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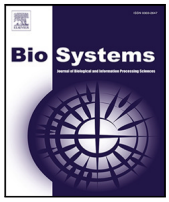

Evolution and maintenance of phenotypic plasticity

UnJin Lee [a,b,*], Emily N. Mortola [a], Eun-jin Kim [c], Manyuan Long [a]

[a] Department of Ecology and Evolution, University of Chicago, Chicago, IL, USA
[b] The Laboratory of Evolutionary Genetics and Genomics, Rockefeller University, New York, NY, USA
[c] Faculty Research Centre in Fluid and Complex Systems, Coventry University, Coventry, UK

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ABSTRACT

We introduce a novel framework for exploring the evolutionary consequences of phenotypic plasticity (adaptive and non-adaptive) integrating both genic and epigenetic effects on phenotype via stochastic differential equations and in-silico selection. In accordance with the most significant results derived from prior models, we demonstrate how plasticity is differentially favored when subjected to small vs large environmental shifts, how plasticity is transiently favorable while accommodating a new environment, and how plasticity decreases during epochs where the environment remains stable (canalization). In contrast to these models, however, by allowing the same phenotypic value to be produced via two different paths, i.e. deterministic, genic, vs stochastic, epigenetic mechanisms, we demonstrate when genic contributions alone cannot produce an optimal phenotype, plastic, epigenetic contributions will instead fully accommodate new environments, allowing for both adaptive and non-adaptive plasticity to evolve. Furthermore, we show that while rates of phenotypic accommodation are relatively constant under a wide range of selective conditions, selection will favor the most efficient route to adaptation: deterministic, genic response, or stochastic, plastic response. As a result, plasticity may evolve or canalization may occur within a given epoch depending on the relative mutation rate of genic and epigenetic contributions to phenotype, highlighting the importance of genetic conflict on the evolution of plasticity.

1. Introduction

1.1. Phenotypic variability

The modern synthesis requires that all populations of organisms have some appreciable degree of phenotypic variation in order for natural selection to occur. Within this framework, phenotypic variation is a result of genetic variation, whereby selection on phenotypes acts as a feedback mechanism to control how genetic variants flow through a population. However, the extent to which variation in quantitative traits is explained by genetic variation is not fully understood. In the context of traits that vary along a continuum, phenotypic variability, often referred to as V_P, is explained by a combination of genetic and non-genetic (environmental) variability, V_G and V_E respectively, such that $V_P = V_G + V_E$. Note that in the absence of explicit parameterization, gene-by-environment interactions are often also contained within the environmental variability term (Zhang and Hill, 2005).

Historically, quantitative genetic models of natural selection do not incorporate the existence of non-genetic phenotypic variability (Ancel, 2000; Zhang and Hill, 2005). Instead, such models frequently portray a one-to-one genotype-phenotype relationship, in which a particular genotype corresponds exclusively to a single phenotype, or else is expressed as a summation of the effects contributed across many loci. Any discrepancies between the additive effect of independent loci and phenotypes is often simply modeled as a linear error term, while in practice such discrepancies are often dismissed by invoking the relatively poorly understood phenomenon of penetrance. However, as our collective understanding of molecular biology grows, effects previously discarded as environmental error must include an increasingly large number of effects, including more complex adaptive and non-adaptive plasticity mechanisms like behavior, epigenetic regulation, diversification, and non-genetic modes of inheritance (Bonduriansky and Day, 2009).

Recent observations indicate the existence of variable relationships between genotype and phenotype, in which a given genotype may in fact produce a range of phenotypes that can fluctuate dynamically (Sigal et al., 2006; McAdams and Arkin, 1997; Blake et al., 2003; Bratulic et al., 2015; Spencer et al., 2009). Even within clonal populations, individuals have been shown to display quantitative differences that may distinguish them from genetically identical individuals. Phenotypic plasticity describes the phenomenon by which such individuals within a population may differentiate from genetically similar members

* Correspondence to: 1230 York Ave., New York, NY, 10065, USA
E-mail address: ulee@rockefeller.edu (U. Lee).

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by epigenetic means. In the context of rapidly fluctuating environmental conditions, possessing variable phenotypes within even genetically similar populations generates the potential for individuals to be randomly suited to uncertain conditions (Beaumont et al., 2009; Siegal and Leu, 2014; King and Masel, 2007; Levy and Siegal, 2012; Ratcliff et al., 2015; Libby and Ratcliff, 2019; Simons, 2009). Alternatively, in the context of a single environmental shift, the ability to produce a phenotype well-suited to new conditions as a response to such changes also increases survival (Lande, 2009; Ancel, 2000). While hypotheses concerning the adaptive value of plasticity have been previously described, such variability largely appears to inescapably exist at the very least on a molecular level, regardless of whether or not it may provide an adaptive advantage. In fact, it has been shown that the minimization of such molecular noise requires the evolution of very specific topological constraints (Ramos et al., 2015).

Understanding the potential evolutionary consequences of such variability has often been contentious, with studies suggesting that there is no evidence to show that plasticity influences adaptation (de Jong, 2005). However, various models and observations have delved into the possible mechanisms by which plasticity may have evolved and the role that it may play in shaping biological pathways (Moxon and Kussell, 2017; Mayer et al., 2017; Donaldson-Matasci et al., 2008; Tadrowski et al., 2018; King and Masel, 2007; Ancel, 2000; Draghi and Whitlock, 2012; Lande, 2009; Pfennig and Servedio, 2013; Price et al., 2003). In classical population genetics, standing genetic variation alone produces a wide variety of phenotypes upon which natural selection may act. As such, in the process of adaptation, genotype precedes phenotype under natural selection. In contrast, studies of phenotypic plasticity have suggested that, within a single given genotype, an organism's interactions with the environment, when paired with mechanisms for both adaptive and non-adaptive phenotypic plasticity, produce a wide variety of phenotypes upon which natural selection acts. Under such models, phenotypic change may pave the way for genotypic change in the process of adaptive evolution in a population. Such a process has variously been referred to as either genetic assimilation (Waddington, 1942) or genetic accommodation (West-Eberhard, 2003).

1.2. West-Eberhard model

According to Mary Jane West-Eberhard, the adaptive evolution of plastic traits may follow a three-step process. *First*, an adapting population must have a degree of phenotypic plasticity. Plastic traits will have the ability to display a range of phenotypes in response to various inputs. These inputs may be simple external variation in the environment, but they could also be novel genetic inputs as a result of mutation. West-Eberhard emphasizes that these plastic phenotypes must have a degree of responsiveness to such inputs; otherwise, environmental or even genetic changes would have no effect on phenotype. This scenario stands in contrast to fully canalized traits with such robust buffering to varying input that no alteration in phenotype would even be possible, resulting in cryptic variation (Siegal and Leu, 2014). *Second*, when presented with a new input, either external or internal, the plastic traits subsequently produce novel phenotypes in response to the new input. Here, a phenotype may have a wide range of adaptive and non-adaptive responses to an altered input, resulting in phenotypic accommodation. While phenotypes overall may have a broader distribution than in prior conditions, phenotypic accommodation will allow for the production of at least some individuals with an optimal phenotype. Regardless, this novel set of phenotypes now constitutes an altered substrate on which natural selection may act. *Third*, if some phenotypic response to the new input provides a selective advantage, these phenotypes may increase in frequency in the population given a recurring input. If this phenotypic response has a genetic component, genetic accommodation may occur, fixing this new phenotype within a population. Notably, this model departs only slightly from the classic mutation-selection view of adaptation, in that the West-Eberhard model allows for the additional possibility of novelty being generated via plasticity and not only through mutational processes alone (West-Eberhard, 2003).

Computational and theoretical models testing various aspects of plasticity have been previously published, but few models exist that fully recapitulate the West-Eberhard model (see Discussion). Tests of the West-Eberhard model must possess two primary properties. Firstly, individuals in a population should be able to produce a variable, non-genetic response to the environment; and secondly, one or multiple optimal genotypes should exist. The production of non-genetic responses to the environment is a pre-requisite for both steps 2 and 3 of the West-Eberhard model, while an optimal genotype (or genotypes) must exist in order for a phenotype to be capable of becoming genetically assimilated.

With the exception of certain theoretical work concerning phenotypic plasticity or phenotypic switching, most evolutionary models continue to maintain a one-to-one genotype-phenotype relationship, while those that do incorporate some form of plasticity cannot fully recapitulate the West-Eberhard model. Generally, models of plasticity and switching are concerned with understanding the role of plasticity mechanisms in adaptive processes, often addressing specific questions regarding the role of plasticity in surviving uncertain conditions, understanding how plasticity is maintained, and determining whether plasticity accelerates adaptation.

1.3. Prior models

Intuitively, populations with greater phenotypic variation will survive a greater number of stressful conditions than those with less variation, which would impart an advantage to having greater V_E. Alternatively, increased variation would also decrease the overall level of fitness for many individuals during periods of stasis. Various classes of models have been produced to explore the evolutionary consequences of such variability. The primary distinguishing features among different model types involves the treatment of genotypes, phenotypes, environments, and fitness functions. The following section provides a discussion of these models and their main results are summarized below (Table 1).

One simplified class of models that specifically examines the consequences of non-genetic variation are phenotypic switching models. Here, a genotype produces random binary phenotypes which are subject to fluctuating binary environmental conditions. Under this class of models, individuals may adopt one of two phenotypes, each of which is well suited to one environmental condition and poorly suited to the other. The phenotypes of these individuals fluctuate randomly between the two possible phenotypic states and the stochastic switching rate between the two states constitutes that individual's given genotype. Importantly, this class of models constitutes a departure from the notion that genotype and phenotype have a direct one-to-one correlation. To wit, at any given moment, the population of individuals in one particular phenotypic state could have a large number of underlying genotypes, or stochastic switching rates, represented in that population. Conversely, the population of individuals in one particular genotypic state should represent both possible phenotypic states given sufficient amounts of time within large populations. As a result, populations will undergo a process of phenotypic diversification after any given selection event where phenotypic diversity re-emerges via stochastic switching.

A key feature captured by this class of models which is often missing in more standard models of genetic adaptation is the ability of these populations to survive multiple catastrophic selection events. In this class of models, the rate at which phenotypic diversification occurs can differ drastically among and across populations, depending upon how beneficial standing phenotypic variation is for long-term survival under uncertain conditions. Importantly, these models demonstrate how phenotypic switching can allow populations to survive disastrous

Table 1
Quantitative models of plasticity.

