with any subsequent lines. In a typical programming language, a conditional statement might compare a variable to a constant and then direct program flow based on whether the variable was larger or smaller than the constant. Here, conditional instructions apply a sigmoid function to the difference of a variable and a constant to produce a probability; a Bernoulli trial is then performed with that probability to determine whether the subsequent line should be executed or skipped. This essentially produces a 'fuzzy' version of an if-then statement, with the chance of an error being proportional to the difference between the variable and the number it is compared to. Conditional instructions are defined by three parameters: the focal variable, which is either the trait z or the cue y, a value to which that focal variable is compared, and a parameter determining the steepness of the sigmoid function near zero. Let x stand for either the phenotype **z** or the environmental cue **y**, *a* stand for the sign of the comparison (i.e. when a is positive, the condition tests if the variable is greater than the constant), let *b* stand for this steepness parameter and *c* stand for the constant against which the variable is compared. The probability that the condition evaluates as 'true' and the subsequent line is executed as:

$$p_{\text{true}} = \frac{1}{1 + e^{-ab(x-c)}} \tag{4}$$

Program execution begins with a genotype's first instruction and continues until either the last line is executed (without a redirection from a *goto* instruction) or until a preset maximum number of executed lines is reached. This maximum is sixty for all the results shown here.

Goto and conditional statements do not individually correspond to any obvious feature of biological regulation; they were implemented in this simplified language because, in combination, they can produce both positive and negative feedback loops. To make sure that evolving programs could readily produce new loops by mutation, I allow for a special mutation operator described below that introduces a *conditional* statement and a subsequent *goto* statement in a single mutation. This feature essentially allows a new regulatory loop to emerge via a single mutational step.

2.2.3 | Reproduction and selection

Reproduction is asexual and based on the Wright-Fisher model of a fixed population size *N*. The next generation is formed by selecting a parent for each of *N* offspring. Each parent is drawn with replacement from a multinomial in which each member of the parent generation

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has a chance to be selected proportional to their fitness, regardless of the environment occupied by that parent. This procedure is often labelled as 'hard selection' because the two environments do not have individual carrying capacities, but rather contribute offspring to a single pool with a single carrying capacity *N*. Two factors would make the inclusion of recombination here problematic: the model does not have an explicit chromosome arrangement of genes, and genotypes in the same population might differ in the lengths of their genetically encoded instructions. I therefore did not pursue variants of the model with sexual reproduction. An individual's fitness is based on the phenotype, *z*, produced by the execution of their genotypic program and the Gaussian fitness function below.

$$w = \varepsilon + (1 - \varepsilon) \exp\left(\frac{-(z - z_{opt}(x))^2}{\omega^2}\right)$$
(5)

Here ω is a constant inversely proportional to the strength of stabilizing selection, x indicates the selective environment, and ε is a small constant, set to 1×10^{-6} , which ensures that the multinomial sampler is robust to round-off error.

The default choices of fitness-function parameters are $\omega^2 = 10,000, z_{opt}(1) = 1,000$ and $z_{opt}(2) = 2,000$. The cues provided in each environment are similarly y(1) = 1,000 and y(2) = 2,000.

2.2.4 | Generating, mutating and testing genotypes

Sequences of the three types of instructions explained above constitute genotypes that, when executed as programs, produce phenotypes. Genotypes are randomly created by first drawing a number of instructions from the uniform distribution of integers [1.10]. Each instruction is then chosen to be an addition, conditional, or goto statement with equal probability. The coefficients and Poisson rates for addition instructions are drawn from exponential distributions with default means β_{coeff} = 50 and β_{rate} = 10, respectively; the sign of the instruction is drawn uniformly from [-,+]. Goto instructions succeed with probability $p_{succeed} = 1 - e^{-f}$, where values of f are drawn from an exponential with default mean β_{fail} = 1. Upon creation, a goto instruction's target line is drawn uniformly from the total length of the program, including the new goto instruction itself. Conditional instructions have a sign parameter which is drawn uniformly from [-,+], a slope parameter which is drawn from an exponential with default mean $\beta_{\rm slope}$ = 0.002, and a threshold constant which is drawn from an exponential with default mean $\beta_{\text{threshold}}$ = 1,000.

