Quantitative genetic models of robustness and evolvability.

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Abstract

Theoretical models of the evolution of discrete phenotypes show that the most evolvable populations are composed of genotypes with intermediate levels of phenotypic robustness. This has been attributed to a special kind of epistasis, the analog of which for complex quantitative traits might not readily apparent. Here, with simulation models, I show that a variety of plausible kinds of quantitative genetic epistasis will do; as long as it increases cryptic genetic diversity and expected allele effect sizes are not too large. In fact, epistasis is not necessary, since cryptic genetic diversity can also accumulate via phenotypic plasticity. But with phenotypic plasticity, the mapping of phenotypic robustness to evolvability is sensitive to the nature and predictability of environmental variation. So, just as for discrete-traits, the robustness of quantitative traits can have complex effects on evolvability, and this depends on exactly how genetic diversity is hidden and revealed.

1. Introduction

Counterintuitively, analyses of discrete-phenotype models have shown that phenotypic robustness can increase evolvability via a special kind of epistasis, one that increases the diversity of neighborhoods of mutationally-accessible alternative phenotypes (Ciliberti et al., 2007; J. A. Draghi et al., 2010; Wagner, 2007, 2012). The evolution of such phenotypic neighborhoods may seem apropos for phenotypes such as RNA molecules and proteins. But the appropriateness of the discrete-phenotype theory for more integrative and quantitative traits is unclear (Paaby & Rockman, 2014). Here our goal is to clarify how phenotypic robustness can affect the evolvability for quantitative traits. One special aim is to articulate the kind of quantitative genetic epistasis that can recapitulate the non-monotonic relationship between genetic robustness and evolvability that has been found for discrete phenotypes (J. A. Draghi et al., 2010; Hardy, 2024). Another aim is see if there are analogous conditions in which evolvability is maximized by intermediate levels of plasticity. Of course, much previous work has looked into the effects of epistasis and plasticity on evolvability (Carter et al., 2005; Gomez-

Mestre & Jovani, 2013; Gros et al., 2009; Lande, 2009). So, a third aim is to place the models developed here in that context.

A good way to start would be with a glance at the discrete-trait models of phenotypic robustness and evolability (J. A. Draghi et al., 2010; Meyers et al., 2005). Much of the behavior of these models can be boiled down to two key properties: (1) allele effects are conditional, and (2) the mutational processes entails a trade-off between accumulating and realizing evolutionary potential. They ask us to suppose that every genotype *i* has a *K*-dimensional neighborhood $\mathbf{k}_i$ of phenotypes that are accessible by one mutation (Wagner, 2007). With probability *q*, mutations are neutral in the sense of lacking direct phenotype effects, but neutral mutations change the phenotypic neighborhood $\mathbf{k}_i$, specifically, by resampling *K* new elements from the global set of phenotypes, **P**. Thus, "neutral" mutations are really only cryptically neutral; they have epistatic effects that can be exposed by subsequent, non-neutral mutations, which occur with probability 1-*q*. These non-neutral mutations also affect the phenotypic neighborhood, again by triggering a re-choosing of *K* elements from **P**. In sum, we have a mutational system that generates and releases potential genetic diversity. All mutations determine a set of potential next steps along an evolutionary path. Non-neutral mutations take such steps.

So, in the discrete-phenotype models, epistasis is the rather subtle notion that the only thing some mutations do is make other mutations possible. How does such epistasis align with the epistasis of quantitative genetics? Well, in classical quantitative genetics, statistical epistasis is what is left over after the phenotypic variance in a population has been apportioned into fixed additive genetic and environmental effects (Aylor & Zeng, 2008; Mackay & Anholt, 2024; Payne & Wagner, 2019). In other words, epistasis is non-additive genetic variance (Carter et al., 2005; Moore & Williams, 2005). Formally, for two di-allelic loci in a haploid genome, epistasis $\varepsilon = f_{ab} + f_{AB} - f_{aB} - f_{Ab}$, where each f_{ij} term gives the quantitative phenotype of a haplotype (Payne & Wagner, 2019). Depending on the sign of ε, one can distinguish between negative epistasis (where combined allele effects are less than the sum of their parts) or positive epistasis (where the sum is greater than its parts). In either case, epistasis may induce a change in the sign of allele's effect, something that may be especially important for adaptive dynamics, as sign-

epistasis can increase the ruggedness of an adaptive landscape (Payne & Wagner, 2019). Of course, epistasis can entail interactions between more than two alleles, and such networks of interaction can be complicated (Gjuvsland et al., 2007; Lozovsky et al., 2021), but regardless, from a statistical quantitative genetic perspective, epistasis is just non-additive genetic variance.