Model	Genotype	Phenotype	Environment	Fitness	Analysis	Major conclusions	Citations
Phenotypic Switching	Continuous; Switching rate	Binary*	Binary*	Phenotype-environment match increases fitness, mismatch decreases fitness	Comp./Analytic	Allows stochastic survival of catastrophe; optimal switching rate matches environmental fluctuation rate; memory evolves under special conditions	Moxon and Kussell (2017), Ratcliff et al. (2015), Libby and Ratcliff (2019), King and Masel (2007), Kussell and Leibler (2005), Skanata and Kussell (2016), Jablonka et al. (1995)
Bet-hedging	Continuous; Adaptive strategy	Discrete*	Discrete*	Specialist strategies produce optimal phenotypes under certain environments, generalist strategies always produce intermediate phenotypes	Graphical/Analytic	Allows stochastic survival of catastrophe; optimal switching rate matches environmental fluctuations rate; memory and generalist strategies evolve under special conditions	Donaldson-Matasci et al. (2008), Mayer et al. (2017)
Norm of reaction Ancel	Continuous; L & R bound of norm of reaction	Continuous	Continuous†	Increased fitness if optimal phenotype within norm of reaction, penalty for larger norms	Comp./Analytic	Plasticity accelerates adaptation when it reduces the time to first-encounter of beneficial phenotypes, but otherwise retards adaptation; two major epochs during adaptation: increased plasticity then canalization	Ancel (1999, 2000)
Norm of reaction Lande	Continuous; Slope of linear norm of reaction	Continuous	Continuous*†	Increased fitness near optimal phenotype	Graphical/Analytic	Two major epochs during adaptation: increased plasticity then canalization; Smaller norms favored during stable periods, larger norms favored during less stable periods	Via and Lande (1985), Lande (2009)
Quantitative Genetics	Continuous	Continuous	Continuous*†	Increased fitness near optimal phenotype	Analytic	Fluctuating environments and/or penalties for homogeneity preserve plasticity; plasticity results in increased genetic variation	Kondrashov and Yampolsky (1996), Zhang and Hill (2005)
Neural Net	Continuous	Continuous	Continuous*	Increased fitness near optimal phenotype	Computational	Acceleration of adaptation possible; plasticity results in increased genetic variation; plasticity results in robustness to environmental change	Hinton and Nowlan (1987), Draghi and Whitlock (2012), Wagner (1996)

* indicates random/fluctuating, † indicates static.

extinction events (Ratcliff et al., 2015; Moxon and Kussell, 2017), with the central result of these studies being that the optimal switching rate is equal to the environmental switching rate (Kussell and Leibler, 2005; King and Masel, 2007). Some of these models of phenotypic switching have been extended to include a spatial dimension with added migration, resulting in an increased risk of disasters through space, therefore favoring an increased switching rate (Ratcliff et al., 2015). Certain extensions of these phenotypic switching models have considered scenarios in which the phenotypic or environmental switching rates may be autocorrelated. When selective environments are increasingly autocorrelated, slower switching phenotypes are favored, as the likelihood of encountering successive environments to which a phenotype is suited increases (Ratcliff et al., 2015). Alternatively, when selective environments are increasingly unpredictable – specifically, when environments fluctuate on random timescales – the phenotypic switching rate will be increasingly autocorrelated (Skanata and Kussell, 2016).

When considering models of phenotypic switching, it is important to clarify the distinction between heritable and non-heritable contributions to phenotype. In the case of models of phenotypic switching, offspring inherit both the initial phenotypic state and switching rate of their parent, subject to mutation. As such, even though genotypes (i.e. stochastic switching rates) are stably inherited within a population throughout time, phenotypes, conversely, are not stably inherited. Such

considerations have deep conceptual consequences in understanding what it means to adapt, as no single genotype can possibly stably produce optimal phenotypes, particularly under variable environmental conditions. Rather, these models of phenotypic switching generally focus on the adaptation of heritable parameters controlling non-heritable contributions to phenotype, like the phenotypic switching rate, to maximize long-term survival under fluctuating conditions (King and Masel, 2007; Moxon and Kussell, 2017; Skanata and Kussell, 2016; Ratcliff et al., 2015; Libby and Ratcliff, 2019; Jablonka et al., 1995).

A similar class of models examines the evolution of bet-hedging behavior. While models of phenotypic switching only model binary phenotypes and environments, models of phenotypic bet-hedging allow for a large number of distinct phenotypes under multiple environmental conditions. At the cost of increased modeling complexity, these models confirm many of the findings from models of phenotypic switching. However, while models of phenotypic switching force individuals to adopt a single survival strategy, namely stochastic switching, more complex models of bet-hedging further allow alternative strategies for survival, i.e. specialist or generalist strategies. Graphical analysis of models of bet-hedging behavior comparing intrinsic trade-offs of fitness between various environmental conditions suggest that the nature of the trade-off may favor various strategies for generating non-genetic variability (Donaldson-Matasci et al., 2008; Mayer et al., 2017). Populations that have adapted to certain environmental conditions deal with an intrinsic trade-off between consistent development under normal environmental conditions and the ability to respond to alterations and new conditions. As such, the degree of variation among extant phenotypes in a given population depends largely upon the benefit verses the cost of evolutionary trade-offs inherent to phenotypic diversification. Here, weaker fitness trade-offs tend to favor a generalist strategy, while strong trade-offs favor specialist strategies (Donaldson-Matasci et al., 2008). Additionally, such models have shown that the fitness trade-off inherent to adaptive solutions may predict whether adaptation or switching will be favored (Mayer et al., 2017).

Further models of plasticity have also been developed with more continuous treatment of phenotypes and environments. However, these models are often more complex and often capture only limited aspects of phenotypic plasticity. One such model is the Ancel model, which defines phenotype as a continuous variable (Ancel, 1999, 2000). Here, rather than having genetic parameters control a single-valued phenotype alone, genetic parameters define instead a lower and upper limit for a norm of reaction. During selection, the environmental conditions select for a single, optimal phenotypic value. In this model, selection directly rewards having a norm of reaction containing the optimal phenotype while simultaneously punishing large norms of reaction via a linear fitness penalty. A key finding of this model is that during the process of adaptation to an new environmental shift, the norms of reaction will undergo two distinct epochs. First, the norm of reaction will expand to accommodate the new environment, greatly increasing the fitness of individuals whose norms contain the new optimal phenotype. Subsequently, the norm of reaction will begin to shrink around the new optimum, increasing fitness even further in comparison to those individuals with a wider norm of reaction, suggesting that under static environmental conditions, plasticity will be deleterious. A second key finding of this model is that phenotypic plasticity may accelerate adaptation under certain conditions. Specifically, if the difference in optimal and initial genotypes is sufficiently large, plasticity will reduce the time until an individual containing a new optimal phenotype is produced. However, if this condition is not met, phenotypic plasticity appears to retard adaption (Ancel, 2000).

A second model, similar in nature with the Ancel model but with differing mathematical formalism, examines the behavior of a continuous phenotype in the context of binary states of a continuous environmental variable. While the norm of reaction in the Ancel model is defined by two bounds, in the Lande model of phenotypic plasticity, an individual's genotype is defined as the slope of its norm of reaction, where the norm of reaction is a linear function where phenotype is determined externally by environmental conditions (Lande, 2009; Via and Lande, 1985). In this model, as the environmental value increases, the phenotypic value will also increase, with the degree of increase determined by the slope of the linear environment-phenotype function. When two different environmental conditions are considered, individuals with a high degree of plasticity (i.e. large slope/norm of reaction) may produce ideal phenotypes at both environmental conditions, while less plastic individuals will be unable to produce differing phenotypes when environmental conditions are varied. Alternatively, under static conditions, plasticity is deleterious, as with small, local environmental fluctuations, a smaller norm of reaction produces phenotypes much closer to the ideal phenotype than if individuals had a larger norm of reaction. Specifically, under static conditions, it is highly favorable to be under-responsive to perturbations. However, this lack of response produces a trade-off when large environmental shifts occur, as individuals with small norms of reaction cannot produce a similarly large changes in phenotype to accommodate such a shift (Lande, 2009).

While the two models of plasticity discussed here differ significantly in implementation, they both reach similar conclusions. First, they agree that during adaptation, phenotypic response undergoes two epochs where the norm of reaction first increases, then decreases around the new optimal phenotype. Initially, under static conditions, strong responses to small fluctuations are deleterious. However, as the environment shifts, increased plasticity is favorable, allowing overall plasticity to increase within the population. As populations continue to adjust to the new environmental regime, sensitivity to environmental changes is then no longer favorable, instead returning to the original state where plasticity is deleterious. Because of this multi-step process, these models have demonstrated that plasticity may accelerate natural selection but only in very limited conditions where the distance between initial conditions and optimal conditions is very large.

Though plasticity is deleterious under static conditions, as previously mentioned, an increase in phenotypic variation will allow for potential adaptation to a wider range of selective conditions, potentially allowing populations to cross otherwise uncrossable fitness boundaries. While this may be beneficial in the context of highly variable and unpredictable environments, after environmental conditions have stabilized long-term, natural selection often decreases unnecessary phenotypic variation. Observationally, however, phenotypic variation is often maintained in natural populations under relatively static conditions (West-Eberhard, 2003). Classically, such phenotypic variation is thought to be maintained by genetic variation via mutation, selection, and epistasis (Barton and Keightley, 2002). Previously discussed models of phenotypic switching, as well as quantitative genetic models (Zhang and Hill, 2005; Kondrashov and Yampolsky, 1996), also suggest that continuously fluctuating environments may play a key role in this process. However questions still remain in understanding how or why environmental variability via plasticity may be maintained in a population during static conditions.

One alternate mechanism that has been proposed as a mechanism for the maintenance of environmental variability is a potential acceleration of genetic adaption provided by phenotypic plasticity (Simpson, 1953). In addition to the Ancel and Lande models of plasticity, other modeling efforts utilize complex neural network models to explore the evolutionary consequences of phenotypic plasticity (Hinton and Nowlan, 1987; Draghi and Whitlock, 2012; Wagner, 1996). While the previously discussed Ancel and Lande models provide evidence that an accelerating effect may not be sufficient for the preservation of phenotypic plasticity within a population (Ancel, 1999, 2000; Via and Lande, 1985; Lande, 2009), others have suggested that, overall, plasticity will tend to produce slower genetic adaptation than in the case of no plasticity (Draghi and Whitlock, 2012), with the overall effect being that of increased genetic diversity and robustness to environmental perturbation (Draghi and Whitlock, 2012; Wagner, 1996).