Mutations can modify an existing instruction, delete it, or insert a new instruction with rates μ_{modify} , μ_{delete} and μ_{insert} . Goto statements point to an instruction, not a line number, and therefore redirect program flow to the same line even if intervening statements are added or deleted. If a goto statement's target statement is deleted, its target is reassigned to an adjacent statement. *Conditional* statements always interact with their subsequent line, such that their behaviour can be changed by an insertion or deletion. Insertion mutations are implemented in two varieties: for one-half of insertion mutations, a new statement is generated as above and added to a uniformly drawn location in the program. For the other half, a pair consisting of a *conditional* statement and a subsequent *addition* or *goto* statement is generating together, as described above, and inserted as a pair. This complex mutation operator is intended to allow a *de novo* regulatory loop to evolve in a single mutational step.

Genotypes are tested by repeated executing their programs and tracking the means ($\bar{z}(1)$ and $\bar{z}(2)$) and standard deviations ($\sigma(1)$ and $\sigma(2)$) of the phenotypes produced in environments 1 and 2. Ancestors for evolution experiments were generated randomly and then rejected if they are too far from the optimum in environment one ($|\bar{z}(1) - z_{opt}(1)| > 50$), too plastic ($\bar{z}(2) - \bar{z}(1) > 50$), or too variable ($\sigma(1) > 800$). The rationale for the first two choices was that I wanted to focus on the evolution of plasticity; the reason behind the third was to exclude extremely unfit genotypes. These statistics are based on at least 10,000 replicate executions of the genotypic program in each environment.

High-fitness genotypes were sampled from populations by first selecting a random sample of fifty individuals, then computing the mean fitness of each sampled genotype in each environment over 10,000 replicates. The individual with the highest mean fitness was then chosen as a representative of the population for further analyses; to avoid bias, its statistics were re-measured with another set of 10,000 replicates and the re-measured values were used to characterize its performance.

In experiments surveying plastic mutations, I simulated the development of each mutant with 1,000 replicate simulations for each environment and screened for mutants that produced a positive plastic response $\bar{z}(2) - \bar{z}(1) > 100$. For any genotypes that met the criterion in this initial screening, I repeated this analysis for 100,000 replicates and averaged the results to more precisely characterize their phenotypes. The purpose of this two-stage procedure was to quickly screen a large number of mutations for their potential to contribute to adaptive plasticity, and then evaluate each candidate mutation at a higher level of statistical certainty. I also performed a modified version of this procedure to assess how phenotypic variability might shift the distributions of the fitness effects of mutations. In these simulations, whose results are shown in Figure S5, Gaussian noise is added to the phenotype of each individual after development and the effects of this noise on both the parent and mutant mean fitnesses are calculated for the case of a heterogeneous environment (both types of environments present in an equal mix). This procedure effectively assays whether a mutation conferring some degree of plasticity would be more likely to be beneficial if it had occurred in a genetic background with a higher degree of phenotypic variability.

2.2.5 | Exploration of the simulation model

To qualitatively explore the evolution of robustness in the simulation model, I applied stabilizing selection for an optimal phenotype of

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 $z_{opt}(1) = 1,000$ to large populations (N = 10,000) of haploid genotypes. Asexual reproduction was accompanied by three types of mutation: an individual's parameters were modified at a rate of 1×10^{-3} /instruction, instructions were deleted at a rate of 2×10^{-4} /instruction, and new instructions were inserted at a rate of 2×10^{-4} /individual. In these initial simulations, each organism was exposed to only one environment with an invariant cue, y(1), and optimal phenotype, $z_{opt}(1)$. I investigated the evolution of plasticity in other simulations by adding the complexity of a second environment with a distinct cue, y(2), and optimum, $z_{opt}(2)$. In each generation, an individual resided in environment 2 with probability p and environment 1 with probability 1 - p; an individual developed and was selected in the same environment, and generations were nonoverlapping with a fixed population size N.

