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Dominance Can Increase Genetic Variance After a Population Bottleneck: A Synthesis of the Theoretical and Empirical Evidence

Andrew J. Mularo, Ximena E. Bernal, and J. Andrew DeWoody

From the Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA (Mularo, Bernal, and DeWoody) Smithsonian Tropical Research Institute, Apartado 0843-03092, Balboa, Republic of Panamá (Bernal) Department of Forestry and Natural Resources, Purdue University, 715 W. State St, West Lafayette, IN 47907, USA (DeWoody)

Address correspondence to A. J. Mularo at the address above, or e-mail: amularo@purdue.edu.

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Abstract

Drastic reductions in population size, or population bottlenecks, can lead to a reduction in additive genetic variance and adaptive potential. Genetic variance for some quantitative genetic traits, however, can increase after a population reduction. Empirical evaluations of quantitative traits following experimental bottlenecks indicate that non-additive genetic effects, including both allelic dominance at a given locus and epistatic interactions among loci, may impact the additive variance contributed by alleles that ultimately influences phenotypic expression and fitness. The dramatic effects of bottlenecks on overall genetic diversity have been well studied, but relatively little is known about how dominance and demographic events like bottlenecks can impact additive genetic variance. Herein, we critically examine how the degree of dominance among alleles affects additive genetic variance after a bottleneck. We first review and synthesize studies that document the impact of empirical bottlenecks on dominance variance. We then extend earlier work by elaborating on 2 theoretical models that illustrate the relationship between dominance and the potential increase in additive genetic variance immediately following a bottleneck. Furthermore, we investigate the parameters that influence the maximum level of genetic variation (associated with adaptive potential) after a bottleneck, including the number of founding individuals. Finally, we validated our methods using forward-time population genetic simulations of loci with varying dominance and selection levels. The fate of non-additive genetic variation following bottlenecks could have important implications for conservation and management efforts in a wide variety of taxa, and our work should help contextualize future studies (e.g., epistatic variance) in population genomics.

Keywords: Additive variance, bottleneck, dominance, dominance coefficient, founder effect, genetic variance, population reduction.

Genetic variation is one of the key drivers in the evolution of complex organisms, as new genetic combinations provide adaptive potential. Bottlenecks, however, can have detrimental effects on the genetic variation of populations of organisms and reduce evolutionary potential (Frankham et al. 1999; Andersson et al. 2010). A bottleneck's drastic reduction in population size can reduce genetic diversity through loss of heterozygosity and allelic diversity via inbreeding and genetic drift (Leberg 1992; England et al. 2003). For example, bottlenecks associated with island colonization can result in established populations that contain lower genetic diversity than their mainland counterparts (Frankham 1997), and such bottlenecks can lead to inbreeding depression and an increased risk of extinction (Frankham 2008). Human-induced bottlenecks can have similar consequences with reductions in population genetic variation due to processes such as habitat degradation (Keyghobadi 2007) and overharvesting (Hutchinson et al. 2003). This pattern of reduced genetic variation through human-induced bottlenecks is well known in many taxa, including mammals (Hoelzel et al. 1993; Houlden et al. 1996; Johnson et al. 2011; Sastre et al. 2011), birds (Chan et al. 2011), amphibians and reptiles (Beebee 2005; Shaffer et al. 2015), fish (Fauvelot et al. 2003; Hutchinson et al. 2003), and insects (Kozol et al. 1994). Despite this pattern of decreased genetic variance, several laboratory experiments show an unexpected increase in variance following a bottleneck. Early empirical evidence of this phenomenon was revealed in fruit flies *(Drosophila silvestris*) and mosquitofish (*Gambusia holbrooki*) by chromosomal inversion and allozyme datasets, respectively (Carson and Wisotzkey 1989; Leberg 1992). Increased genetic variation for specific quantitative traits has also been shown in laboratory colonies of mice (Cheverud et al. 1999), houseflies (Bryant et al. 1986), *Drosophila* (Carson 1990; Van Heerwaarden et al. 2008), butterflies (Saccheri et al. 2001), and for domesticated agricultural crops (Briggs and Goldman 2006). Despite such patterns, the genetic processes that promote an increase in variation due to a bottleneck are poorly understood.

In general terms, overall genetic variance (V_G) in a population results from a combination of additive variance at

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Table 1. Terms used herein to describe quantitative aspects of genetic diversity

Variable	Definition
V_G	Overall genetic variance
V_A	Additive variance, or variance of a single allele at a single locus
V_D	Dominance variance, or variance of the interaction among alleles at a specific locus
V_I	Epistatic variance, or variance of the interaction among multiple loci
$V\mu$	Mutational variance
V_{Amax}	Maximum additive variance in the post-bottleneck population
h	Dominance coefficient, or the degree to which a given allele is dominant over others in the heterozygote (h = 0.0–0.5, where 0.0 describes complete recessivity of allele under selection, and 0.5 describes complete additivity)
p	Frequency of the dominant allele
q	Frequency of the recessive allele, often a deleterious "new" mutant
N_f	Number of founding individuals after the bottleneck
N_e	Effective population size
s	Degree of selection against deleterious recessive allele
α	Parameterization of the relationship between the dominance and the selection coefficient
H	Avereage dominance coefficient between all 50 loci used in SimBit simulations
S	Average selection coefficient between all 50 loci used in SimBit simulations
$\varphi(p,x)$	Probability distribution that a mutation will start at frequency p and end at frequency x
$v_{\delta p}$	Variance of the change in mutant frequency
ν	Number of sites on the genome where a given mutant appears
$G(x)$	Probability of ultimate fixation of a mutant