Table 2
Key definitions.

Term	Definition
Genetic	Related to stably inherited model parameters, subject to mutation, including genic control parameters (i.e. γ_i and ϵ_i) and epigenetic control parameters (i.e. D_i and τ_i), but exclusive of epigenetic parameter $\xi_i(t)$
Plastic	Related to non-genic variation in phenotype
Genotype	Collection of an individual's genetic parameters (i.e. $\{\gamma_i, \epsilon_i\}$ or $\{\gamma_i, \epsilon_i, D_i, \tau_i\}$)
Genic	Related to deterministic genetic contributions to phenotype (e.g. genic control parameters γ_i and ϵ_i)
Epigenetic	Related to stochastic parameter $\xi_i(t)$, representative of an individual's unique organismal response to environmental conditions and life-history (e.g. epigenetic control parameters D_i&τ_i)
Transient Epigenetic Inheritance	Usage of parental epigenetic value $\xi_i(t)$ as initial conditions for the next generation
Epigenetic Compensation	The ability to produce fit individuals through epigenetic means, exclusive of or in combination with genic means

Table 3
Summary of variables.

Symbol	Variable
N	Population size
i	Individual $i \in \{1, 2, \ldots, N\}$
P_i	Phenotype of individual i
$\xi_i(t)$	Epigenetic value of individual i
γ_i	Deterministic growth parameter of individual i
ϵ_i	Deterministic repression parameter of individual i
D_i	Magnitude of plasticity parameter of individual i
τ_i	Auto-correlation of plasticity parameter of individual i

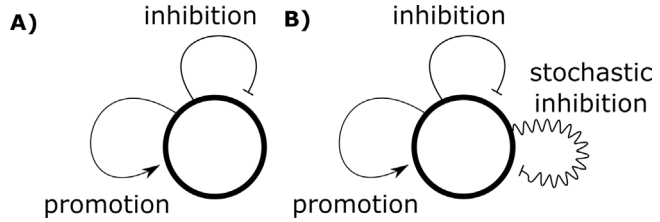

Fig. 1. *Self-regulating traits.* Phenotypes are modeled as the result of a minimal self-regulating system. Non-plastic phenotypes (A) have two feedback loops, one positive and one negative, while plastic phenotypes (B) have three feedback loops, one positive and two negative, one deterministic, and one stochastic.

While the models reviewed here broadly fall into many different categories of approaches, all incorporate different aspects of plasticity, such as a separation of phenotype and genotype or random fluctuations in either the environment and/or environmental response. However, none of these models can fully recapitulate the steps of the West-Eberhard model. Only in models of phenotypic switching and bet-hedging are genotype and phenotype segregated, allowing phenotypic accommodation to precede the establishment of genetic accommodation of new conditions. In these models, a genotype is defined strictly as the switching rate between phenotypes, with actual phenotype being entirely independent of genotypic state. As the occurrence of a swapped phenotype occurs independently of environmental conditions, such models may only capture certain limited aspects of non-adaptive plasticity. Alternatively, unlike in models of phenotypic switching or bet-hedging, other models of phenotypic plasticity allow for a broad range of phenotypes to exist, rather than simple binary phenotypes. In these models, phenotype is the result of genotypic state (e.g. slope of the norm of reaction) interacting with the current environmental state. As phenotype is a direct result of genotype, and all individuals in a population are subject to the same environmental conditions, phenotype thus has a one-to-one correlation to genotype and is therefore only able to capture limited aspects of adaptive plasticity. Due to this, these models of phenotypic plasticity are also unable to recapitulate the West-Eberhard model.

In the following section, we present a minimal model that allows for the study of adaptive and non-adaptive plasticity in a single model that satisfies the conditions for testing the West-Eberhard model.

1.4. Model

The aim of this section is to describe our minimal model of phenotypic plasticity with the goal of comparing the results of in-silico selection between populations that have either plastic or non-plastic phenotypes. In order to model phenotypes with long-term stability and convergence, we model these self-regulating phenotypes as either the result of two feedback loops (one positive, one negative) for non-plastic traits, or three feedback loops (one positive, one negative, one negative but noisy) for plastic traits (Fig. 1). The simplest such model is a logistic growth model. Key definitions for terminology may be found in Table 2.

We first model non-plastic phenotypes, where an individual i in a population of size N has a phenotype P_i, where

$$\frac{dP_i}{dt} = \gamma_i P_i - \epsilon_i P_i^2. \tag{1}$$

Here, P_i is controlled by a set of genotypic parameters $\{\epsilon_i, \gamma_i\}$, representing the total deterministic, genic contribution to phenotype. Phenotype is thus represented by an ordinary differential equation which has the minimum requirements necessary to dynamically maintain a static trait value. There is one positive feedback loop promoting an increase of said trait according to parameter γ_i and a second, negative feedback loop repressing said trait according to parameter ϵ_i, working in concert to maintain the phenotype at a specific value $P_i = \gamma_i/\epsilon_i$ over sufficiently long periods of time. We may assume that this initial phenotypic value is produced as the result of a population having previously adapted to environmental conditions, such that the static phenotype is the optimal phenotype. Notably, this model does not yet have any plasticity, so that phenotype $P_i = \gamma_i/\epsilon_i$ over long periods. As such, all variability in a population's phenotypes (V_P) should be a direct result of population differences in parameters γ_i or ϵ_i.

To introduce non-genetic variability into these populations, we may change the ordinary differential equation of non-plastic phenotypes represented in Eq. (1) into a stochastic differential equation

$$\frac{dP_i}{dt} = \gamma_i P_i - (\epsilon_i + \xi_i(t))P_i^2, \tag{2}$$

with additional epigenetic parameter $\xi_i(t)$, representing the total epigenetic contribution to phenotype (Table 3). $\xi_i(t)$ represents the accumulation of random responses an individual in a population produces in response to externalities throughout its lifetime, including environmental, developmental, and behavioral variation, resulting in a plastic, epigenetic response $\xi_i(t)$. This epigenetic response results in a decoherent feedback response via the second term of the SDE, as $\xi_i(t)$ is a *time-dependent* random variable produced by a Wiener process ($\frac{dW}{dt}$) (Lee et al., 2015; Kim et al., 2016). Importantly, in contrast to the non-plastic model represented in Eq. (1), the accumulation of random epigenetic variation results in a distribution of phenotypes within any given genotype. As individuals are subjected to a wide variety of life-history events and complex genetic interactions during development, we use a stochastic differential equation with multiplicative noise to model the plastic genotype-phenotype relationship, resulting in log-normal-like distributions of phenotypes (Lee et al., 2015; Kim et al., 2016). Similar heavy-tailed distributions have been observed for widely varied phenotypes, such as intercellular protein levels, cell size, or even clutch size (Osella et al., 2014; Jetz et al., 2008; Sigal et al., 2006).

The consequences of this epigenetic variability on population phenotypes are modeled by $\xi_i(t)$ and its genetic control parameters, D_i and

τ_i, where $\xi_i(t)$ is a random variable with mean 0 resulting from a Wiener process. $\xi_i(t)$ is also autocorrelated with magnitude D_i and time τ_i such that

$$\langle \xi(t_0), \xi(t) \rangle = D_i e^{-(t-t_0)/\tau_i}. \quad (3)$$

Notably, the genetic parameters D_i and τ_i control the epigenetic value $\xi_i(t)$ but cannot directly dictate its value, which is still a random variable. As D_i simply controls the magnitude of plasticity, this represents genetic control of the *non-adaptive* plastic response to environmental and developmental changes. Similarly, τ_i controls the auto-correlation, or memory, of plasticity, allowing subsequent generations to have responses similar to the favorable epigenetic responses produced in prior generations. This represents genic control of the *adaptive* plastic response to environmental and developmental changes. Therefore, in contrast to the two genic control parameters of the non-plastic model, individuals controlled by Eq. (2) should have four total genetic parameters $\{\gamma_i, \epsilon_i, D_i, \tau_i\}$, two genic and two epigenetic (Tables 2 & 3). We also note that as an individual's genotype does not have a one-to-one correlation to a given phenotype, phenotypic space is degenerate, where any given phenotype may have been produced by a number of different combinations of genotypes.

If the effects of $\xi_i(t)$ are increased (increased D_i), there is greater randomness that is not buffered and is therefore integrated into an individual's phenotype (higher phenotypic variation). Once selective pressures are applied to populations, the auto-correlation term, τ_i, allows for a more or less consistent response to selection. With a longer auto-correlation time (larger τ_i), offspring will produce similar responses to successive selective events as their parents (more autocorrelated), whereas with a shorter auto-correlation time (smaller τ_i), offspring are likely to have a more varied and heterogeneous response than their parents (less autocorrelated). As $\xi_i(t)$ has unique autocorrelated properties, $\xi_i(t)$ is generated by using a colored-noise Runge–Kutta method (Honeycutt, 1992).

This SDE has two key properties: the mean remains γ_i/ϵ_i, and the phenotypic distribution results in a steady-state distribution over sufficiently long periods of time (Lee et al., 2015; Kim et al., 2016). As such, under a quantitative genetics framework (Barton and Keightley, 2002; Ancel, 1999) where $V_P = V_G + V_E$, the contribution of $\xi_i(t)$ on phenotype P_i allows V_E to now be non-zero, even in the case of clonal populations where $V_G = 0$. Note that the addition of a stochastic term to a simple logistic growth model satisfies the first step of the West-Eberhard model, as a trait can now have differential responses to input.