To a certain extent, the epistasis of discrete-phenotype models resembles a kind of quantitative genetic negative statistical epistasis. As for an underlying mechanism, that is, for a more functional take on epistasis (Bank, 2022), we could imagine that the effects of one class of alleles are suppressed until exposed by subsequent mutations affecting a modifier phenotype. This corresponds nicely to so-called “capacitor” models of genetic robustness (de Visser et al., 2003; Masel & Siegal, 2009). An oft-touted real life example is a heat-shock protein that buffers the phenotypes of several target proteins against environmental and mutation perturbations, with the upshot being that when the heat-shock protein itself is sufficiently perturbed, large stores of cryptic diversity can be released (Rutherford, 2000; Rutherford & Lindquist, 1998; Waddington, 1953). Can we use a quantitative capacitor model to replicate the discrete-phenotype model dynamics?

2. A quantitative epistasis model

Each of the models I describe here were developed using the SLiM v4 framework (Haller & Messer, 2023). Model parameters are summarized in Table 1.

Table 1. Capacitor model parameters.

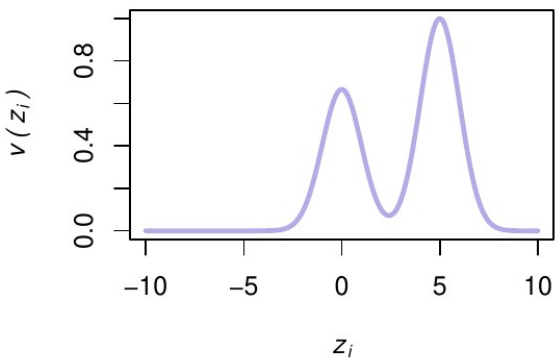
Parameter	Description	Values
K	Environmental carrying capacity	500
b	Birth rate	1.5
L	Genome size	1e4
μ	Mutation rate	1e-5
q	Probability mutation is a β allele that epistatically modifies the effect of one or more α alleles	$0.0 < q < 0.9$

$1\text{-}q$	Probability mutation is an α allele	$0.1 < 1\text{-}q < 1.0$
σ	Standard deviation of α allele effects	5.0
ψ	Default epistatic capacitance	{0.0, 0.1, 0.5}
ω	Weakness of selection	1.0
O_i	Phenotypic optimum in environment i	{0, 5}

Imagine an unstructured population of individuals in an environment with a carrying capacity, K = 500 (Supplementary File S1). Each individual has a one-chromosome, diploid genome of length L= 10,000. The life cycle entails clonal reproduction, viability selection, and density-dependent regulation. Generations are non-overlapping. The fecundity of each individual that survives selection is determined by a draw from a random Poisson distribution with an expectation, b, of 1.5. Offspring production entails mutation at rate μ=1e-5 per site, per genome, per individual, per generation. Two classes of mutation may occur. With probability $1\text{-}q \in \{0.1 < q < 1.0\}$, an α mutation directly affects an individual's phenotype, z_i. Such effects are drawn from a zero-meaned random normal distribution with a standard deviation σ = 5.0. But α mutations are subject to a capacitor phenotype, and by default – that is, with a wild-type capacitor phenotype – α allele effects are scaled by factor $\psi \in \{0.0, 0.1, 0.5\}$. Conversely, with probability q, a β mutation indirectly affects z_i, by changing the capacitor phenotype, and thus releasing cryptic α allele diversity. Specifically, a β allele multiplies each effect of a randomly chosen set of α alleles, of size n_k, by a n_k-dimensional vector of factors $\mathbf{c}$ sampled from a random uniform distribution $\{-1 < c < 1\}$. The value of n_k for each β allele is determined as a proportion $\rho \in \{0.1, 0.6\}$ of active α alleles, with that constraint that $n_k < 20$. All β mutations that happen before the first α mutation are neutral. If more than one β mutation modifies the effect of the same α allele, the modifier effects are summed. Thus, an individual phenotype value, $z_i = \Sigma\, \alpha_{ij} * \psi + \Sigma\, \alpha_{ij'} * \Sigma\, \beta_{ikj}$, where α_{ij} denotes the jth α allele of individual i, $\alpha_{ij'}$ specifies that allele j is subject to a mutated capacitor, and β_{ikj} denotes the kth β allele affecting the jth α mutation of individual i. It is a subtle point, but to be clear, although a β allele does not contribute directly to a genotype's potential diversity, since the capacitor phenotype is polygenic and quantitative, a particular capacitor phenotype configuration can be produced by many different combinations of

β alleles. Any compensatory effects between β alleles constitute another form of cryptic genetic variance.