a single genetic locus (V_A), dominance effects among alleles at a locus (V_D), mutational variance ($V\mu$), and the epistatic interactions among multiple loci in the genome (V_I) (Table 1). Most genetic variance is due to variance in additive effects (Hill et al. 2008; Zhu et al. 2015), but a number of studies suggest that variance in non-additive effects (V_D and V_I) plays an important role in the recovery of genetic variance after a population re-expansion from an initial decline (Carson 1990; Willis and Orr 1993; Cheverud and Routman 1996; Zhang et al. 2004). Epistasis can contribute to V_G following a bottleneck (Goodnight 1987, 1988; Routman and Cheverud 1997; Cheverud et al. 1999; Barton and Turelli 2004; Turelli and Barton 2006), but in this paper we focus on a constant genetic background and effectively ignore V_I in an effort to highlight the contributions of dominance to post-bottleneck V_G.

Dominance variance (V_D), or the variation due to the degree of dominance of 1 allele relative to others, is hypothesized to play an important role in increasing V_G following bottlenecks (Willis and Orr 1993; Zhang et al. 2004). In empirical studies, dominance effects have impacted the accumulation of deleterious mutations in humans as a result of the bottleneck that took place prior to the colonization of Europe (Balick et al. 2015). Similarly, mathematical theories of bottlenecks predict an increase in V_A due to the specific degree of dominance one allele has over another (Willis and Orr 1993; Zhang et al. 2004). Although an increase in additive variance has been documented in bottleneck experiments (e.g., Bryant et al. 1986; Carson 1990; Cheverud et al. 1999; Van Heerwaarden et al. 2008), the specific measurement of the degree of dominance between 2 alleles, termed the dominance coefficient, has not been empirically evaluated in the context of population bottlenecks. The lack of empirical evidence for the role of dominance in bottlenecks may be partly due to the large variation and lack of consistency in the methods available to measure dominance coefficients (e.g., Mukai et al. 1972; García-Dorado et al. 1999; Agrawal and Whitlock 2011; Huber et al. 2018). Mutation-accumulation experiments in laboratory organisms provide an opportunity to measure selection and dominance for recessive traits, but the lack of modern, genomic-level data across a broad range of taxa makes it challenging to address how dominance between functional alleles at specific loci influences the genetic variation of natural populations. Furthermore, dominance estimates require relatedness estimates (e.g., Class and Brommer 2020) to provide necessary insights into autozygosity (e.g., McQuillan et al. 2008; Narasimhan et al. 2017; Saleheen et al. 2017). These methodological challenges to measuring dominance have contributed to a gap in our knowledge of how V_G responds following a bottleneck. Herein, we critically evaluate the influence of V_D under various demographic scenarios relative to the conservation, management, and evolution of natural populations. For this review, we first synthesize the empirical and theoretical evidence illustrating an increase in V_A due to V_D after a population reduction. As V_A at the start of a bottleneck can influence the V_G of the population as it recovers, we then analyze 2 existing theoretical models to generate demographic predictions on how dominance influences the number of bottleneck survivors (founders) required to maximize V_A immediately after a bottleneck. To validate these concepts, we compare our analytical predictions of these models to forward-time population genetic simulations under various levels of dominance and numbers of founders. Finally, we attempt to synthesize this large body of work with a focus on applying dominance to conservation genetic principles, such as the 50/500 rule for viable effective population sizes (Jamieson and Allendorf 2012; Frankham et al. 2014).

Empirical Evidence of a Bottleneck's Effect on Additive Variance (V_A)

Early theory suggests a reduction in V_G following a population bottleneck (Nei et al. 1975). This reduction in V_G has been empirically validated in various experimental studies, with a decrease in the additive portion of V_G for wing characteristics in *Drosophila* (Whitlock and Fowler 1999) and the butterfly *Bicyclus anynana* (Saccheri et al. 2001), as well as pupal weight in *Tribolium* (Wade et al. 1996) due to heightened inbreeding levels. However, other studies (reviewed and cited below) have suggested that, for specific quantitative traits, the V_A component of V_G can increase once populations recover from a sharp reduction in size. To evaluate the extent to which V_A increases after a bottleneck, we searched for studies that found an increase in additive variance for quantitative

traits that could be explained by non-additive genetic effect and will briefly summarize the most salient points.