Given both plastic and non-plastic models, we then apply in silico selection for haploids with Gaussian fitness centered on an optimal phenotype, P_{opt}, resulting in a new selective environment (Fig. 2, Supp. Fig. **S1**). Since selection is applied only to phenotype and fitness is related simply to the phenotypic distance between the individual's phenotype and the optimal phenotype, there is no direct penalty for plasticity in this model. We note that in these simulations, individuals initially inherit the epigenetic value $\xi_i(t)$ in reproduction, followed by the accumulation of noise, resulting in a new epigenetic value that fits the relationship Eq. (3). We stress that as $\xi_i(t)$ is a time-dependent random variable, parents and offspring share identical $\xi_i(t)$ values instantaneously during the moment of reproduction, after which each individual's epigenetic value $\xi_i(t)$ will begin to fluctuate in time. As such, this epigenetic inheritance is transient, as the values of $\xi_i(t)$ randomly drift during development and throughout the individual's lifetime, resulting in an transient inheritance of $\xi_i(t)$ over multiple generations that decreases according to the auto-correlation parameter τ_i, mimicking a similar auto-correlation effect that has been observed for protein levels within natural populations (Spencer et al., 2009). This transient inheritance may be removed by resetting all $\xi_i(t)$ values to 0 during reproduction, with the overall effect of a slight retardation of adaptation processes (Supp. Fig. **S2**). Assuming that $\xi_i(t)$ is analogous to the concentration of some inter-cellular factor, resetting $\xi_i(t)$ to zero is akin to depleting this factor entirely during replication, providing an intuitive understanding of this retardation effect. Additionally, while memory cannot be removed entirely, a large decrease in memory also retards adaption. (Supp. Fig. **S3**). We also note that the random value $\xi_i(t)$ is specific to each individual/lineage, and is not shared across all individuals in the shared environment. We stress, therefore, that $\xi_i(t)$ should not be seen as environmental fluctuations, but instead as each individual's unique response to the common, shared environmental conditions defined by the fitness function. The optimal phenotype for the given environment, P_{opt}, does not vary between individuals — it is the same for the entire population.

We apply two selective conditions, which we refer to as "stringent" and "relaxed" selection, varying only in the parameter that determines the width of the Gaussian fitness function by an order of magnitude (See Supp. Methods) while P_{opt} is unchanged. When P_{opt} is far from the initial distribution of phenotypes, the application of Gaussian fitness represents directional selection via an environmental shift with a new phenotypic optimum, with differences in width corresponding to the degree of strictness imposed on phenotypes by the new environmental conditions. We restrict mutations to be only in one genic control parameter, ϵ_i or in epigenetic control parameters D_i and τ_i. The genic control parameter γ_i is fixed at 1 and unmutable in all simulations presented here. We begin with initial conditions with an initial phenotype $P_i = 1/67$, corresponding to a genotype of $\epsilon_i = 67$, and with an optimal phenotype on $P_{opt} = 1/90$, corresponding with an optimal genotype of $\epsilon_i = 90$. In the case of plastic populations, we also allow populations to undergo an initialization period and thus settle on their steady-state distribution before selection is applied.

2. Results

2.1. Phenotypic accommodation

The second step of the West-Eberhard model is the development of phenotypic accommodation. Specifically, in a shifting environment, certain individuals will be able to produce an advantageous phenotype either prior to or in response to altered conditions. To determine whether our simulations would be able to produce phenotypic accommodation, we set the mutation rate for genic control parameters to 0 (i.e. mutation rate for ϵ_i is zero) while allowing mutations in epigenetic control parameters (i.e. $\{D_i, \tau_i\}$) in 100 replicate populations of size N=1000. We challenged populations with stringent directional selection and allowed individuals to adapt. Given these conditions, epigenetic parameter $\xi_i(t)$ alone could produce fully adapted individuals (Fig. 3), even when the mutation rate for genic control parameters is zero. This accommodation is rapid, with the population fully adapting within approximately fifty generations. Crucially, for all individuals in this population, the genic control parameters remain identical at $\epsilon_i = 67$. While the expected behavior for these populations is convergence on a steady-state phenotypic distribution centered on P_i=1/67, surprisingly, individuals are able to consistently produce phenotypes near P_{opt}.

As the genic control parameters were not allowed to mutate, full adaptation was compensated for by a response in epigenetic variable $\xi_i(t)$ alone via epigenetic compensation (Fig. 3). Note that, in the initial steps of adaptation, $\xi_i(t)$ produces a strong response out of equilibrium before eventually settling on an equilibrium value far from 0 (Fig. 3B). As $\xi_i(t)$ is the result of a Wiener process, $\xi_i(t)$ should have a mean of 0, but the system is pushed far from that equilibrium value. By allowing the magnitude of plasticity D_i and the memory parameter τ_i to mutate, these simulations produce a response where increased plasticity and increased memory are favorable. In this scenario, we can consider the shift in selective environment as a recurrent selection input, and due to this recurrence and the inability of the genic control parameters to mutate, greater plasticity and memory is advantageous. While we have disallowed genic control parameters to mutate at all in

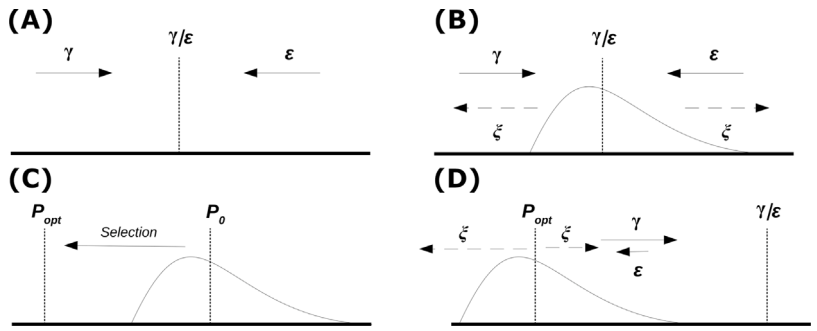

Fig. 2. Differential equation illustration. (A) Non-plastic phenotypes. For non-plastic phenotypes, phenotype is strictly defined by genic control parameters, γ_i and ϵ_i, where the trait value is the equilibrium between the "forces" of growth (ϵ_i) and repression (γ_i). (B) Plastic phenotypes. For plastic phenotypes, phenotype is defined by genic control parameters, γ_i and ϵ_i, as well as the epigenetic parameter $\xi_i(t)$, which is controlled by genetically inherited epigenetic control parameters D_i (magnitude of plasticity) and τ_i (auto-correlation). With plasticity, trait value is random, but converges on a steady-state distribution around γ_i/ϵ_i. (C) Adaptation. Populations are challenged with a new environmental condition, favoring an optimal phenotype far from the initial conditions. (D) Phenotypic accommodation. By disallowing mutation of genic control parameters, when challenged with a new environmental condition, populations adapt to the new environmental conditions through epigenetic means alone. As a whole, the genic control parameters pull populations towards a distribution around γ_i/ϵ_i. To maintain populations around the optimum, epigenetic parameter $\xi_i(t)$ compensates by favoring larger, non-zero values of $\xi_i(t)$, while increasing the degree of plasticity and auto-correlation (c.f. Fig. 3).

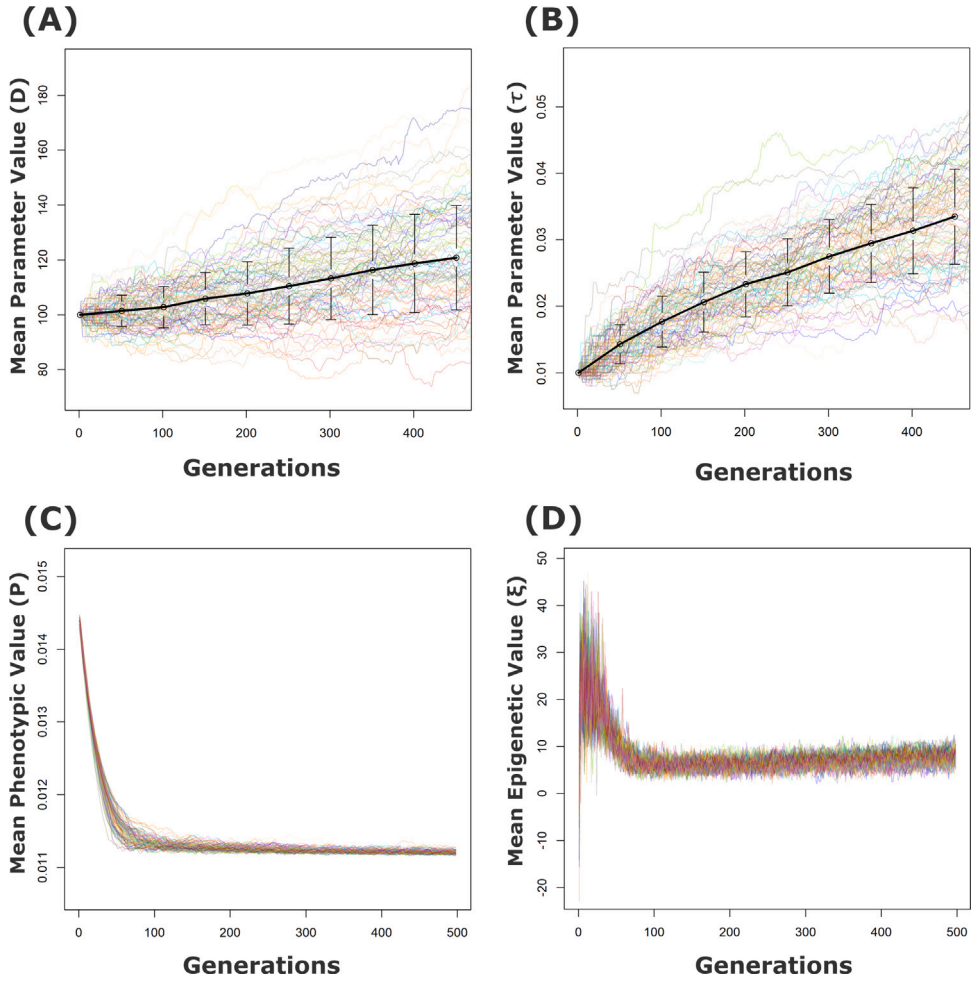

Fig. 3. *Phenotypic accommodation favors increased plasticity and auto-correlation* 100 replicate populations of 1000 plastic individuals ($T = 2\tau$) were subjected to stringent ($\mu = 1/90, \sigma = 10^{-4}$) directional selection, with mean parameter values for each replicate population shown above for D_i (A) and τ_i (B), one line per replicate population. Though genic control parameters were not allowed to mutate, population phenotypes fully adapted to new environmental conditions (C) through epigenetic compensation (D). The epigenetic parameter ($\xi_i(t)$) compensates for a non-optimal genic configuration (γ_i/ϵ_i far from P_{opt}), consistently remaining far the expected value of 0. Under such conditions, increased D_i (non-adaptive plasticity) and τ_i (adaptive plasticity) are favored.