Figure 1. *A rugged adaptive landscape. After t_x=100 generations of stabilizing selection about O_0=0, a second, higher adaptive peak is added at O_x=5.*

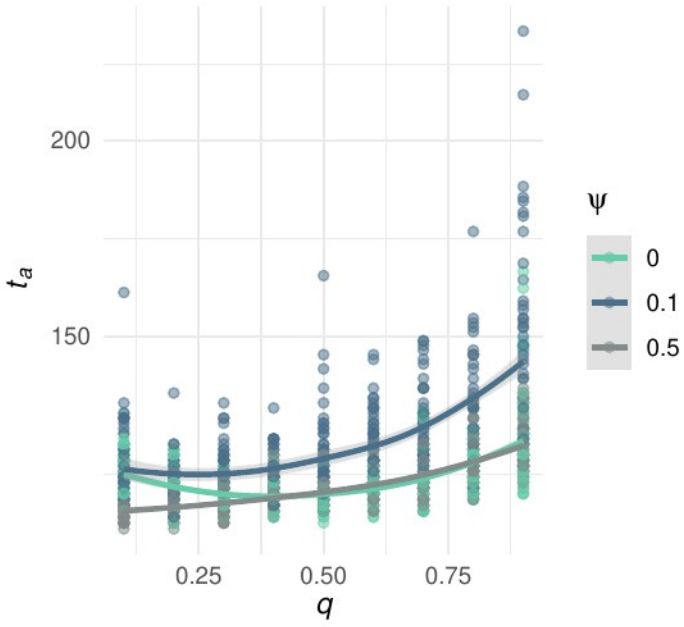


Initially, genomes are empty containers for mutations and the population is monomorphic for the optimal phenotype. But after some generations, a second, higher peak is added to the adaptive landscape. Concretely, before t_x=100, the mapping of phenotypes to viabilities, $v(z_i)$, is via a Guassian fitness function with a mean of 0.0 and a standard deviation ω=1.0, scaled such that a perfect match confers a fitness of 0.67: $v(z_i) = P_0(z_i)/(1.5*P_0(O_0))$ for $X \sim N(O_0, \omega)$, where O_0 is the initial phenotypic optimum, and division by $1.5*P(O_0)$ sets the viability of individuals with that optimal phenotype to 0.67. After t_x, we make a more rugged adaptive landscape, and render O_0 suboptimal, by adding a second normal distribution to the fitness function: $v(z_i) = P_0(z_i)/(1.5*P_0(O_0))$ for $X \sim N(O_0, \omega) + P_x(p_i)/(P_x(O_x))$ for $X \sim N(O_x, \omega)$, where $O_x = O_0 + 5.0$. See Figure 1. If it helps to think of something tangible, you can imagine these two peaks as corresponding to two high-fitness gape sizes given a distribution of prey sizes, or two levels of mating aggressiveness given a social milieu. In addition to phenotype-by-environment matching, the viability of all individuals is negatively density dependent, as per a Beverton-Holt function (Beverton & Holt, 1957).

To summarize, at the start, the population is perfectly adapted to its environment, and although the direct effects of α mutations can be large, they are suppressed by a wild-type capacitor phenotype. This capacitance can be altered by β mutations, which can thereby release some of the cryptic genetic diversity of α alleles. Initially, any such release would be deleterious and so

the capacitor phenotype is under strong purifying selection. But when the environment changes, a release of cryptic genetic diversity can help a population pass through a valley in the adaptive landscape and evolve to a new, higher optimal phenotype, that is, do stochastic tunneling (Guo et al., 2019; Iwasa et al., 2004).

Figure 2. *How, q, the probability of mutation affecting an epistatic capacitor affects t_a, evolvability, measured as the expected number of generations for adaptation across a valley in a rugged fitness landscape. Results are for when the proportion of active α alleles targeted by β mutation, ρ, is 0.6. Results are qualitatively similar for other values of ρ. Each point represents the outcome of an individual simulation. Lines are loess regressions. The colors of points and lines correspond to different values for ψ, the default capacitance phenotype, that is, the initial rescaling of the effects of α alleles.*



If we iterate this life cycle and count t_a, the number of generations it takes the population to evolves a mean phenotype within 25% of O_x, running 25 replicated simulations for each combination of values for model parameters q and ψ, we recover a relationship between q and t_a similar to what has been found for discrete-phenotype models (Fig. 2). If the combination of σ and ψ is sufficiently large for there to be a decent probability that an α mutation can carry a genotype across the valley in the adaptive landscape (Fig. 1), mutational robustness trades off with evolvability; t_a increases monotonically with q. This corresponds to the behavior of discrete-phenotype models when all possible phenotypes are in the one-mutation-accessible phenotypic neighborhood (J. A. Draghi et al., 2010). But with smaller ψ values – that is, higher wild-type capacitance – the relationship between robustness and evolvability is non-monotonic; evolvability is maximized at intermediate robustness. Moreover, increasing the default

capacitance – that is, shrinking ψ – increases genotype evolvability across the range of q values, since this tantamount to hiding more genetic variance. And this effect is strong enough that at intermediate values for q, genotypes with ψ=0 are more evolvable than genotype with ψ=0.5. (In Figure 2, the gray and green lines cross.) This is a robustness effect on evolvability stronger than anything observed with discrete-phenotype models.