Taft and Roff (2012) conducted a meta-analysis on quantitative traits and found a general increase in post-bottleneck V_A when assuming a low to moderate level of inbreeding. This increase in V_A following bottlenecks has been demonstrated empirically for morphological traits, including wing and body size in the domestic housefly (*Musca domestica*) (Bryant et al. 1986; Bryant and Meffert 1995) and for body weight in mice (Cheverud et al. 1999). Furthermore, V_A also increased post-bottleneck for traits directly linked to fitness, including egg-to-adult viability (López-Fanjul and Villaverde 1989) and desiccation resistance in *Drosophila* (Van Heerwaarden et al. 2008), as well as egg hatching rate in *B. anynana* (Saccheri et al. 2001). Increased V_A has also been observed after laboratory bottlenecks in some artificially selected traits, such as cotyledon size in *Brassica rapa* (Briggs and Goldman 2006). Overall, the unintuitive increase in quantitative trait V_A following a bottleneck appears to be due to the non-additive effects of dominance or epistasis (Bryant and Meffert 1993). While often ignored in most measurements of genetic variance, V_D is clearly a strong contributor toward V_G for many life-history associated traits (Crnokrak and Roff 1995; Roff and Emerson 2006; Wolak and Keller 2014; Balick et al. 2015). Direct measurements of fitness illustrate how an excess of V_D has been observed when compared to V_A in *Drosophila serrata* (Sztepanacz and Blows 2015). Thus, the V_A portion of quantitative traits may be overestimated if V_D is not considered (Class and Brommer 2020), which unfortunately is almost always unknown in non-model organisms. Thus, quantifying the role of dominance in the context of demography is needed to accurate predict changes in V_A (and thus evolutionary potential), but V_D is difficult to quantify empirically because genetic architecture is often complex and usually incompletely understood.

Outside of the context of laboratory experiments, most of the evidence for the effect of V_D following a bottleneck comes from genome-level analyses of human populations. One such study capitalized on exome sequencing to assess the role that V_D plays in promoting genetic variation following the historic bottleneck that occurred when human populations originally radiated out of Africa into Eurasia (Balick et al. 2015). Balick and coauthors used the "Burden Ratio", defined as the ratio of deleterious mutational load in the ancestral population relative to the post-bottleneck population, to quantify the role that dominance plays in human autosomal recessive diseases. They found that dominance can reduce the accumulation of rare nucleotide variants through purging of deleterious recessive alleles. Despite the fact that the overall deleterious mutation load is indistinguishable between both post-bottleneck and ancestral populations in humans (Simons et al. 2014; Do et al. 2015), specific autosomal recessive diseases (e.g., such as certain types of deafness) follow a pattern of purifying selection against deleterious recessive homozygotes (Balick et al. 2015). Analyses similar to the Burden Ratio have been conducted in agricultural systems, also revealing reduced deleterious variant accumulation in modern cultivars due to inbreeding and variant purging (Yang et al. 2017). Although the Burden Ratio has not yet been explicitly tested in naturally occurring bottlenecks, signatures of deleterious variant accumulation have been seen in bottlenecks associated with woolly mammoths (Rogers and Slatkin 2017), wolves (Marsden et al. 2016), and lynxes (Lucena-Perez et al. 2021) indicating that bottlenecks may not successfully purge deleterious variants. In principle, the Burden Ratio could help characterize the role of V_D in shaping phenotypes of interest in other organisms that have experienced severe bottlenecks, such as dwarfism in California Condors (Romanov et al. 2006) or water retention in invasive cane toads (Tingley and Shine 2011; Tingley et al. 2012). Overall, there is evidence that V_D can lead to an increase in V_A in laboratory bottlenecks and that large V_D leads to purifying selection against deleterious variants in natural bottlenecks. However, we are not aware of any empirical evidence that firmly documents how V_D responds to bottlenecks in natural populations despite its apparent importance in determining V_A and V_G.

This lack of empirical evidence on how specific levels of dominance influence V_A may be due to the challenges involved in measuring dominance coefficients. Many different techniques have been developed to assess the degree of dominance between 2 alleles, most of which are performed in laboratory experiments. Dominance coefficients of quantitative traits in laboratory organisms have largely been measured by mutation accumulation (MA) experiments, where selective pressures are relaxed to allow for mutations to evolve and increase in frequency within a strain (García-Dorado et al. 1999). Under MA experiments, a direct comparison of viability between heterozygote (v_{ij}) and homozygote (v_i and v_j) individuals, as well as the genotypic variance among the homozygous lines $\left(\sigma^2_{G(B)}\right)$, was originally used to quantify the dominance coefficient, h, calculated as (Mukai and Yamazaki 1968):

$$h = Cov(v_i + v_j, v_{ij})/(2\left(\sigma^2_{G(B)}\right)), \tag{1}$$

To further include the viability of the original homozygotes (v_0), current homozygotes after MA experiments (v), and heterozygotes (v'_B), this Equation 1 further translates into the dominance Equation 2 (Mukai and Yamazaki 1968; Ohnishi 1977):

$$h = (v_0 - v'_B)/2(v_0 - v) \tag{2}$$

Mutational viability, however, is context-dependent and the results from such comparisons are thus highly dependent on environmental effects (García-Dorado et al. 1999). As a prime example, both MA experiments conducted by Mukai and Yamazaki (1968) and Ohnishi (1977) contained previously undetected signatures of non-mutational viability decline (García-Dorado and Caballero 2000). In addition, these viability comparison experiments are impractical to perform with most non-model organisms. An indirect way of measuring dominance coefficients from MA experiments uses estimates of allele frequencies (p and q) and associated selection coefficients (s, which measures the intensity of purifying selection against deleterious alleles such that neutral alleles have s = 0 and immediate purging occurs when s = 1), as shown below with the estimator β_{yx} to denote h (Mukai et al. 1972):

$$\beta_{yx} = (\sum p_i q_i s_i^2 h_i)/(\sum p_i q_i s_i^2) = h \tag{3}$$

However, novel methods to measure dominance outside of the context of mutation-accumulation experiments, ideally

using genetic or genomic data (e.g., the Burden Ratio), will no doubt provide needed insights into how V_D varies in natural populations.