Figure 2 shows examples chosen to qualitatively illustrate how genotypes evolve to produce either a single phenotype or a plastic response. Developmental programs could evolve to become more robust to the internal noise generated by the fuzzy logic of their components. Plastic responses could also evolve and become more robust over time, as exemplified in the bottom of Figure 2. Figure S1 illustrates some of the diversity of reaction-norm shapes seen among genotypes selected for plasticity, confirming that the computational model could produce a variety of nonlinear relationships between the cue and the mean and variability of the trait. These reaction norms give an indication that the pleiotropic effects of a mutation are likely to vary substantially depending on the genotype.

2.2.6 | Measuring the evolvability of plasticity

To measure evolvability, many independent subpopulations were founded using the sampled genotype and allowed to evolve in parallel for a thousand generations in a scenario with within-generation environmental heterogeneity (p = .5). This procedure focuses on measuring the evolvability associated with mutations arising in the context of a single genotype; the alternative of subjecting the entire population to evolution experiments would confound the influence of a genotype's mutational variability with the standing genetic variation present in that population. After a test period of a thousand generations, I measured the evolved plasticity of a high-fitness individual in each test population as the mean phenotype in environment 2 minus the mean phenotype in environment 1; the fraction of populations in which this plastic response exceeded 200 units (20% of the expected optimal response) was taken as a measure of the propensity of a genotype to evolve plasticity in a heterogeneous environment. None of the assayed genotypes had attained significant plasticity in their original, single-environment populations, and changing the threshold of 200 units to larger values did not change the pattern of the results (data not shown).

I also performed a version of this procedure simulating strong selection, weak mutation conditions: each mutation is allowed to fix or go extinct before another is introduced. The purpose of this protocol was to eliminate any possible constructive role for deleterious mutations; this was an important control because phenotypic variability also affects the strength of genetic drift and therefore the chances of deleterious mutations reaching high frequencies. To begin this procedure the mean fitness of a resident genotype is computed over 10,000 trials in each environment. Then, a random mutant is generated from this genetic background and its fitness assessed. If the mutant is more fit on average, it replaces the resident; otherwise it is discarded. In either case, this process is repeated for a set number of cycles (here, 1,000), and the plasticity of the final resident was evaluated. This process was repeated in replicate for each of the two hundred genotypes assayed above, and the mean evolvability for plasticity was calculated and compared to the results obtained from the individual-based simulations reported in Figure 3.



FIGURE 3 Evolution of phenotypic variability (standard deviation of replicate development trials) and the propensity to evolve plasticity. (a) Mean and confidence intervals at four time points for an ensemble of fifty replicate populations (see Methods). (b) Values for each population at t = 100,000 generations (note the change in y-axis scale versus the (a) panel). Variabilities are measured over 100,000 replicate developmental simulations and evolvability is averaged across 500 trials per population

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2.2.7 | Statistical analyses

All analyses were carried out in R v.3.3.3. Generalized linear mixedeffect models were performed using the 'lme4' package v.1.1–15.

2.2.8 | Code and data management

Code for simulating genotypes and populations was written in C. All code, including R scripts and data files, will be archived at the Dryad Digital Repository.

3 | RESULTS

3.1 | The potential for plasticity to evolve decreases as robustness evolves in a homogenous environment

To quantify both the evolution of robustness and the propensity for genotypes to rapidly evolve plasticity (i.e. evolvability for plasticity), I evolved fifty replicate populations under stabilizing selection for a single environment (p = 0). These populations were initiated by randomly producing genotypes and selecting fifty individual ancestors that were close to the optimal phenotype, were not plastic, and were not excessively phenotypically variable—see *Model & Methods* for details. Each ancestor was used to found a distinct population, and populations evolved in parallel for 100,000 generations. A high-fitness genotype was sampled from each population at t = 0, 1,000, 10,000 and 100,000 generations and its phenotypic variability and ability to evolve plasticity in the appropriate environment were measured as described above. Examples of evolved plastic responses are shown in Figure S1.