So, a genetic variance capacitor is one specific form of epistasis that can translate an increase in quantitative genetic robustness to an increase in evolvability. More specifically, our model shows us that it can help populations traverse rugged adaptive landscapes. Indeed, qualitatively, the dynamics of the model are robust to the addition of a third class of mutation that is not subject to the capacitor phenotype: Suppose that class γ mutations occur as often as either α or β mutations, and their effects are drawn from a random normal distribution with a mean of zero and standard deviation of one. Given that distribution, the odds of a γ mutation having an effect large enough to move a population directly between peaks in the adaptive landscape is about one in a million, so adaptation via γ mutation would depend on the combination of several alleles. But for a population with a mean phenotype value centered on O_0, each allele on its own would have a deleterious effect on fitness and be selected against. Therefore, populations stochastically tunnel to the new optimal phenotype by building-up and releases α allele diversity. That is the beauty of cryptic genetic variance (Kawecki, 1994).

What connects robustness to evolvability is a positive relationships between robustness and cryptic genetic variation. In a quantitative genetic context, we can get there by assuming that alleles with potentially large effects are suppressed by a capacitor, which when mutated, can stop suppressing. But a similar epistatic damping of allele effects can occur without capacitors per se. In fact it could apply to any system with a so-called bow-tie architecture, that is, wherever a system's dynamics are governed by a few highly-connected hubs in an interaction network, and conversely, system dynamics are little affected by variation at other nodes in the network (Bergman & Siegal, 2003; Kitano, 2004). Such architectures are typical of metabolic, developmental, and gene regulatory networks. Hence, the dynamics inferred from our capacitor model should apply more broadly to any bow-tie system that promotes genetic robustness.

3. Cryptic genetic variation not with epistasis but plasticity.

To repeat the theme, phenotypic robustness can boost evolvability by increasing a population's stores of cryptic genetic variance (Paaby & Rockman, 2014). In Section 2, we saw that mutational robustness via quantitative genetic epistasis can cause such increases. Cryptic genetic diversity can also arise via phenotypic plasticity, that is, some departure from complete environmental robustness (Gomez-Mestre & Jovani, 2013; Ledón-Rettig et al., 2014; Scheiner, 2013; Schlichting, 2008). In this section, to get a better sense for how the manner in which genetic diversity is concealed and released affects evolvability, I describe and analyze two models of phenotypic plasticity. See Table 2 for a summary model parameters and variables. These models show that when it comes from plasticity, the relationship between phenotypic robustness depends not just on the distribution of exposed and hidden allele effect sizes, but also on how the environment varies. As predicted by other authors (Paaby & Rockman, 2014), in comparison to epistasis, it is harder to find conditions in which cryptic genetic variation predicated on plasticity does not increases evolvability. Nevertheless, there are such conditions, and they are plausible.

Table 2. Plasticity model parameters and variables are as for the epistatic capacitor model, but for the following changes.

Parameter	Description	Values
e_j	Environmental sate	{0, 1}
λ	Per-generation probability of environmental change	0.05
m	Migration rate between demes	0.3
μ	Mutation rate	1e-4
p	Probability that mutation is plastic (analogous to q)	$0.1 < p < 1.0$
σ	Standard deviation of allele effects	{0.1, 0.2, 0.4}
ω	Weakness of selection	1.3
O_i	Environmental-state-specific phenotypic optimum	{-2.5, 2.5} : Temporal variation. {0, 3} : Spatial

variation.

Variable	Description	Range
t_a	Number of generations to adapt to novel environmental state	$0 < t_a$
φ_m	Phenotypic variance of migrants to *deme*$_2$	$0 < \varphi_m$
φ_o	Phenotypic variance of offspring of migrants to *deme*$_2$	$0 < \varphi_o$

3.a. Phenotypic plasticity in environments that vary over time.

Consider the evolution of a population like that described above, but for a few changes (Supplementary File S2). Let the external environment vary over time. Specifically, suppose the environment can be in one of two states e_j {0, 1}, with parameter λ=0.02 determining the per-generation probability of a change in state. Suppose the adaptive landscape has the same rugged, two-peaked surface as in our epistastic capacitor model, but shift the peaks so they are equally distant from zero, O_1 = -2.5, and O_2=2.5, and relax the steepness of the selection gradients some by setting ω to 1.6. (The combinations of these parameters values were found via trial and error, to reveal interesting transitions in the mapping of robustness to evolvability. But admittedly, they are rather arbitrary.) Let the phenotype value of each individual be determined by summing the effects plastic and non-plastic alleles. Mutations occur at rate μ=1e-4 per site, per individual, per generation, and with probability $p \in \{0.1 < p < 1.0\}$, allele effects are phenotypically plastic. Call these *B* mutations. Conversely, with probability 1 - p an *A* mutation occurs that has an effect that is insensitive to the state of the environment. For a mutation j of either type, a genotype effect, G_j, is drawn from a zero-meaned random normal distribution with a standard deviation σ {0.1, 0.2, 0.4}. For *A* mutations this genotype effect contributes directly to an individual's phenotype. For *B* mutations, in addition to a genotype effect G_j, each allele j has an environmental specificity S_j {0, 1}. Plastic *B* alleles only contribute to the phenotype when they are in an environment of the correct state, $S_j = e_j$.