A mathematical relationship based on data from *Drosophila* MA experiments suggests a general inverse relationship between the dominance coefficient (h) and the selection coefficient (s) of mutants (Mukai et al. 1972; Lynch et al. 1995). This relationship has been evaluated experimentally using gene knockout data in *Saccharomycetes cerevisiae* (Phadnis and Fry 2005; Agrawal and Whitlock 2011) and mutational data in *Arabidopsis thaliani* (Huber et al. 2018). The inverse relationship between h and s indicates that more recessive alleles (i.e., lower h) are associated with stronger purifying selection. In principle, this idea could be extended to genomic data. Under the assumption of mutation-selection balance, the relationship between dominance and selection can be parameterized as (Deng and Lynch 1996):

$$h = \frac{e^{-\propto s}}{2} \tag{4}$$

Here, the α parameter accounts for context-specific factors influencing the relationship. The ability to detect and measure selection at specific regions of an organism's genome is increasingly possible based on recent advances in sequencing technology, and thus the inverse relationship between h and s is now testable in a wide variety of natural populations.

To obtain estimates of s from genomic data, tests incorporating nucleotide substitution rates, such as the ratio of non-synonymous to synonymous substitutions (dN/dS), can be used to locate regions of high selective potential. Once areas of high selective potential have been identified, selection estimates can be generated through maximum-likelihood simulations to evaluate the strength of selection at particular genomic sites (Kim and Stephan 2002) or the distribution of selection coefficients across sites (Nielsen and Yang 2003). These, in principle, can be linked to functional phenotypes within populations (e.g., Grossman et al. 2010) and be used to infer dominance coefficients based on the selection-dominance inverse relationship (Equation 4—Deng and Lynch 1996). Although challenges remain, including the measurement of an α parameter to account for external variables influencing the relationship between h and s, it is becoming more tractable to estimate V_D from population genomic datasets while considering demographic effects (e.g., Grossen et al. 2020).

Mathematical Theory Unifying Dominance and Genetic Variation

Many theoretical studies predict that dominance is responsible for the overall increase in V_G after a population bottleneck (Willis and Orr 1993; Wang et al. 1998; Zhang et al. 2004). Early models evaluated how the dominance coefficient between 2 alleles and their corresponding frequencies influence genetic variance (Willis and Orr 1993). Subsequent models extended their parameters to include measurements of the site frequency spectrum (SFS) of alleles, or the frequency of particular alleles in a set of loci, or haploid mutation rate, overall genetic load, and selection coefficients (Wang et al. 1998; Kirkpatrick and Jarne 2000; Zhang et al. 2004; Balick et al. 2015). Most of the models are similar in that they also evaluate genetic variance in the context of demography. Below, we elaborate on 2 demographic models of dominance (Willis and Orr 1993; Zhang et al. 2004) that address how single-locus genetic parameters including population size, allele frequencies, dominance, and selection coefficients influence V_A immediately following a population bottleneck. We focus on these 2 mathematical models as they integrate both genetic and demographic effects to explain V_A. The evaluation of single locus dominance effects provide a framework for future demographic studies on genetic variance at various individual loci (e.g., Balick et al. 2015), as well as the theoretical analyses of multi-locus effects (Cheverud and Routman 1996; Kirkpatrick and Jarne 2000).

To help understand the magnitude of bottleneck effects on V_A, we use these 2 models to illustrate how demography limits the maximum V_A after a bottleneck. In order to conceptualize the relationship, we established a parameter denoting the number of founders after a bottleneck that maximizes additive genetic variance (V_{Amax}). As population genetic diversity is finite at a single time point, analytical predictions indicate that V_G will increase in a logistic manner (i.e., level off) with respect to the number of individuals in the founding population (Supplementary Figure S1). Finding the number of founders of a population where V_A peaks is important because, by definition, more founders beyond those required to achieve V_{Amax} do not further increase V_A. The number of founders has obvious implications for genetic rescue or other conservation efforts designed to restore demographic and evolutionary capacity (Tallmon et al. 2004; Mathur and DeWoody 2021). The parameter V_{Amax} also allows us to observe how the interaction of both V_A and demography changes with respect to the level of dominance and allele frequencies within a population, and illustrate why allelic dominance is an important component of genetic diversity.

Both models consider an infinitely large population that has a single drastic bottleneck followed by an immediate expansion (Supplementary Figure S2). For each model, we combined values for the dominance coefficient (h) and allele frequencies (p and q) to generate a matrix of the ratio of post-bottleneck and pre-bottleneck V_A values under demographic scenarios of 20 and 200 founding individuals to extend and evaluate the author's original predictions of 2 individuals. We extended their original predictions to assess the influence of the number of founders (N_f) on the post-bottleneck V_A upon considering various combinations of dominance coefficients, selection coefficients, and allele frequencies. Furthermore, to determine demographic impacts on V_{Amax}, we calculated the derivative of the post-bottleneck additive variance model with respect to N_f. We then used all combinations of these parameters to generate a matrix that predicts V_{Amax} as a function of N_f using the R package rootSolve (Soetaert 2009; Soetaert and Herman 2009). Lastly, we evaluated the applicability of the analytical predictions generated from these 2 models using SimBit (Matthey-Doret 2021), a forward-time population genetic simulation software.