Figure 3(a) shows the mean phenotypic variability (standard deviation in environment 1) and evolvability for plasticity for the four sampling intervals. There is a clear trend for both variability and evolvability for plasticity to decrease in concert. This trend is also found at lower and higher mutation rates (Figure S2). I explored the possibility of a causal link between variability and evolvability by first performing a more rigorous statistical analysis of these data. As the evolved levels of plasticity is bimodal, with one mode near zero and a second near the optimal value of 1,000, I treated evolvability as a binomial variable within each trial (again using a cut-off of a mean plastic response of 200 units) and calculated the log odds ratio of success for the five hundred replicate trials performed for each examined genotype. I then applied linear regression to this response variable with evolutionary time (generations in the static environment) and variability as predictors (each centred and scaled by their standard deviations). Both variables are highly significant with or without the inclusion of their interaction, and together they capture around half of the variation in evolvability among genotypes (R^2 is 0.487 without the interaction and 0.573 with that term). The predictive value of variability is evident within a time point, as in Figure 3(b), which shows variability and evolvability for the 100,000-generation time point only. Note, however, that there is little relationship between phenotypic variability and evolvability for plasticity among the genotypes at t = 0, before evolution has occurred (Spearman's ρ = 0.07).

The significance of both time and the phenotypic standard deviation suggests that some additional, unknown aspect of the genotype or its dynamics is evolving with the effect of reducing evolvability for plasticity. I considered three candidates-skew of the phenotypic distribution, number of instructions in the genotype, and the mean number of developmental steps (i.e. instructions executed) in the genotype's development. Skew might arise if a genotype's program occasionally executed a line that made a large, positive contribution to the phenotype, and might allow a genotype to produce large, adaptive phenotypes more often than expected from the mean and variance of the distribution. Each variable was added individually to the simpler model (without the interaction) described above. Only the addition of the mean number of developmental steps substantially improved the fit (from an R^2 of 0.487 to 0.686) and lowered the AIC (from 611.9 to 515.5). Removing evolutionary time from this model decreases the R^2 and AIC only marginally (R^2 is 0.672 and AIC is 522.4), suggesting that the number of developmental steps captures most of the information in the time variable.

I then asked whether the mean number of developmental steps was higher in programs that used negative feedback to reduce phenotypic variability. I inferred the presence and strength of negative feedback by perturbing the initial phenotype before development. Although normally the trait value begins at zero, in these assays each individual instead began with a phenotype drawn from a Gaussian with mean of zero and standard deviation of σ_{initial} and was then allowed to develop according to its program. The phenotypic variability in these perturbed genotypes, $\sigma_{\text{perturbed}}$, can be compared to the variability seen in the absence of feedback, σ_{control} . We can then write a measure of the response to this perturbation:

$$r = \frac{\sigma_{\text{perturbed}}^2 - \sigma_{\text{control}}^2}{\sigma_{\text{initial}}^2} \tag{6}$$

Without feedback control, the variance contributed by development is predicted to combined additively with the variance of the starting phenotype. Therefore, the response r is expected to be one for genotypes without feedbacks, with deviations towards zero measuring the extent to which negative feedback diminishes the added variability (values above one would indicate positive feedback). Although initial genotypes show little evidence of feedback control over variability, over time many populations evolve substantially lower values of r (Figure S3) which was associated with more complex development (higher mean number of steps). Figure 4 shows that negative feedback, as measured by Equation 6, is associated with both lower variability and lower evolvability. This figure also explains the bimodality in evolvability and robustness seen in Figure 3(b): most populations have either a high degree of negative feedback or very little. The fit of a linear regression including evolutionary time, variability, and the response variable in Eq. (6) is nearly



FIGURE 4 Relationships between phenotypic variability and the ability to evolve plasticity for genotypes with little (open circles), moderate (grey circles), or strong (black circles) negative feedback. (a) Genotypes sampled from t = 1,000; (b) genotypes sampled from t = 100,000. 'Little' feedback is defined as a response to perturbation above 0.9 (see Eq. 3), 'moderate' as a response between 0.5 and 0.9, and 'strong' as a response below 0.5. Note the different axes ranges between (a) and (b)



FIGURE 5 Evolvability for plasticity under strong (ω^2 = 10,000) and weak $(\omega^2 = 20,000)$ selection, separated by the generation of the sampled genotype

identical to the model with time, variability and mean developmental steps (R² of 0.669 and 0.686, respectively), suggesting that this response measure is capturing the relevant information in developmental complexity.