As for the epistatic capacitor model, before generation t_x=100, the population adapts to O_1. Then the second and higher adaptive peak is added at O_2, and the population is challenged to cross the adaptive valley between the peaks. In this case, fluctuations between environmental states work as a kind of cryptic diversity pump; cryptic genetic diversity accumulate during one environmental phase, and then is converted to additive genetic diversity when the environment changes.

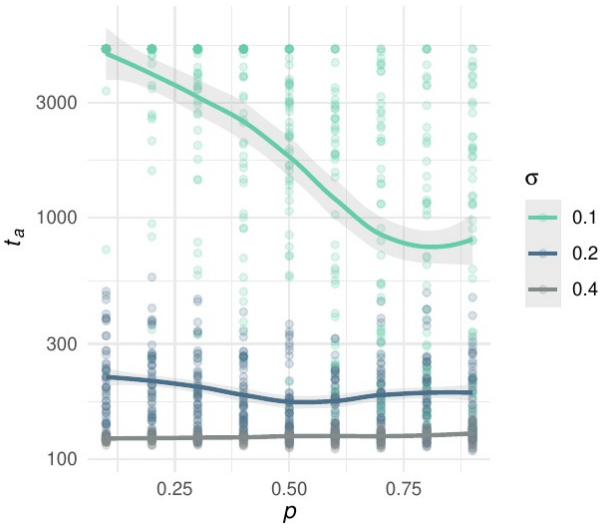


Figure 3. *How, p, the probability of a mutation being conditionally neutral in one of the environmental states e_i, affects t_a, the expected number of generation for adaptation across a valley in a rugged fitness landscape. Each point represents the outcome of an individual simulation. Lines are loess regressions. The colors of points and lines correspond to different values for sigma, the standard deviation of the allele effect distribution.*

More routinely, in individual-based models, plasticity is modeled at the genotype level; genotype effects of plastic alleles are summed, and then this summed value is multiplied by an environmental effect (or cue) to determine the overall plastic contribution of the genotype to the phenotype (J. Draghi, 2020; Scheiner, 2013; Scheiner & Holt, 2012). Here, we model it at the allele level to highlight the parallels with our models of epistasis. Also note that class *A* alleles can be equally well described as non-plastic, or as contributing to the elevation (i.e., intercept) of a plastic reaction norm (Lande, 2009). Indeed, the latter emphasizes the integrative process by which the phenotype is determined. Even if only a few of many alleles affecting a phenotype are plastic, the phenotype is plastic. But here, to emphasize differences in the environmental sensitivity of allele effects, we will just call them non-plastic.

Figure 3 shows a summary of 50 replicated simulations for every combination of above-given values for p and σ, that is, the probability of plastic B mutations and the spread of allele genotype values, G. Here, with a relatively broad distribution of allele effects (σ=0.4), as for our epistasis models with low default capacitance (that is high values for ψ) we see a monotonically increasing relationships between p and t_a, the time for adaption to O_2. And as for our epistasis models with higher default capacitance (low values for ψ), here with smaller expected allele effects, $\sigma \in \{0.1, 0.2\}$, we find a convex-functional mapping of p to t_a, with evolvability (t_a^{-1}) maximized at intermediate value of environmental robustness (p^{-1}). Decreasing the variance of allele effects, σ=0.1, pushes the maximum evolvability to higher p values such that as p approaches one there is only a slight decrease in evolvability. With yet tighter dispersions of allele effects, evolvability would be maximized at p=1. So, the effects on evolvability of phenotypic robustness via this kind of plasticity, in this kind of environment, are similar to those inferred for phenotypic robustness via epistasis, except that when allele effects tend to be small, and hence adaptation to O_2 depends on cryptic genetic diversity across many loci, evolvability is greatest when most, if not all, alleles are plastic. In fact, as allude to above, the conditions required for a non-monotonic relationship between p and t_a are much more stringent that for a monotonically decreasing or increasing relationship. Hence, what might have seemed rather arbitrary choices for the values of some model parameters, e.g., λ, σ, and ω.