Neutral Model

Robertson (1952) was among the first to show that recessive alleles within a population can promote an increase in V_G because of drift and inbreeding. In particular, if recessive

alleles remained at a low frequency within a population, V_A within a population is predicted to increase coincident with inbreeding until it reaches its peak value (Robertson 1952). Thus, assuming that inbreeding is modest and the recessive allele at a given locus occurs at low frequencies, it is possible to increase V_A even after a bottleneck. Willis and Orr (1993) extended Robertson's (1952) work by evaluating the influence of dominance on the increase in V_A in the context of a population bottleneck of N_f founding individuals. The Willis and Orr (1993) model is based on 3 parameters: the coefficient or degree of dominance (which we represent as h, not d as in the original model, to facilitate comparisons to other models), the frequency of a dominant allele (p) in the pre-bottleneck population, and the number of founding individuals in a post-bottleneck population (N_f). The frequency of the recessive allele in the pre-bottleneck population, $(1 - p)$, is denoted as q. This model assumes: 1) random mating; 2) that the founder population will immediately expand to achieve Hardy–Weinberg (e.g., no evolution), linkage, and identity equilibrium; and 3) that there is no genetic drift in the pre-bottleneck and expanded post-bottleneck population. Under the neutral model, V_A of a particular trait in the ancestral population is calculated as:

$$V_A = 2pq[1 + (-2h + 1)(q - p)]^2 \quad (5)$$

where h ranges from 0.0 to 0.5 (0.5 conferring complete additivity between alleles and 0.0 conferring complete recessivity between alleles [note the coefficient change from Willis and Orr 1993, where $d = -2h + 1$]). Using binomial sampling of the first 4 gene frequency moments from Crow and Kimura (1970; see Supplementary Information), when reducing the population to a new founder size N_f, the expected additive variance after the bottleneck can be shown to be:

$$\begin{aligned} E(V_A) = \left[pq\frac{2N_f - 1}{N_f^3}\right] \{&((-2h + 1)N_f + N_f - (-2h + 1))^2 \\ &-2(-2h + 1)p(N_f - 1) \\ &[2N_f((-2h + 1) + 1) - 3(-2h + 1) \\ &-(-2h + 1)(2N_f - 3)p]\} \end{aligned} \quad (6)$$

Willis and Orr (1993) calculated the ratio of post-bottleneck to pre-bottleneck V_A (i.e., the "V_A ratio") under an extreme bottleneck of 2 individuals. We extend these predictions to bottlenecks of 20 and 200 individuals to reflect more accurately what might happen in an applied (e.g., conservation) context. We evaluated these bottleneck sizes with a range of dominance coefficients, as well as the frequency of the recessive allele ($0 < q < 1$). Recessive allele frequencies at 0.0 and 1.0 were not evaluated, as no additive variance can be maintained with only 1 allele present. The predictions for the V_A ratio for various combinations of dominance coefficients and recessive allele frequencies are shown in Figure 1. For all 3 bottlenecks of varying intensities (N_f = 2, 20, and 200), $E(V_A)$ exceeds V_A with a combination of high levels of recessivity (h = 0.0–0.2) and a rare recessive allele frequency ($q < 0.5$) in the population. Increasing N_f shows a decrease in the V_A ratio, indicating that $E(V_A)$ is reduced as more founders are added. When the recessive allele is common ($q > 0.6$), the level of dominance is unlikely to produce an increase in $E(V_A)$, indicated by a V_A ratio of less than 1.