The main hypothesis detailed in the analytical model is that phenotypic variability is a primary driver of the evolvability of plasticity in this model specifically because of its effects on the balance of selective forces on plastic mutations with pleiotropic effects. To test hypotheses (2) and (3) described in the Introduction, I examined one hundred thousand random single mutations for each of the high-fitness genotypes selected at t = 10,000. Among these mutations, I found no relationship between phenotypic variability and the

ø Correlation • 4 o. 0.35 0.45 0.55 0.65 p (Freq. of env 2) Mean evolvability 0.00 0.06 0.12 0.00 0.35 0.55 0.45 0.65

FIGURE 6 Evolvability depends on both phenotypic variability and the frequency of the new environment. *Top*: Spearman's rank correlation coefficient of evolvability for plasticity and phenotypic standard deviation for genotypes sampled from t = 100,000, across various values of the frequency, p, of the novel environment. Bottom: The mean evolvability for plasticity across these same genotypes

ability to produce plastic mutations with high fitness in environment 2 (measured as the highest-fitness mutant in environment 2 alone; Figure S4(a)). Among mutations that produced a significant plastic response, correlations between the change in z(1) and z(2) were typically high (mean Pearson's r is ~.93) and not correlated with phenotypic variability (Figure S4(b)). I also examined the distribution of potentially beneficial, plastic mutations in more detail for a random set of five populations. Across each of the four time points, I simulated two million random mutations as described above, but also calculated the selection coefficient of those genotypes with the addition of varying amounts of Gaussian noise to both the parental and mutant phenotypes. These selection coefficients were calculated as the average fitness across both environments, representing the relevant fitness landscape for the evolution of plasticity as modelled here. After the initial time point, there is a general trend for additional variability to increase the chances that a mutation is beneficial or highly beneficial (Figure S5). These examples illustrate that many genotypes can produce plastic mutations that would have been beneficial, had they occurred in a genetic background that produced a higher degree of phenotypic variability.

The next expectation-that weaker selection will improve evolvability for plasticity-was tested by repeating the evolvability assay described above with weaker selection (ω^2 = 20,000 rather than 10,000). Evolvability was higher under weaker selection (Figure 5); using nonparametric paired Wilcoxon tests, these differences were significant at all four time points (t = 0: mean evolvability was higher by 29%; t = 1k: mean evolvability was higher by 30%; t = 10k: mean evolvability was higher by 47%; t = 10k: t = 100k: mean evolvability was higher by 77%). To test the evolvability of genotypes in another context (hypothesis 5) I performed short evolvability assays which

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presented populations with a single, shifted environment ($z_{out}(1)$) was shifted to 2000 to present a single, changed environment, while maintaining the value of the cue at 1.000). Evolvability in these simulations was typically high; genotypes with very high phenotypic variability were actually less evolvable, and among evolved genotypes there was a slight deficit in genotypes with very low variability (Figure S6). These results confirm that phenotypic variability has a specific, positive effect on evolvability for plasticity not found in other contexts.

Finally, I tested whether deleterious mutations played a significant role in the evolution of plasticity by repeating the evolvability assays with a version of strong selection, weak mutation conditions (see 'Measuring the Evolvability of Plasticity' above). This comparison, shown in Figure S7, showed that the basic pattern of diminishing evolvability with lower phenotypic variability was preserved using this alternate evolutionary algorithm, in which deleterious mutations could play no constructive role.

3.2 | Pleiotropic effects on performance in the initial environment impose the main limitations on evolvability of plasticity in this model

The evidence in the preceding section is consistent with the hypothesis that phenotypic variability improves the performance of plastic mutants relative to their parent genotypes in both the initial and novel environment, but would also fit a model in which the effects of random variability in one of the two environments are insignificant or even detrimental. I therefore repeated the evolvability assays while varying p, the frequency of environment 2 to allow the relative advantage in environment 2 to vary. The correlation between phenotypic variability and evolvability remains high across a range of values of p, supporting the original hypothesis (Figure 6(top)). However, there is an across-the-board increase in evolvability as the frequency of the novel environment increases (Figure 6(bottom)). Because increasing p diminishes the importance of fitness in the original environment, the pleiotropic effects of plastic mutants on the phenotype in environment 1 must be the primary constraint on the evolution of plasticity. These results also reinforce the inference that phenotypic variability is not correlated with the ability of a genotype to produce a plastic mutation, but instead shapes evolvability by relaxing selection on such mutations.