This disparity with the epistasis model can be explained by the fact that with plasticity, the trade-off between cryptic genetic diversification and release is relaxed somewhat, and consequently the positive effects of phenotypic robustness on evolvability are diminished. With epistasis, increasing q – the probability that a mutation is an epistatic modifier – causes a direct and proportional decrease in the rate of non-neutral mutation. Moreover, non-neutral mutations affect the phenotype only indirectly, via the release of cryptic genetic diversity. In contrast, with plasticity, increasing p – which is analogous to q and gives the probability that a mutation's effects can be masked by one of the environmental states – causes a less than proportional decrease in the rate on non-neutral mutation, since some fraction of plastic mutations will be exposed in their natal external environment. Moreover, with plasticity, non-neutral mutations directly affect the phenotype, with cryptic diversity released by changes in the environment. So,

in environments that change over time but not space, evolvability can indeed be maximized by intermediate levels of phenotypic plasticity, but only given the right combination of allele effect sizes, environmental sensitivities, and environmental variations.

3.b. Phenotypic plasticity in environments that vary over space.

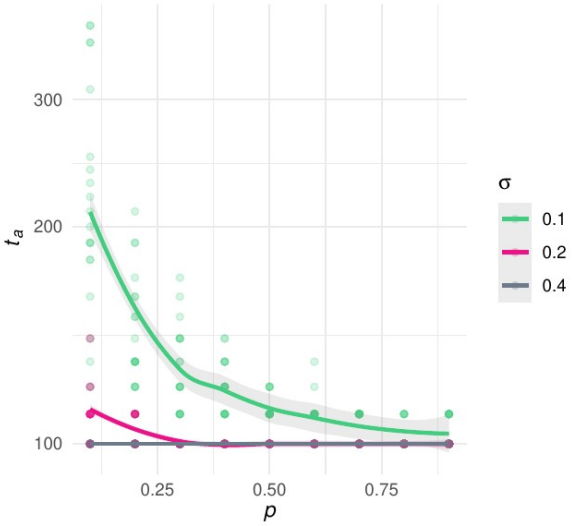
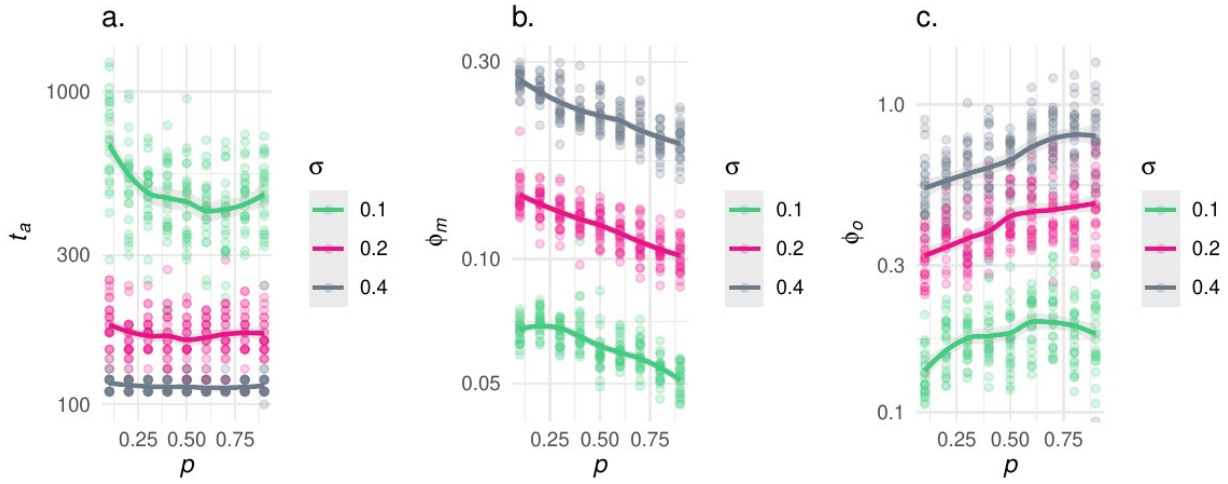


Figure S1. *How, p, the probability of plastic mutation, affect t_a, the number of generations it takes to adapt to a marginal habitat. Each point represents the outcome of an evolutionary simulation. Lines are loess regressions through points grouped, and color-coded, according to values for σ, that is, the spread of allele effects.*

In the previous model, we let the environment vary over time. Suppose instead that it varies over space. To keep things simple, let the population be split into two subpopulations (*deme*$_1$, *deme*$_2$) of equal carrying capacity, K=500, that occur in different environments such that optimal phenotype values also differ (O_1 = 0, O_2 = 3). Each simulation starts with 500 individuals in *deme*$_1$ and none in *deme*$_2$. Then, starting in generation 101, in each iteration of the life cycle, individuals migrate between demes at per capita rate m = 0.3. In the simplest case, this occurs after offspring production but before development of the adult phenotype that is subject to selection (Scheiner, 2013, 2014), a sequence of events typical of lineages that could be described as having 'larval' dispersal, for example, seed plants and barnacles (Supplementary File S3). In this case, the relationship between p and t_a is uncomplicated; evolvability – t_a, here the number of generations until deme2 achieves half of its carrying capacity – is maximized when p=1 (Fig. S1).