this case, a similar response of increased plasticity and memory may also be favorable in conditions where genetic mutation is significantly slower than mutation in epigenetic parameters as well (Section **Establishment and Maintenance of Plasticity**). To understand the detailed dynamic of phenotypic accommodation and epigenetic compensation under these selective conditions, we may consider the equilibrium phenotypic value produced by this population's genotype. In this case, the genic values γ_i and ϵ_i act in concert to pull phenotypic values of

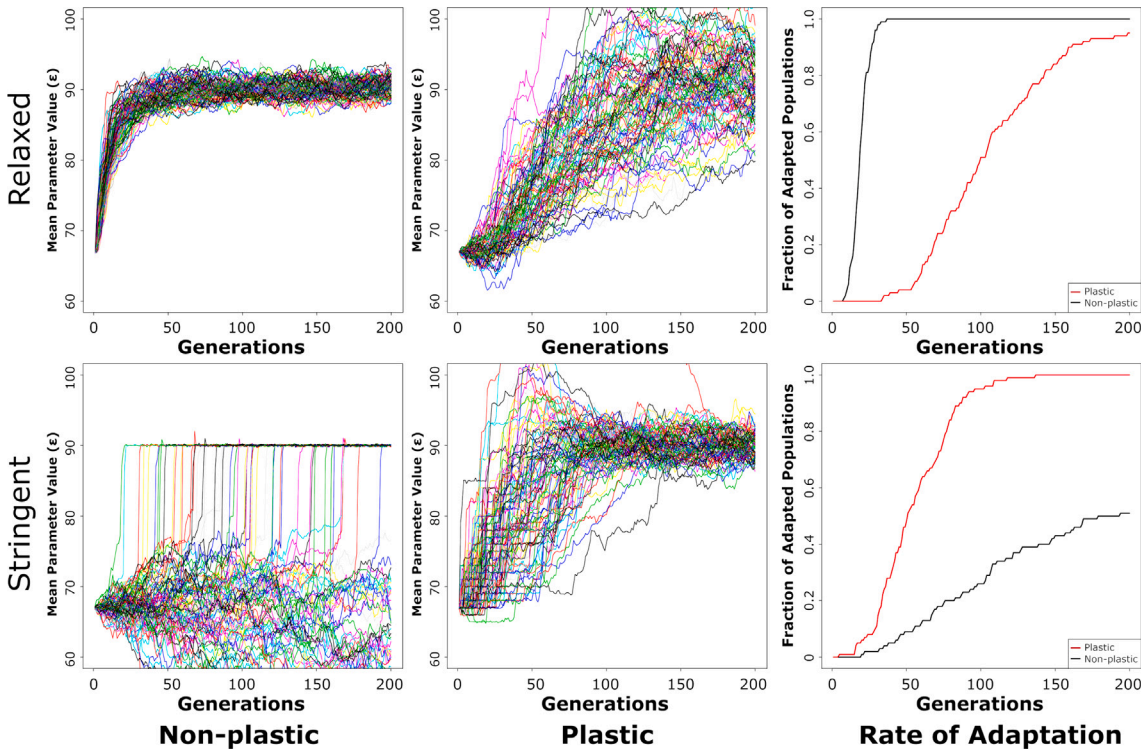

Fig. 4. *Plastic populations are robust to changes in selective forces.* 100 replicate populations of 100 individuals were subjected to stringent ($\mu = 1/90, \sigma = 10^{-4}$) and relaxed ($\mu = 1/90, \sigma = 10^{-3}$) directional selection regimes for non-plastic or plastic traits, simulating an environmental shift. The mean values for genic control parameter ϵ_i are shown, one line per replicate population, demonstrating how plasticity allows populations to have more robust responses to changes in selection pressures. When relaxed directional selection is applied, non-plastic populations converge more rapidly and smoothly on the optimal genotype than plastic populations (top row). However, when stringent directional selection is applied, non-plastic populations undergo drift until an advantageous genotype is found, followed by rapid fixation, while plastic populations converge smoothly and rapidly on the optimal genotype (bottom row). The cumulative fraction of genetically adapted replicate populations (±5% of ϵ_{opt}) within non-plastic simulations (black) are significantly more sensitive to differences in selection than plastic simulations (red). In conditions of relaxed directional selection, non-plastic populations (black) adapt faster than plastic populations (red), however in conditions of stringent directional selection, plastic populations adapt first.

the population towards the predicted steady-state distribution around γ_i/ϵ_i (i.e. 1/67). However, due to selection for a phenotypic optimum that is departed from γ_i/ϵ_i, phenotype must be compensated for by the action of epigenetic parameter $\xi_i(t)$ (Fig. 2D).

Being the result of a Wiener process, $\xi_i(t)$ should accumulate randomness, thereby returning to mean 0 with variability D_i. However, there are two demands on $\xi_i(t)$. The first is the demand that epigenetic parameter $\xi_i(t)$ is sufficiently large so that at least some phenotypes that may be near the new optimum. Overall, plasticity magnitude alone, controlled by D_i, increases the overall variability in P_i in an unbiased, non-adaptive fashion. To increase the chance of producing offspring with the correct epigenetic parameter $\xi_i(t)$ when far from 0, D_i increases. The second demand is that epigenetic parameter $\xi_i(t)$ *remains* sufficiently large *over time*, thus not returning to being distributed around 0. That is to say that, given a parent with an epigenetic parameter $\xi_i(t)$ producing fit parents, the offspring will now be likelier to have a similarly adapted $\xi_i(t)$ as its parents. This results in an increase in the auto-correlation parameter τ_i. Together, these steps represent the second step of the West-Eberhard model: phenotypic accommodation.

2.2. Genetic accommodation

Given that our model can produce phenotypic accommodation, we then allowed only the genic control parameter ϵ_i to mutate in our model, excluding mutations in epigenetic control parameters D_i and τ_i. To test for genetic accommodation, we performed 100 replicate simulations of populations of 100 individuals under stringent and relaxed directional selection (c.f. Materials and Methods). In this case, while phenotypic distributions begin near initial conditions at $P_i = 1/67$, as $\epsilon_i = 67$ initially for all individuals, selection is then applied for $P_{opt} = 1/90$, simulating an environmental shift like in the Ancel and Lande models (Ancel, 1999, 2000; Via and Lande, 1985; Lande, 2009). This population size was chosen to exaggerate certain features of genetic accommodation in plastic regimes (i.e. transient fixation events due to successive bottlenecks, see below & Fig. 4). Allowing only the genic control parameter ϵ_i to mutate, simulations were performed for populations with both plastic and non-plastic phenotypes, representing the differences in accommodation for these populations when encountering new environmental conditions.

Fig. 4 provides a representation of mean genic (i.e. ϵ_i) changes for replicate populations with plastic and non-plastic phenotypes under two directional selection regimes, relaxed (Fig. 4, 1st row) and stringent (Fig. 4, 2nd row). By allowing only for mutations in ϵ_i alone, we can see that changes in genic parameters allow for the eventual genetic accommodation of new environmental conditions — the last step of the West-Eberhard model. In plastic populations, epigenetic compensation occurs during early generations as $\xi_i(t)$ helps to stochastically produce selectively advantageous phenotypes as indicated by the large initial spike in $\xi_i(t)$ (c.f. ***Phenotypic Accommodation***). However, as mutations in genic control parameters allow for the production of optimal phenotypes through genic means alone, the epigenetic response is no longer needed to produce fit individuals. Due to this, the epigenetic parameter $\xi_i(t)$ returns back to 0 Supp. Fig. (**S4**), in contrast to in the case of phenotypic accommodation (Fig. 3). This effect is similar in nature to the increased plasticity seen in the Ancel and Lande models (Ancel, 1999, 2000; Via and Lande, 1985; Lande, 2009), however, this initial epigenetic compensation occurs via stochastic means and is thus closer in nature to prior models of phenotypic switching (Kussell and Leibler, 2005).

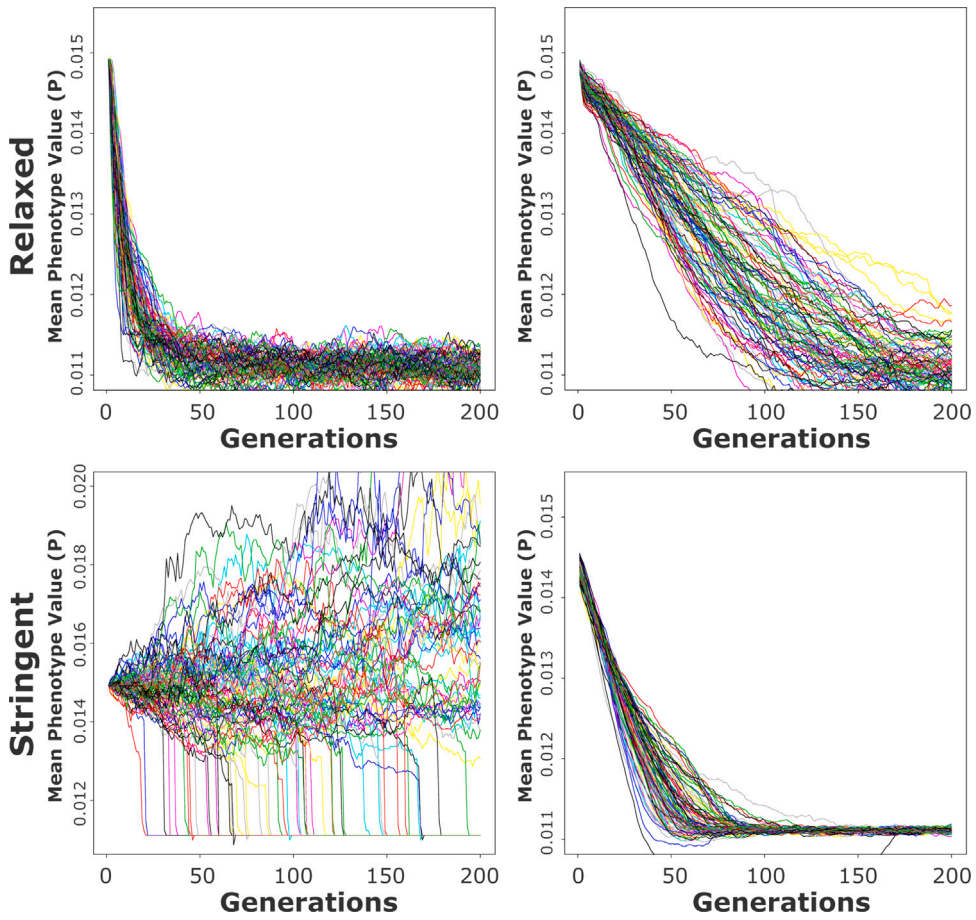

Fig. 5. *Populations with plastic phenotypes converge smoothly on optimum* Mean phenotypic values for populations shown in Fig. 4 are plotted, one line per replicate population. The behavior of non-plastic phenotypes match the behavior of population genotypes due to the one-to-one relationship between genotype and phenotype. However, while these phenotypic trajectories for non-plastic populations vary greatly (left column), phenotypic trajectories for plastic populations converge smoothly on the pre-defined optimum (right column). This effect is more pronounced in conditions of stringent directional selection (bottom row).