3.3 Evolutionary history can constrain plasticity by favouring negative feedback

To explore the finding that negative feedback control of developmental noise is associated with lower evolvability for plasticity, I evolved additional populations under conditions that might select more strongly for robustness to noise and negative feedback specifically. Twenty populations evolved in a single environment (p = 0) exactly as above, except that all individuals developed from a random initial phenotype drawn from a Gaussian with σ = 200. These populations did evolve negative feedback more rapidly and to a greater

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FIGURE 7 Populations with noisy initial phenotypes (open circles) evolve greater negative feedback and less evolvability for plasticity. (a) r, the response ratio, is calculated according to Eq. 6 and is based on 100,000 replicate simulations with and without a Gaussian perturbation with σ = 200. (b) Evolvability assays from Figure 3 plotted with similar assays of twenty populations evolved in the presence of Gaussian noise in their initial phenotype

extent (Figure 7(a)) than did the cohort in the original experiment without initial noise. This difference was correlated with a greater decrease in their propensity to be able to evolve plasticity in the appropriate environment (Figure 7(b)).

4 DISCUSSION

The goals of this paper are to focus on selection and mutation in a population faced with a novel opportunity: new heterogeneity in a resource such that individuals may encounter either the new environment or the old, with distinct optimal phenotypes and informative cues characterizing each. The nature of these environments and traits is treated abstractly here, but particularly relevant examples can be found when consumers interact with invasive hosts or prey (Strauss, Lau, & Carroll, 2006). For example, soapberry bugs in Florida show evolutionary differentiation in response to the introduction of a novel plant host (Carroll, 2008). Australian snakes, welladapted to handling native prey, are maladapted to invasive toxic cane toads (e.g. Hagman, Phillips, & Shine, 2009), and may adapt through learning or evolution (Shine, 2012). Another example-the divergence of the apple maggot fly into host races specializing on the native hawthorn and the introduced apple tree-demonstrates divergent selection (Michel et al., 2010) and is well-known as a case study in sympatric speciation in progress. These examples differ from the simple scenario considered here in significant ways-this model considers plasticity evolving from initially nonplastic genotypes, whereas, for example, plasticity across hosts in the soapberry bugs is maladaptive and opposed by genetic differentiation (Cenzer, 2017). Nonetheless, mapping the circumstances favouring the emergence of a plastic generalist may also shed light on when evolution may follow alternative paths such as local adaptation or speciation, contributing to a synthetic picture of how communities react on both fast and slow time-scales to invasive species.

Natural selection drives adaptation, and yet the results presented here show that weakening the ability of selection to discriminate among phenotypes can sometimes accelerate the leap from a single phenotype to a plastic response. A link between relaxed selection and innovation is historically associated with Sewall Wright's ideas of shifting balance: movement between local optima on an epistatic fitness landscape driven by the joint action of drift and selection in small populations (e.g. Wright, 1982). The argument in this paper has superficial similarities to this, with the key difference that the model here does not rely on the fixation or success of deleterious mutations. Here, mutants conferring plasticity are more likely to be deleterious when stochastic variability is low and selection is stringent, and become beneficial when phenotypic variability or relaxed selection blur the fitness differences between a well-adapted parent and a mutant with a perturbed phenotype. This switch in the selective coefficient of mutations, seen most clearly in the simplified calculations presented in Figure 1, occurs because early, imperfect plastic responses must preserve a well-adapted response in one environment whereas radically changing the phenotype in another. Given these constraints, strong selection only exaggerates the imperfections of a partially adaptive, plastic mutant relative to its parental genotype in the original environment. An interesting empirical connection is that relaxed selection has been linked empirically to the evolution of polyphenisms in social insects: Hunt et al. (2011) found that genes recruited to plastically differentiate the phenotypes of insects in different castes or life-stages tended to have a prior history of relaxed selection, as measured by dN/dS. A similar result was found in spadefoot toad tadpole morphs (Leichty, Pfennig, Jones, & Pfennig, 2012). The results here strengthen the case that relaxed selection supports the innovation of a polyphenism and adds a potential mechanism-differences in phenotypic variability-by which the strength of selection in genes or traits may vary across the organism. Some studies have looked for correlations between plasticity and

developmental variability at the level of traits (e.g. Scheiner, Caplan, & Lyman, 1991) and a recent paper has documented such a relationship (Tonsor, Elnaccash, & Scheiner, 2013), reinforcing that greater empirical examination of this relationship would be very productive.