Now, suppose instead that migration occurs after development but before reproduction, for example, as in butterflies (Supplementary File S4). Individuals develop in one environment, but are then subject to selection in another. Therefore, the plastic reaction norms of the would-be

294 founders of *deme*$_2$ are quite different from the reaction norms of their offspring; each is
295 predicated on a different set of *B* alleles. This makes the relationship between *p* and t_a more
296 interesting (Fig 4.a.): unless allele effects tend to be quite large, t_a varies non-monotonicaly
297 across the range of values for σ; evolvability is highest with intermediate levels of plasticity.



298 ***Figure 4.*** *How, when migration and selection take place after plastic development, the odds of*
299 *plastic mutation affects (a) evolvability, parameterized as* t_a*, time in generation for adaptation to*
300 *a marginal habitat, (b)* φ_m*, the phenotypic variance of migrants from the core habitat, and (c)* φ_o*,*
301 *the phenotypic variance expressed by the offspring of migrants from the core habitat. Each point*
302 *represents the outcome of an evolutionary simulation. Lines are loess regressions through points*
303 *grouped, and color-coded, according to values for σ, that is, the spread of allele effects.*

304 To understand this pattern, consider that there are two main factors affecting the odds of adapting
305 to O_2: φ_m, the variance of phenotypes expressed by migrants from *deme*$_1$, and φ_o, the variance of
306 phenotypes expressed by their offspring. For such offspring, the odds of survival go up if their
307 parents have brought stores of cryptic *B* alleles. Therefore, the odds of plastic mutation, *p*, and
308 the rate of adaptation to O_2, t_a^{-1}, should have a positive relationship. On the other hand, For
309 migrants to *deme*$_2$ to have a decent chance of surviving to reproduce, they need to carry *A* and *B*
310 alleles that would have been selected against in *deme*$_1$ had they remained. But only half of *B*
311 alleles are expressed in either deme, so when *p* increases, the effective rate of non-neutral

mutation in *deme*$_1$ decreases. Therefore, the odds of plastic mutation, *p*, should have a negative effect on the rate of adaptation to O_2. In sum, *p* has countervailing effects on t_a^{-1}.

A further complication is that the offspring of migrants to *deme*$_2$ can move back to *deme*$_1$, from whence their parents came, before they are subject to selection. Consequently, another potential effect of increasing the odds of plastic mutation, *p*, is an increase in the phenotypic variance in *deme*$_1$ via immigration of individuals that developed in *deme*$_2$. But this effect would be much attenuated by selection in *deme*$_1$ prior to the next round of reproduction and migration.

Figure 4.c. shows that the phenotypic variance of the offspring of migrants from *deme*$_1$ to *deme*$_2$ increases with the probability of plastic mutation. This explains why over the bottom end of its range, increasing *p* boosts evolvability. On the other hand, Figure 4.b. shows that across values for *p*, the phenotypic variance of migrants from *deme*$_1$ decreases. This effect explains how, over the top half of its range, *p* decreases evolvability. So, to put a point on it, when cryptic genetic diversity arises from phenotypic plasticity in an environment that varies over space, and there is a lag between development and selection, unless allele effects tend to be large relative to the distance between peaks in the adaptive landscape, evolvability is maximized with intermediate levels of developmental plasticity. With too little plasticity, the offspring of migrants to a new environment have too little cryptic genetic diversity to draw from. But with too much plasticity, the would-be parents of those offspring have too little genetic diversity to make it through selection before reproduction.

4. Contextualizations

Using discrete-phenotype models as a springboard, we identified plausible conditions in which epistasis and plasticity have non-monotonic effects on the evolvability of quantitative traits. From what I can tell, this has yet to be widely appreciated. Take adaptive landscape theory. Building on ideas proposed almost a century ago by Sewell Wright (Wright, 1931), modern probabilistic genotype-fitness landscape models – such as rough Mount Fuji Models (Aita et al., 2000) and NK-Modles (Kauffman & Weinberger, 1989; Østman et al., 2011) – cast epistasis as the *de facto* cause of ruggedness in adaptive landscapes and hence unequivocally a hindrance for