In the case of our non-plastic model, the genic responses under relaxed directional selection form a relatively smooth curve, with minimal noise on the upward trajectory revealing a consistent progression of all populations towards the optimal genotype. Because relaxed directional selection allows for a wider range of advantageous genotypes, adapting populations successively gain increasingly beneficial mutations and follow a selective gradient until reaching an optimum. The genotypes of these adapting populations rapidly converge near the predetermined optimum of $\epsilon_i = 90$, with small, mutation-driven deviations. Additionally, these non-plastic populations rapidly reach an optimal state within fifty generations. By contrast, plastic populations under relaxed directional selection show a slower pattern of convergence on the optimal genotype within 200 generations (Fig. 4 right column). Rather than progressing steadily and consistently towards an optimum, the plastic populations show a very large degree of variation in phenotype, sometimes severely over- or undershooting the ideal. Such an effect occurs due to selection acting on phenotype, rather than genotype. However, phenotypic convergence on the optimum remains smooth (Fig. 5). As the range of possible phenotypes becomes larger due to plasticity, genetic accommodation in plastic populations is less smooth and directed than in the case of populations with plasticity under conditions of relaxed directional selection. When combined with relatively relaxed selection, this phenomenon causes the genotypes of plastic populations to converge slowly on the optimum phenotype. In contrast to the non-plastic populations, they do not steadily progress directly towards the ideal and therefore do not adapt as efficiently.

Results differ significantly when one compares the effects on genotype under stringent directional selection for plastic and non-plastic populations (Fig. 5, 2nd row). In the latter case, genotypes vary widely among replicate populations as a result of drift driven solely by mutational variance in genic parameter $\xi_i(t)$. As opposed to conditions of relaxed directional selection, non-plastic populations under stringent directional selection do not progress continuously along a selective gradient towards the optimum, since only phenotypes at or near the ideal confer a survival advantage. Here, phenotypes instead appear to be, in a sense, discretized, as they are either largely beneficial to selection or effectively neutral. These non-plastic populations develop various neutral mutations until hitting upon one at random that provides a large selective advantage. This effect results in a series of rapid fixation events, as each population reaches an optimum and then deviates very little from it.

A measurement of the fraction of genetically adapted populations (Fig. 4 right column) supports the observation that plastic populations converge on the pre-determined optimum more efficiently under stringent directional selection, while those that are non-plastic adapt more quickly in response to relaxed directional selection. Within 150 generations, all non-plastic populations under relaxed directional selection and all plastic populations under stringent directional selection have genetically adapted fully to the new selection conditions. In both cases, accommodation occurred along a clearly defined selective gradient. Meanwhile, a number of populations under plastic/relaxed conditions and under non-plastic/stringent conditions have failed to adapt to their respective optima within 200 generations. In particular, non-plastic populations on average adapt far more slowly under stringent directional selection, as they are limited by the appearance of beneficial alleles through mutations alone.

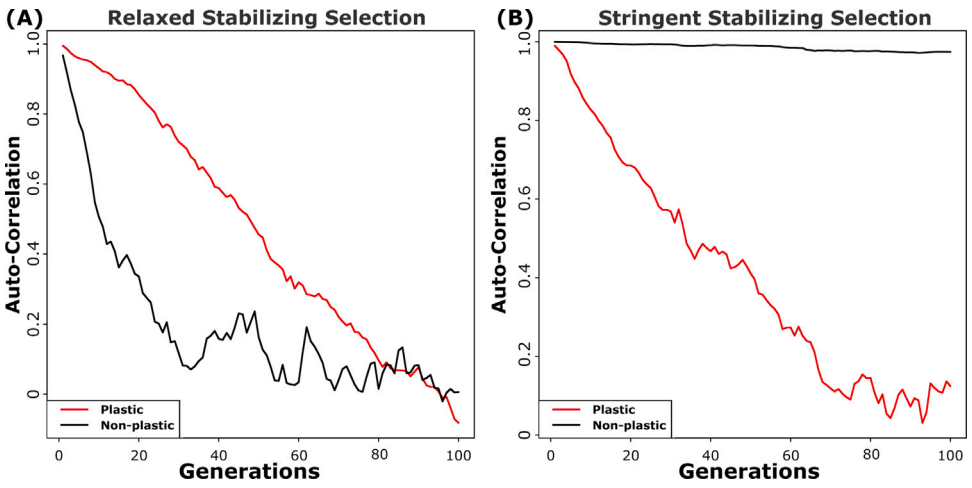

Fig. 6. *Genetic turnover in plastic populations is robust to varying stabilizing selection conditions.* At mutation-selection-drift (MSD) balance, turnover of alleles still occurs. Using 100 replicate populations of 1000 individuals at MSD balance, the degree of genetic turnover is represented here by the auto-correlation of the mean genic control parameter ϵ_i for the set of 100 replicate populations. Under relaxed stabilizing selection conditions, non-plastic populations turn over more frequently than plastic populations ((A)). Under stringent stabilizing selection conditions, plastic populations turn over less frequently than non-plastic populations ((B)). Plastic populations appeared to be less responsive to various selection conditions (relaxed (A), stringent (B)) than non-plastic populations.

Unlike in the Ancel and Lande models (Ancel, 1999, 2000; Via and Lande, 1985; Lande, 2009), the actual degree of plasticity in these sections is not allowed to change in the process of adaption. Despite this, the two distinct epochs appear in a manner similar to those observed in the Ancel and Lande models — first epigenetic compensation allows for initial survival followed secondly by genetic compensation. Furthermore, the accelerating effect seen in the Ancel model is seen here as well, as plasticity allows populations to produce beneficial phenotypes more rapidly than without populations in the case of stringent directional selection (Fig. 5). However, when the benefit of reduced time to first-encounter is eliminated, as in the case of relaxed directional selection, plasticity appears to retard accommodation, as seen in the Ancel model. Intuitively, under uncertain conditions, plasticity allows for the ability to produce a large range of potentially advantageous (or deleterious) phenotypes and thus provides a mean for population survival, whether it is through a combination of adaptive and non-adaptive plasticity, as in the case of our model, or adaptive plasticity alone, as in the case of the Lande and Ancel models. Alternatively, production of phenotypes via plastic means is an inefficient process, resulting in later genetic accommodation if possible.

While our models do not incorporate disasters and total-population extinction due to our fixed-population-size simulations, it should be noted that under conditions of stringent directional selection, all non-plastic replicate populations would have experienced total extinction in the first few generations of applied stress. Rather than allowing for such scenarios, our model instead allowed populations to undergo mutation-limited random walk. Such results indicate that there is a certain degree of plasticity that is required for survival under extreme selective conditions, in concordance with results from models of phenotypic switching and bet-hedging behavior (Ratcliff et al., 2015; Libby and Ratcliff, 2019; Donaldson-Matasci et al., 2008; Mayer et al., 2017).

2.3. Genetic turnover and mutation-selection-drift balance

To further examine how phenotypic plasticity affects mutation-selection-drift (MSD) balance, we determined the degree of genetic turnover for all populations shown in Fig. 4 under regimes of both relaxed and stringent *stabilizing* selection. We performed an auto-correlation analysis to determine the degree of turnover in mean genotype values for genic control of phenotype (ϵ_i) in plastic and non-plastic populations (Fig. 6) after these populations have fully genetically accommodated their environmental conditions. Specifically, we took replicate populations at this MSD equilibrium, and plot the auto-correlation of mean population genotype values for genic control parameter ϵ_i.

The results of the auto-correlation analyses reveal a much higher degree of genetic turnover for genic control parameter ϵ_i within plastic populations in comparison to non-plastic populations under stabilizing selection. Regardless of the degree of selection, each generation of plastic individuals gradually diverges from its previous state under plastic conditions. Meanwhile, non-plastic populations do not display this same, continuous turnover. Under relaxed stabilizing selection, the degree of auto-correlation rapidly diminishes for non-plastic populations, while those under stringent stabilizing selection show an extremely low rate of genetic turnover, with the auto-correlation value varying very little in the examined time frame. Overall, populations display a buffering of the degree of turnover from various selective conditions.

These results provide interesting insight into the forces guiding the evolution of generation time. For example, to reduce the effects of deleterious mutations, populations may evolve mechanisms to decrease the effective generation time of individuals or similarly reduce heterogeneity within reproductive and developmental processes. Similarly, if a higher degree of steady-state genetic variation may be advantageous, such as in the case of genetic capacitors (Jarosz et al., 2010; Siegal and Leu, 2014), longer generation times may be selectively advantageous. However, as selection for genetic variability would be a second order evolutionary process, such tuning may only be possible in the context of highly variable, long-term fluctuations of environmental conditions.

2.4. Loss of variability

The previous sections have demonstrated how plasticity is beneficial under conditions of directional selection. Additionally, we have shown that plasticity buffers genetic turnover from variations in stabilizing selection. We now consider whether it is deleterious during static selective conditions. To test whether phenotypic plasticity presents a selective disadvantage at MSD balance, we applied relaxed and stringent stabilizing selection on plastic populations, making the only mutable parameter the degree of variability (D_i).