Understanding how constraints on plasticity arise and evolve is aided by the concept of modularity, defined in this context as the degree to which two traits are able to vary and evolve independently (Wagner & Altenberg, 1996). Snell-Rood, Dyken, Cruickshank, Wade, and Moczek (2010) drew attention to the double-edged role of modularity for plasticity: genes with expression limited to only one or a few environments would be free to contribute to plasticity without pleiotropic constraints, but would also experience relaxed selection. Here, the model represents the evolution of modularity as a single set of genetic instructions that evolves to code for distinct traits. Future work could explore how pleiotropy continues to evolve and shape evolvability as parts of the genome experience both relaxed selection due to environment-specific expression, and intensified selection as the organism adapts to produce a less noisy, more precise response in each environment.

In a comprehensive exploration of evolution and plasticity in simulated RNA secondary structures, Ancel and Fontana (2000) noted that phenotypic variability correlated with evolvability because genotypes that produced little variability were also unable to produce phenotypic novelties via mutation. These results exemplify the notion that random phenotypic variation is correlated with a genotype's mutational variation-essentially, that developmental heterogeneity acts as preview of which phenotypes might be expressed constitutively after a mutation (reviewed in Meiklejohn & Hartl, 2002). This hypothesized link between developmental and mutational variability is an intriguing hypothesis for a role of phenotype variability in innovation (Tawfik, 2010) and evolvability (Stewart, Parsons, & Plotkin, 2012). Although superficially similar, this role of variability is distinct from the mechanism by which variability boosts evolvability in this paper; essentially, here variability changes how selection sees the phenotypes of mutations, rather than changing what those mutant phenotypes are. Therefore, the two mechanisms by which random phenotypic variability shapes evolvability might occur in concert and reinforce each other.

Stochastic phenotypic variability has interested evolutionary biologists for many decades, with several models considering random phenotypic variation as one of several alternative, competing strategies whereby populations could adapt to environmental uncertainty. Bull (1987) was one of the first papers to examine stochastic phenotypic variation and genetic variation as competing solutions, inspiring other models that ask if stochastic variation can outcompete other solutions like specialization and local adaptation (Scheiner, 2014a; Svardal, Rueffler, & Hermisson, 2011) or plasticity (Scheiner, 2014b; Tufto, 2015). The results here illustrate a relationship between plasticity and stochasticity that is orthogonal and complementary to the approaches in Scheiner (2014b) and (Tufto, 2015): plasticity might adaptively outcompete random phenotypic variation, but that same variation may be a necessary stepping stone allowing plasticity to emerge. This perspective particularly complements the findings in RNAL OF Evolutionary Biology 。

a recent model of the relationship between expression variability and the evolution of gene regulation (Wolf, Silander, & Nimwegen, 2015). This paper shows that evolved promoters may be noisier than expected given the space of possible promoters, and highlights that noisy regulation, even without any signal associated with an informative cue, can evolve through the benefits of diversifying bethedging. This result highlights another aspect of stochasticity and plasticity: the reliability of cues. Previous models have shown that cue unreliability decrease the optimal plastic response (Tufto, 2000) and, in models with explicit ecology, put high-plasticity populations at a greater risk of extinction (Reed, Waples, Schindler, Hard, & Kinnison, 2010). More recent work has continued to probe the complex relationship between bet-hedging and plasticity (Tufto, 2015): by modelling the specific nature of cue stochasticity (Donaldson-Matasci, Bergstrom, & Lachmann, 2013), measuring their correlation in wild populations (Simons, 2014), or experimentally evolving bet-hedging through sensitivity to an uninformative cue (Maxwell & Magwene, 2017). Consideration of these studies and the current paper highlight the complexity of the relationship between stochasticity and plasticity and argue for precision in how that stochasticity is discussed and quantified.