evolvability (Bank, 2022). This may be true enough in a classical population genetic framework, that is, if we assume a direct mapping of genotypes to fitness without any inter-mediating interactions with phenotypes and environments. But otherwise, such an assertion is hard to justify; ruggedness in the adaptive landscape could just as well arise from ecological contingencies. The other main branch of adaptive landscape theory, Fisher's Geometric Model (FGM), is explicitly quantitative genetic (Tenaillon, 2014), but dismisses *a priori* the possibility of function epistasis – that is, non-additive allele effects on phenotypes – and explains epistasis as solely the statistical consequence of a non-linear functional mapping of phenotypes to fitness (Bank, 2022) In other words, Fisher's concept of epistasis boils down to a kind of relativity for the fitness effect of additive alleles (Hardy & Forister, 2023). (Although, since Fisher's days, much empirical evidence has pointed to the ubiquity of functional epistasis (de Visser & Krug, 2014; Fowler et al., 2014; Johnson et al., 2019).) So, the adaptive landscape theory gives us two extreme perspectives on how functional epistasis affects evolvability: it gets in the way, or it is not a factor. The FGM does allow for more open-ended effects of statistical epistasis on evolvability, which depend on its sign and direction (Carter et al., 2005). And FGM analyses have indicated a fundamental connection between epsistasis and genetic robustness (Gros et al., 2009; Wilke & Christoph, 2001). But the connection between epistasis and quantitative phenotypic robustness has been missed.

Outside of adaptive landscape theory, some previous theoretical work has demonstrated ways in which epistasis can increase cryptic genetic diversity, and hence evolvability (Barton & Turelli, 2004; Cheverud & Routman, 1996; Hansen & Wagner, 2001). But the focus has been on how epistatic variation can be converted to additive variation via genetic drift or genetic draft (Neher, 2013; Paaby & Rockman, 2014). Here, by contrast, we consider the release of epistatic variation by epistatic mutation, that is, at genes encoding capacitor proteins, or the hubs of bow-tie regulatory networks. Consequently, we consider situations in which there may be a trade-off between the rate at which cryptic diversity grows and the rate at which it is exposed. This trade-off is at the core of the discrete-phenotype models of robustness and evolvability (J. A. Draghi et al., 2010; Hardy, 2024). But it is not an obvious feature of drift and draft scenarios. It seems that the mechanisms by which genetic diversity is concealed and exposed matter.

Which brings us to plasticity. Much intuition and previous work points to positive effects of plasticity on evolvability, and more specifically, via cryptic genetic diversity affecting reaction norm slopes (Lande, 2009; Ledón-Rettig et al., 2014). Moreover, analyses of gene-regulatory-network (GRN) models have shown that (1) selection for a plastic developmental system tends to reshape the distributions of allele effects such that populations become more evolvable (J. A. Draghi & Whitlock, 2012; Gomez-Mestre & Jovani, 2013), (2) in comparison to populations evolving simple linear reaction norms, populations of plastic GRNs – which can evolve non-linear reaction norms – evolve more adaptive and evolvable plasticity, and (3) this is because plastic GRNs accumulate more cryptic genetic variation (van Gestel & Weissing, 2016). But such analyzes have use rather stylized measures of evolvability, and have not considered the specific life history and meta-population structures for which we found non-monotonic effects of plasticity on evolvability. One such life history feature in particular is unpredictable change in the environment during a lag in the life cycle between plastic development and selection. This has previously been shown to curtail the evolution of adaptive plasticity, but previous work has focused on how such unpredictability affects the evolution of plasticity per se, rather than evolvability (Lande, 2009; Scheiner & Holt, 2012). So, as for epistasis, to my knowledge, this is the first clear demonstration that certain types of plasticity map non-monotonically to evolvability.

In comparison to the more traditional quantitative genetic approaches that we have used here, a GRN framework offers a much richer and more evolvable mapping of genotypes to phenotypes. Therefore, it can yield insights into how the developmental systems underlying quantitative phenotypes might themselves evolve adaptively. Further analysis of GRNs is sure to further advance our understanding of the effects of phenotypic robustness on evolvability, for example, by telling us about how specific network properties or subsystems affect evolvabilty, and about how the mechanics of evolvability depend on the nature of the adaptive challenge and developmental system constraints. On the other hand, the complexity of GRN models makes their analysis and interpretation more challenging (Hardy, 2024). The main selling point of the quantitative genetic approaches we have taken here is that they are easy to interpret. So, to close,

let us repeat our main interpretations: As for discrete phenotypes, when it increases cryptic genetic diversity, quantitative epistasis can have non-monotonic effects evolvability. This is true of both capacitor and bow-tie network models of functional epistasis. This can also be true of phenotypic plasticity, but only with the right combinations of environmental variation, life history, population structure, and genetic architecture.

Data Accessibility

Models codes are provided as supplementary documents, and are also available via a GitHub repository (https://github.com/n8-rd/QuantGenEvo). [Upon acceptance, these codes will also be archived as a Zenodo repository.]

Competing Interests

None to declare.

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