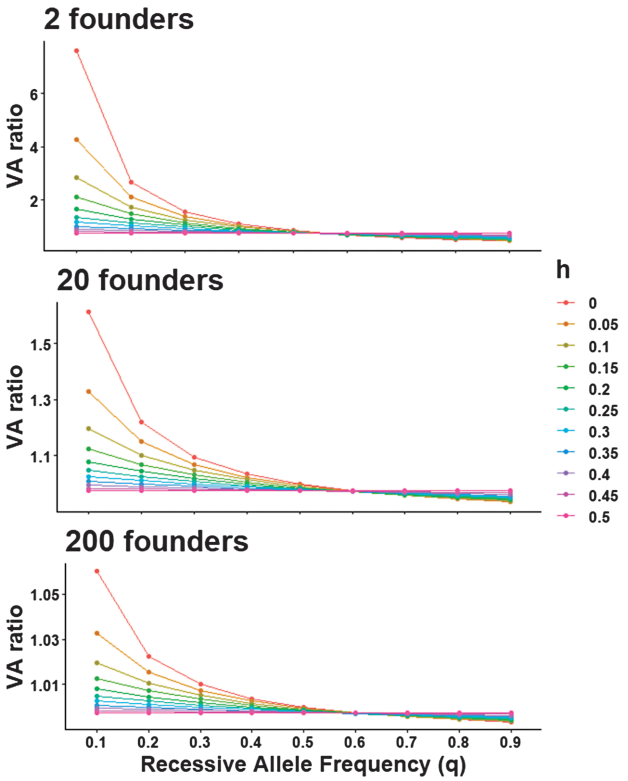

Figure 1. Analytic results of the V_A ratio (post-bottleneck V_A/pre-bottleneck V_A) under various dominance coefficient (h = 0.0–0.5) and recessive allele frequency ($0 < q < 1$) combinations, under a bottleneck of 2, 20, and 200 individuals for the neutral model (Willis and Orr 1993). [Note that no V_A can be maintained at q = 0.0 and q = 1.0.]. The V_A ratio increases when the recessive allele is rare compared to the dominant allele, and higher level of recessivity equates to a higher increase in V_A following a bottleneck. Note the change in the scale of the y-axes between each bottleneck size. Increasing the number of founders within a population decreases in the potential increase of V_A in the post-bottleneck population, as indicated by the decrease in the V_A ratio.

To evaluate a wider range of founder sizes in this model, we generated analytical predictions of $E(V_A)$ expected across a continuous number of founders for various combinations of dominance and allele frequencies. We also confirmed the likelihood of producing $E(V_A)$ by simulating a binomially sampled set of 10 000 allele frequencies with a size of 100 trials per sampling event and a probability of 0.5 for each allele, using the base R function rbinom() (R Core Team 2020). Allele frequencies were used to calculate post-bottleneck V_A across a continuous number of founders and various levels of dominance (Supplementary Figure S3). Irrespective of the level of dominance, more additive variance is produced in the post-bottleneck population when the recessive allele is common than when it is rare (Figure 2). A combination of high levels of recessivity with high recessive allele frequency will produce the most additive variance in a post-bottleneck population, but will result in a net loss of V_A due to the high levels of pre-bottleneck variance (Figure 1). In contrast, high levels of recessivity with rare recessive alleles will exceed the pre-bottleneck V_A and result in a gain of additive variance while producing comparatively lower post-bottleneck V_A. V_{Amax} occurs with lower N_f under rare allele frequencies, as noted by an inflection point on each curve with an N_f <50. These values, in turn, are expected to exceed the pre-bottleneck V_A,