In accordance with expectations, populations under stringent stabilizing selective pressures show a strong downward trend in phenotypic plasticity over many generations (Fig. 7B). Most of these populations show a significant decrease in their degree of variability, with some having their average plasticity decreased by nearly half. Therefore, while plastic populations under stringent stabilizing selection can reach

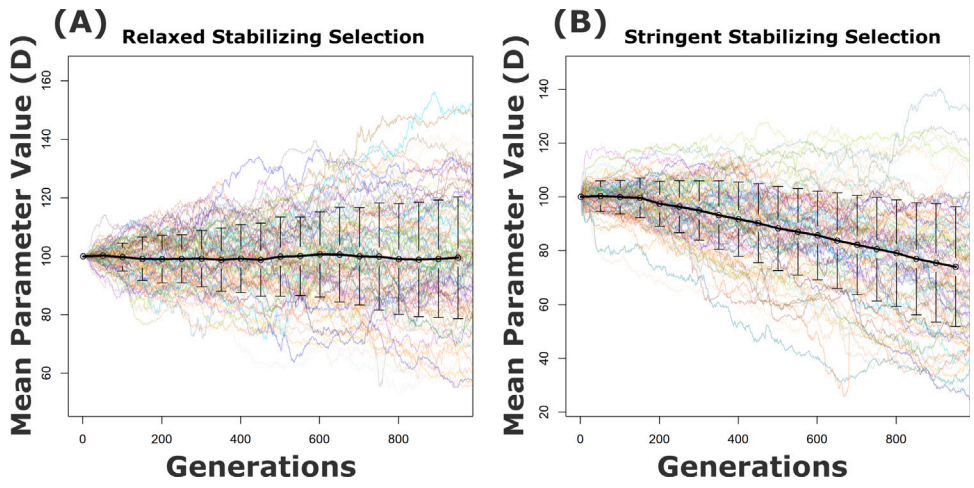

Fig. 7. *Phenotypic plasticity under static conditions is weakly deleterious.* Unlike during directional selection, at mutation-selection-drift balance under stabilizing selection, plasticity does not to contribute any meaningful selective advantage. Shown are mean D_i values for 100 replicate populations of 1000 individuals at mutation-selection-drift balance, one line per replicate population. So long as the phenotypic variability is sufficiently within the bounds of the applied stabilizing selection, as in the case of relaxed stabilizing selection, plasticity is near neutral and thus may be maintained in a population for extended periods (A). However, if the stringency of stabilizing selection is increased, plasticity is weakly deleterious (B).

a MSD balance more quickly than non-plastic populations, once the system has come to an equilibrium by reaching an ideal phenotype, the advantage imparted by phenotypic variety becomes less useful.

By contrast, populations under relaxed selection do not show a decrease in plasticity after 1000 generations (Fig. 7A). Unlike in the case of stringent stabilizing selection, small populations under relaxed selection have a broader range of phenotypes which could be considered beneficial. So long as the result of phenotypic variability, which includes both V_E and V_G, is sufficiently smaller than the width of the Gaussian fitness function, the degree of plasticity within a population should not be highly detrimental. Under these conditions, the variability originating from plasticity is not as harmful as it may be for populations under stringent stabilizing selection.

2.5. Establishment and maintenance of plasticity

While prior studies have shown how plasticity is often deleterious under constant environmental conditions (c.f. ***Prior Models***), at best serving to avoid extinction during dramatic environmental shifts, we have demonstrated that under certain static conditions, plasticity can both be advantageous (Fig. 3) or deleterious (Fig. 7). In our model, phenotype is a single-value variable, produced by a combination of both genic and epigenetic contributions. As multiple mechanisms can produce the same phenotype, any given phenotypic value in our model is highly degenerate, with a broad set of genotypic parameters (genic and epigenetic) being able to produce the same outcome. However, while phenotype may be degenerate, allowing individuals to survive a single selection event, the degree to which a phenotype is produced through genic pathways vs epigenetic pathway produces trade-offs in subsequent generations. The more a phenotype is dependent on epigenetic compensation, the less likely that subsequent generations will produce a similar response in comparison to producing the same phenotype through mostly genic means. Intrinsically, this effect forces a strong trade-off during the evolution of plasticity — progeny may be better optimized for current conditions but will be less likely to survive environmental changes.

Consideration of this trade-off leads to the natural conclusion that under constant conditions, quantitative traits should begin to canalize and lose plasticity. However, under recently changed environmental conditions, natural selection will also favor the fastest route to accommodation of a new environment, whether it be by genic or epigenetic means. Indeed, this effect manifests itself as the Baldwin Expediting Effect (Ancel, 2000; Lande, 2009), where plasticity appears to be transiently beneficial during adaptation by allowing a more rapid encounter with advantageous phenotypes. Similarly, maximization of the long-term adaptation rate also explains why the switching rate in models of phenotypic switching (King and Masel, 2007; Moxon and Kussell, 2017; Skanata and Kussell, 2016; Ratcliff et al., 2015; Libby and Ratcliff, 2019; Jablonka et al., 1995) will match the rate of environmental fluctuations.

While previous studies suggest phenotypes would begin to canalize under static conditions, we have demonstrated under certain conditions that plasticity may in fact be advantageous (Fig. 3). To further explore this tradeoff, we constrain the relative mutation rates of genic and epigenetic control parameters. We define a new variable $\mu_{rel} = \mu_{genic}/\mu_{epigenetic}$, where μ_{genic} and $\mu_{epigenetic}$ are the mutation rates for genic and epigenetic control parameters respectively. We can see now that in the case of full epigenetic compensation, plasticity increases when $\mu_{rel} = 0$ (Fig. 3), and when genic control is mutable, decreases when $\mu_{rel} = 1$ (Fig. 8).

We applied stringent directional selection on 100 replicate populations of 1000 individuals while varying the relative mutation rate μ_{rel} (Fig. 8). As μ_{rel} is varied, the relative rate of phenotypic accommodation remains roughly the same in all cases (Fig. 8A), though, slightly more rapid accommodation is seen at higher μ_{rel} values. Alternatively, under relaxed directional selection, a stronger separation in phenotypic accommodation rates was observed (Supp. Fig. (**S5**)). While the mean phenotype in these populations remains similar, the genic contribution to phenotype (Fig. 8B) varies dramatically as the relative mutation rate for genic contributions is decreased. In the case of low μ_{rel}, as the new environment is phenotypically accommodated, the epigenetic value $\xi_i(t)$ instead compensates for the inability to produce an optimal phenotype using genic means alone (Fig. 8C). As seen in previous sections, $\xi_i(t)$ compensates for sub-optimal genotypes initially, then within the given epoch, for large μ_{rel}, $\xi_i(t)$ is no longer needed, returning to a mean of zero reflecting the canalization of this phenotype by genic means. However, for small μ_{rel}, $\xi_i(t)$ continues to be important for the production of optimal phenotypes, subsequently increasing again. The genetic control of $\xi_i(t)$ similarly stratifies depending on μ_{rel} (Fig. 8D-E). As μ_{rel} decreases, epigenetic compensation becomes an increasingly important mechanism for survival, causing both non-adaptive and adaptive plasticity to be more advantageous within the given epoch. A similar effect was observed under relaxed directional selection (Supp. Fig. (**S5**)). Should a further shift in environment occur after the current epoch, the net result would be that both adaptive and

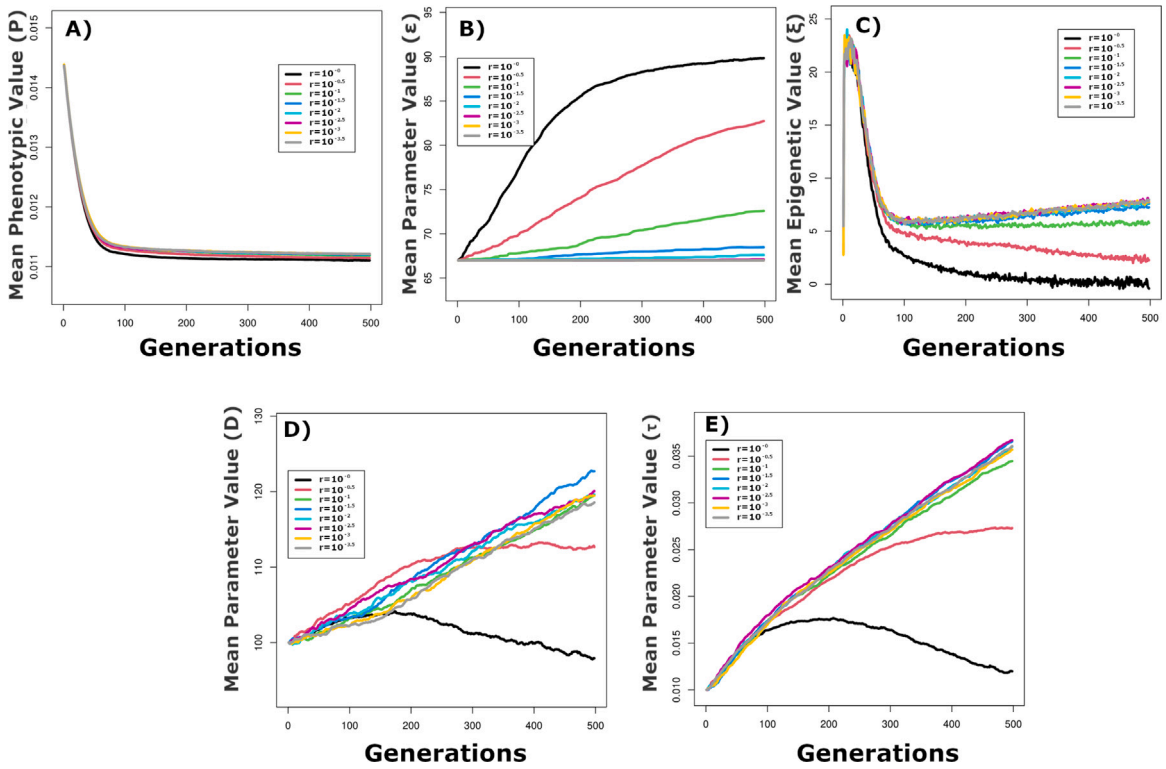

Fig. 8. Relative mutation rate determines evolution of plasticity Populations (100 replicates) consisting of plastic individuals ($N = 1000$) were presented with a new environment (stringent directional selection) while the relative rate of mutation of genic and non-genic control parameters (μ_{rel}) was varied. Shown here is the mean population behavior at each μ_{rel} value, averaged over 100 replicate populations, one line per μ_{rel} value. While in all cases, (A) phenotypic accommodation of the new environment occurred rapidly, **(B)** the ability of individuals to provide a genic solution (e_i) to new conditions was hindered. **(C)** Where genic solutions were not easily produced, epigenetic compensation occurred, **(D-E)** allowing both non-adaptive and adaptive plasticity to be advantageous within the given epoch.

non-adaptive plasticity are overall increased within a population, rather than canalizing.