There are a number of differences between the gene-expression framework of Wolf et al. (2015) and the reaction-norm concept in this paper that could lead towards productive future work. One intriguing difference is the role of variability contributed by the expression of a transcription factor; the results in Wolf et al. (2015) suggest that transcription factors with noisier expression might be more likely to be beneficial if recruited during the evolution of regulation. Further modelling studies could decouple the roles of *cis* and *trans* sources of noise for the evolution of a focal gene and therefore derive predictions for the ways in which gene networks could evolve to gain adaptive plasticity.

The choice to invent a 'toy' programming language as the genotype-phenotype model for this study was driven by the urge to address very general questions about plasticity and its evolution. This fuzzy-logic programming language serves as a high-level model for a system of biological decision-making in which noise affects every level: perception of a signal, computation of a response, and execution of that response. Although the language of the simulation model was inspired by the particulars of decision-making in a computer program, the choices of instructions were also motivated by biological dynamics. The addition instruction uses a Poisson distribution to represent the effects of randomness in gene expression with a cell, whereas the conditional and goto statements act jointly to mimic feedback in the regulation of a gene. Although negative feedback dynamics are ubiquitous in biology, autoregulation at the level of gene expression has been shown to reduce (Becskei & Serrano, 2000) but not eliminate expression noise (Lestas, Vinnicombe, & Paulsson, 2010), making such systems a particularly interesting target for evolutionary modelling. The specific choices made in developing the syntax and rules of this language may have shaped the results, and follow-up work should aim to generalize these results across models and at different levels of abstraction. However, one advantage to

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this specific approach became evident in the unexpected discovery that negative feedback imposes limits on the evolution of plasticity beyond those associated with lower variability per se. The result that evolution in a noisy environment can, by selecting strongly for robustness via negative feedback, impede the later evolution of plasticity is an example of how evolvability depends on a population's evolutionary history. But this evolutionary downside of negative feedback is particularly interesting in light of recent theory showing that cells might evolve lower phenotypic variability by multiple mechanisms (Draghi & Whitlock, 2015). These results point to the value of further integrating the study of biological information-processing into the debate over the evolution of plasticity.

Recent advances in measuring this variability in microbes have started to connect this rich history of thought in evolvability biology with microbiology and systems biology (Ackermann, 2015; Draghi, 2018; Norman, Lord, Paulsson, & Losick, 2015). Bacteria produce polyphenisms by integrating environmental cues and internal stochasticity (Chastanet et al., 2010; Lopez, Vlamakis, & Kolter, 2009), providing highly tractable systems for connecting plasticity and evolution. Recently, experimental work has shown how subtle forms of phenotypic heterogeneity can impact evolvability in microbes (Bódi et al., 2017). Although recognition of some connection between random phenotypic variation and evolvability dates to the foundations of population genetics (Crow & Kimura, 1970), deeper appreciation of these connections and their applications particularly to microbes is an active and exciting area of research (Wang & Zhang 2011; Draghi, 2018; Mineta, Matsumoto, Osada, & Araki, 2015).

The evolution of plasticity is evident and variable in populations subject to anthropogenic disturbances (Crispo et al., 2010), suggesting that understanding the evolvability of plasticity is a key component of predicting the futures of threatened species. Plasticity already plays a complex role in models of evolutionary rescue, in which a declining population might adapt to a sustainable growth (Chevin, Gallet, Gomulkiewicz, Holt, & Fellous, 2013). The results in this paper point to another facet of this complexity: how quickly a novel plastic response might evolve to allow a species to maintain its range, exploit new niches opened up by extinctions or disturbances, or otherwise thrive in the face of change. Future empirical work can test how the interplay of internal variability and the strength of natural selection shape a population's ability to find innovative solutions to rapid environmental change.

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Phenotypic variation conditions the fitness effects of new, plastic mutants in heterogeneous environments, such that greater stochastic variability can help plasticity evolve.