3. Discussion

3.1. West-Eberhard model

Mary Jane West-Eberhard has proposed that plasticity plays a central role in the process of adaptation. Under this model, phenotypes that produce differential responses to input encounter a newly recurring input that is both phenotypically and genotypically accommodated. However, previous genetic models have been limited in their capacity to recapitulate this idea. In particular, quantitative genetic models involving explicit and parameterized phenotypes, while able to provide insight into forces acting on overall non-genetic phenotypic variability, typically cannot produce differential responses to a new input and do not allow for the possibility of phenotypic accommodation (Zhang and Hill, 2005; Wagner et al., 1997; Price et al., 2003; Via and Lande, 1985; Lande, 2009). Even models of phenotypic switching-which allow for the possibility of variable responses to a new input, degenerate genotype-phenotype relationships, and phenotypic accommodation (Kussell and Leibler, 2005; King and Masel, 2007)–cannot model genetic accommodation beyond adjusting the switching rate to maximize survival to fluctuating environmental conditions (or decreasing the switching rate to zero under static conditions).

The model used in this study provides a way of examining the behavior of populations that are phenotypically responsive to novel environmental inputs. As demonstrated by replicate simulations of populations in which no genic parameters were allowed to mutate in response to stringent directional selection, full adaptation to new environmental conditions occurred within fifty generations (Fig. 3). All populations reached a new optimum phenotype that was then maintained solely through epigenetic means rather than any kind of deterministic genic change, as shown by the fact that the epigenetic parameter $\xi_i(t)$ remained at a quantity above 0. As such, our model not only shows the progression of plastic populations' phenotypic change in response to novel inputs, but our model also has the capacity to distinguish between genetic and phenotypic methods of accommodation as described in West-Eberhard (2003). It therefore stands in contrast to otherwise similar models, including neural network models of gene regulation (Wagner, 1996; Draghi and Whitlock, 2012). Such models, which can provide differential responses to input, may demonstrate complex behaviors given relatively few assumptions and have even been shown to canalize when applied to real data (Manu et al., 2009a,b). However, they cannot phenotypically accommodate environments that have not been previously encountered. Such models are able to produce networks that are robust to fluctuating environmental conditions; however, such networks must be evolved or trained to be able to produce such responses. As such, segregation of phenotypic accommodation and genetic accommodation is difficult in such models.

A key feature of the model presented here is a combination of both deterministic and stochastic effects on phenotype. While the model chosen here utilizes second-order stochastic repression to emulate environmental and epigenetic variability, multiplicative noise is not likely a necessary requirement for most of the conclusions presented here, as it is easy to imagine that the same generalized conclusions may be drawn from a wider class of stochastic differential equations (e.g. linear noise) that include auto-correlation.

3.2. Changing environments

Our model shares conceptual similarities to other models of phenotypic plasticity, as well as to learning behaviors (Ancel, 2000, 1999; Hinton and Nowlan, 1987; Via and Lande, 1985; Lande, 2009). In prior

models (Ancel, 2000, 1999; Via and Lande, 1985; Lande, 2009), the survival of an individual depends upon whether or not the selected phenotype is within an individual's norm of reaction when selection is applied. Similarly, in our model, a genotype is more likely to survive depending on whether or not the optimal phenotype is contained within the phenotypic distribution produced by a given genotype. However, this result is contingent upon the individual with said genotype being in a favorable phenotypic state at the time of selection, a key difference between these prior models and our model. Specifically, the former are unable to distinguish between genic and epigenetic effects. To wit, in prior models, genotype strictly defines the bounds of the norm of reaction, where individuals possess elevated fitness only if a new optimal phenotype is contained within that norm of reaction. Such a model is not only unable to recapitulate the West-Eberhard model, but also assumes that plasticity may only be adaptive in response to an environmental shift. This stands in contrast to our model, where an optimal phenotype may be well outside the phenotypic distribution associated with a given genotype but can still be produced regardless (Fig. 3). Conversely, it is possible that no individuals of a given genotype may produce optimal phenotypes despite said phenotypes being well within that genotype's associated phenotypic distribution.

Nevertheless, prior models provide insight into how plasticity may ameliorate the effects of an environmental shift (Ancel, 1999, 2000; Via and Lande, 1985; Lande, 2009). The Ancel model is primarily concerned with understanding whether plasticity/learning may accelerate adaptation by examining the ideas behind the Baldwin expediting effect (Hinton and Nowlan, 1987). Using that model, the author is able to demonstrate that plasticity may only "expedite the search from an initial population distribution to the first encounter with the optimum phenotype" and that this effect is observed for "initial genotype distributions sufficiently distant from the target". (Ancel, 2000). Our model produces similar results in that plasticity does indeed expedite a population's first encounter with a more fit phenotype, in the case of both relaxed and stringent directional selection. However, whether or not plasticity ultimately increases a population's rate of adaptation depends upon the conditions under which selection occurs, not necessarily the linear distance between initial and optimal genotypic distributions. Further effects not previously described are also seen with our model. In the case of populations under stringent directional selection, once both genic and epigenetic parameters are allowed to mutate, plastic populations show a much more consistent and directed progression towards the optimum genotype as opposed to non-plastic simulations. Unlike in the case of the non-plastic simulations, many of the individual plastic populations transiently display several extremely sharp spikes followed by plateaus. As such, the populations adopt genotypes progressively nearer to the optimum. The genotypic development of the plastic populations under stringent directional selection forms a well-defined curve before reaching a plateau around $P_i = 90$, with deviations caused by random mutations. Plasticity thus allows them to adapt more quickly as they progress along a selective gradient that has become sufficiently smoothed in comparison to the non-plastic populations. This same trend is not seen in plastic populations under relaxed directional selection, where plastic populations fail to converge on an optimum phenotype in the same number of generations that non-plastic populations do.

In summary, we find that the rate of adaptation, as reflected by the cumulative fraction of genetically adapted populations, is dependent on both the manner of selection and the degree of plasticity in a population. This result is in agreement with the Ancel model, which states that plasticity does retard adaptation when both plastic and non-plastic populations readily adapt to a new optimum. However, in contrast to the Ancel model, genotype in this case may be completely segregated from phenotype due to the random (epigenetic) component of phenotype, and as such, initial genotypic distributions for all simulations in this section were identically delta distributions with $\epsilon_0 = 67$. Our results also suggest that while non-plastic populations are highly sensitive to the conditions of selection that are applied, plasticity allows populations to be more robust to such variation, a feature that is absent from the Ancel model. Such results may have broader implications for interpreting substitution rates based on sequencing data.

Given these limited conditions, a question remains regarding the maintenance of plasticity and V_E. For plasticity to be maintained in a population, the results of the Ancel model as well as models of phenotypic switching (Kussell and Leibler, 2005; King and Masel, 2007) suggest that a constantly and randomly fluctuating environment may be the only method by which plasticity could be maintained. How, then, may plasticity be maintained under static conditions?

3.3. Maintenance of plasticity under static conditions

The maintenance of plasticity under static conditions remains an open problem in the field. A model proposed by Zhang and Hill (Zhang and Hill, 2005) agrees with results from prior sections, stating that fluctuating environments may help to maintain plasticity. The Zhang and Hill model additionally proposes that certain "engineering" costs to precise expression of phenotypes may allow for the maintenance of non-genetic phenotypic variability within a population. This analysis agrees with chemical models of gene regulation where expression variability may exist in an "infra-Fano" regime only under extraordinarily specific conditions (Ramos et al., 2015). A model proposed by Wagner, Booth, and Bagheri-Chaichian shows how either pleiotropy or associations between decreases in plasticity and changes in the mean phenotype may also allow plasticity to be maintained under static conditions (Wagner et al., 1997).

Our model has shown how plasticity may variously increase, decrease, or be maintained under different selective conditions. Specifically, we have shown that when mutation of genic control parameters is disallowed, increased plasticity is selected for under static conditions (c.f. ***Phenotypic Accommodation***). We have also shown that, so long as the range of phenotypes produced both by genic and epigenetic variability is sufficiently within the bounds of directional selection, plasticity may be maintained in a population under static conditions. Alternatively, if the range of phenotypes produced exceeds the bounds set by directional selection, decreased plasticity is advantageous (c.f. ***Loss of Variability***). Our results indicate the existence of a trade-off between optimization under static conditions and readiness for changing conditions. When undergoing change to adapt to unfavorable environments, populations that express a variety of phenotypes are more likely to be able to adapt quickly, since beneficial phenotypes are more likely to be present and selected for. However, this same trait may act as a detriment under steady-state conditions, as the potential for variation causes the phenotypes to deviate from the ideal. As such, phenotypic plasticity within populations, under certain conditions, may be reduced over time.

Importantly, our results demonstrate how plasticity may be favored and subsequently increase within a population within static environmental conditions (c.f. ***Establishment and maintenance of plasticity***). Central to this result is variation in the relative mutation rate for genic and non-genic control of phenotype. Various factors contributing to μ_{rel}, such as pleiotropy, linkage, epistasis, essentiality, or other genetic conflict can prevent the occurrence of certain types of changes. Similarly, the architecture of genetic networks underlying both genic and non-genic control of phenotype may also provide a larger or smaller substrate for mutations, either through a variable number of mutable positions within the genome or through pleiotropy and genetic conflict. Such genic-plastic conflict may be a wide-spread mechanism by which plasticity evolves within a population.

We also note that the trajectory of genetic control of plasticity is not only dependent on μ_{rel}, but also the duration of time considered to be an epoch. The simplest way to define the end of an epoch would be a subsequent shift to a new environment. In this case, plasticity may continue to increase in a population so long as the time before

a subsequent environmental shift is shorter than the time required to undergo genetic accommodation of a new environment. Alternatively, the considered epoch may also end when the relative mutation rate μ_{rel} is altered. Given that in our model, where the primary driver of the evolution of plasticity is genic-plastic conflict, such conflict may also be resolved via gene duplication or new gene evolution (Long et al., 2013), altering μ_{rel} either upwards or downwards.

Additional information

The authors affirm that all data necessary for confirming the conclusions of the article are present within the article, figures, and tables. Code to simulate and generate figures may be found at : https://github.com/avianalter/sde_evo.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.biosystems.2022.104791. Further information on simulation details and additional simulation conditions may be found in the supplements.

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