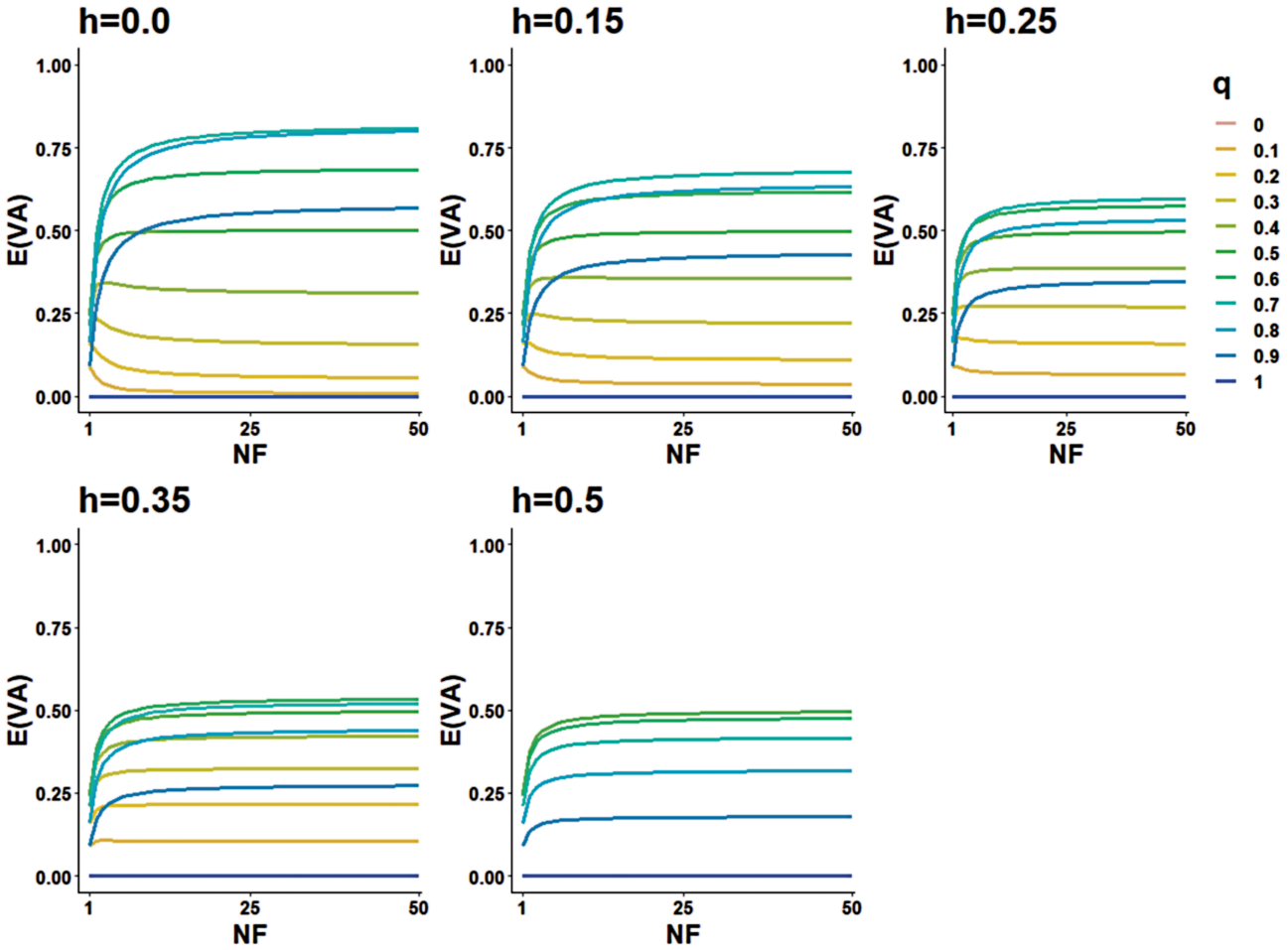

Figure 2. Analytic results of expected post-bottleneck V_A as a result of the number of founders (N_f) as recessive allele frequencies (q) and dominance coefficients (h) vary for the neutral model. Note the differences in the y-axes; increasing q and decreasing h generally maximizes post-bottleneck V_A.

depending on the degree of recessivity. Based on the simulation of binomially sampled allele frequencies, the production of low levels of $E(V_A)$ is less likely than intermediate to high levels of $E(V_A)$ (Supplementary Figure S3). Despite this, a high degree of recessivity (h = 0.0) allows for a wider variance in $E(V_A)$ than a high degree of additivity. Dominance, thus, will likely influence how many founders are required to achieve the maximum level of post-bottleneck additive variance (V_{Amax}), and if that variance will exceed that of the pre-bottleneck population.

To find the number of individuals needed to produce V_{Amax}, we took the derivative of the expected post-bottleneck V_A shown in Equation 6 with respect to N_f, as shown below in Equation 7:

$$\frac{dE(V_A)}{dN_f} = -\frac{1}{N_f^4}((1-q)-1)(1-q)\left((-2h+1)^2(2(1-q)^2 \left(12N_f^2-22N_f+9\right)-2(1-q)\left(12N_f^2-22N_f+9\right)+5N_f^2-8N_f+3\right) +2(-2h+1)N_f((1-q)(4-6N_f)+3N_f-2)+N_f^2) \quad (7)$$

A general visual depiction of this 4th-degree polynomial and the point of V_{Amax} across a variety of parameter combinations is shown in Supplementary Figure S4. By finding the root of this derivative, we can predict the N_f that produces V_{Amax} with various dominance coefficients and allele frequencies (Figure 3). This reveals that when the recessive allele is common (q > 0.5), more individuals are needed to achieve V_{Amax} than if the allele is rare. Furthermore, when an allele is rare (q < 0.5) with a high degree of dominance (h < 0.25) fewer founding individuals are needed to produce V_{Amax} than in the case of a highly additive allele. When considering all of these parameter values and combinations, V_{Amax} is at its apex when N_f ~ 139–141 (q = 0.77 and 0.88, h = 0.0; Figure 3). Although commonly assumed that V_A will continue to increase in concert with N_f, this model predicts that more individuals do not necessarily increase the V_A ratio, especially if the recessive allele is common. Under the model predictions, V_{Amax} in a post-bottleneck population occurs with approximately 80–140 founders.

Purifying Selection Model

To evaluate selection intensity against recessive deleterious alleles, we also analyzed a joint-effect model of both stabilizing and pleiotropic selection of fitness and morphological (i.e., non-fitness) associated mutations developed by Zhang et al (2004). The joint-effect model has been applied to population bottlenecks using Kimura's (1969) diffusion approximations of the balance of accumulation and loss of mutations within a population. Further details on the derivation of the model can be found in the Supplementary Information.

The overall estimated additive genetic variation within the post-bottleneck population is defined as:

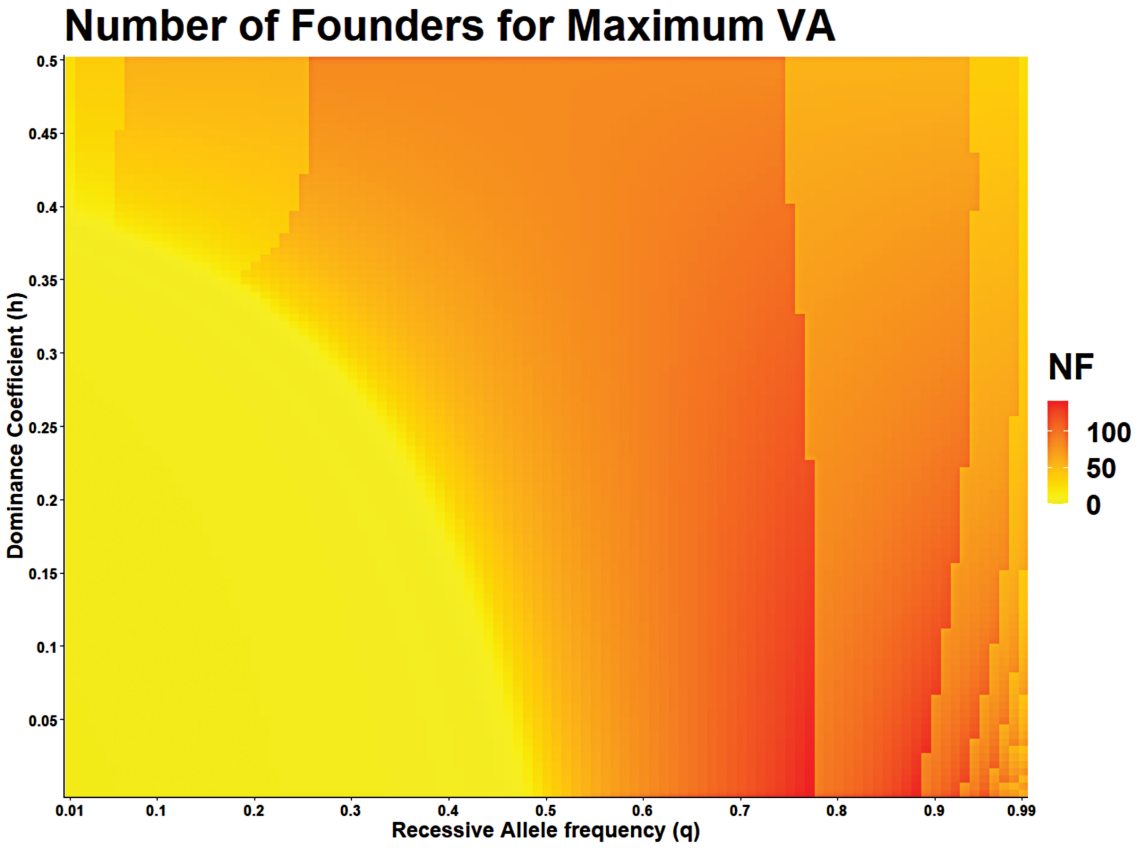

Figure 3. Analytical results of the number of founders (N_f) required to obtain the maximum amount of additive variance (V_{Amax}) under a neutral model (Willis and Orr 1993). Each parameter combination indicates V_{Amax} at a given N_f. If the recessive allele is either exclusively present (q = 1.0) or absent (q = 0.0), then no variance can be maintained and therefore we focus on 0.01 ≤ q ≤ 0.99. V_{Amax} occurs with smaller N_f when the recessive allele is rare.

$$E\left[f_{VA}\left(q\right)\right] = \frac{s^2}{4} f_1 \{\left[1 + \left(2h - 1\right)^2 \left(1 - 2f_1 + 2f_1 f_2\right)\right] H_0 + 2f_2 \left[\left(2h - 1\right) C_0 - f_3 \left(2h - 1\right)^2 K_0\right]\} \quad (8)$$

where q is the final frequency of the recessive mutant allele (Zhang et al. 2004). The variable q is simplified through the terms H_0, C_0, and K_0, where $H_0 = 2q(1 - q)$, $C_0 = 2q(1 - q)(1 - 2q)$ and $K_0 = 4q^2(1 - q)^2$. The post-bottleneck population size N_f is simplified with the term f_i, where $f_i = 1 - i/2N_f$. Full details on the derivation of Equation 8 can be found in the Supplementary Information. This prediction assumes that the bottlenecks involve a population of randomly mating individuals, in which all mutations are deleterious, and the population immediately expands to a large size (i.e., negligible inbreeding and genetic drift). In addition, both overdominance, whereby heterozygotes are at a competitive advantage over homozygotes, as well as epistatic interactions are assumed to exert no influence the post-bottleneck V_A.

We extended the predictions of 2 founding individuals made by Zhang et al. (2004) to include bottlenecks of 20 and 200 individuals. Similar to the neutral model, we evaluated these bottlenecks under various parameters of h and q. Figure 4 shows the V_A ratio as predicted under the purifying selection model under weak selection (A: s = 0.01) and strong selection (B: s = 0.1) on the deleterious mutation for a bottleneck of 2, 20, and 200 individuals. These selection coefficients are at the lowest and highest level of detectability without being neutral or lethal, respectively, for an extreme bottleneck of 2 founders (Zhang et al. 2004). Across all 3 bottleneck sizes evaluated herein, V_{Amax} occurs when mutant alleles are rare (q = 0.1 – 0.3); furthermore, the V_A ratio increases with the degree of recessivity. Conversely, slightly deleterious but common mutant alleles will decrease the V_A ratio, and dominance has little to no effect under these conditions. Similar to the neutral model, increasing the number of founders will reduce the V_A ratio. As the ratio of $E[V_A]$ to V_A cancels out selection coefficients, a similar V_A ratio is obtained irregardless of the selective pressures.

We conducted a similar analysis as the neutral model to evaluate the effects of N_f on V_A as a function of allele frequencies and dominance coefficients (Figures 5 and Supplementary Figure S5). In these situations, V_{Amax} in the post-bottleneck population occurs when the recessive mutant allele is at a high frequency (q > 0.6) and there is a high degree of recessivity (h << 0.5) (Figure 5). Because $E[f_{VA}]$ does not exceed V_A, there is a general loss in variance due to the bottleneck at high-allele frequencies, consistent with the neutral model. While rare alleles result in less post-bottleneck V_A, this is expected to exceed pre-bottleneck levels (Figure 4). According to the simulated dataset of binomially sampled allele frequencies, $E[f_{VA}]$ exceeding V_A is more likely to occur under high levels of recessiviy due to the wider variance of post-bottleneck V_A, again consistent with the neutral model (Supplementary Figure S5). With the addition of various

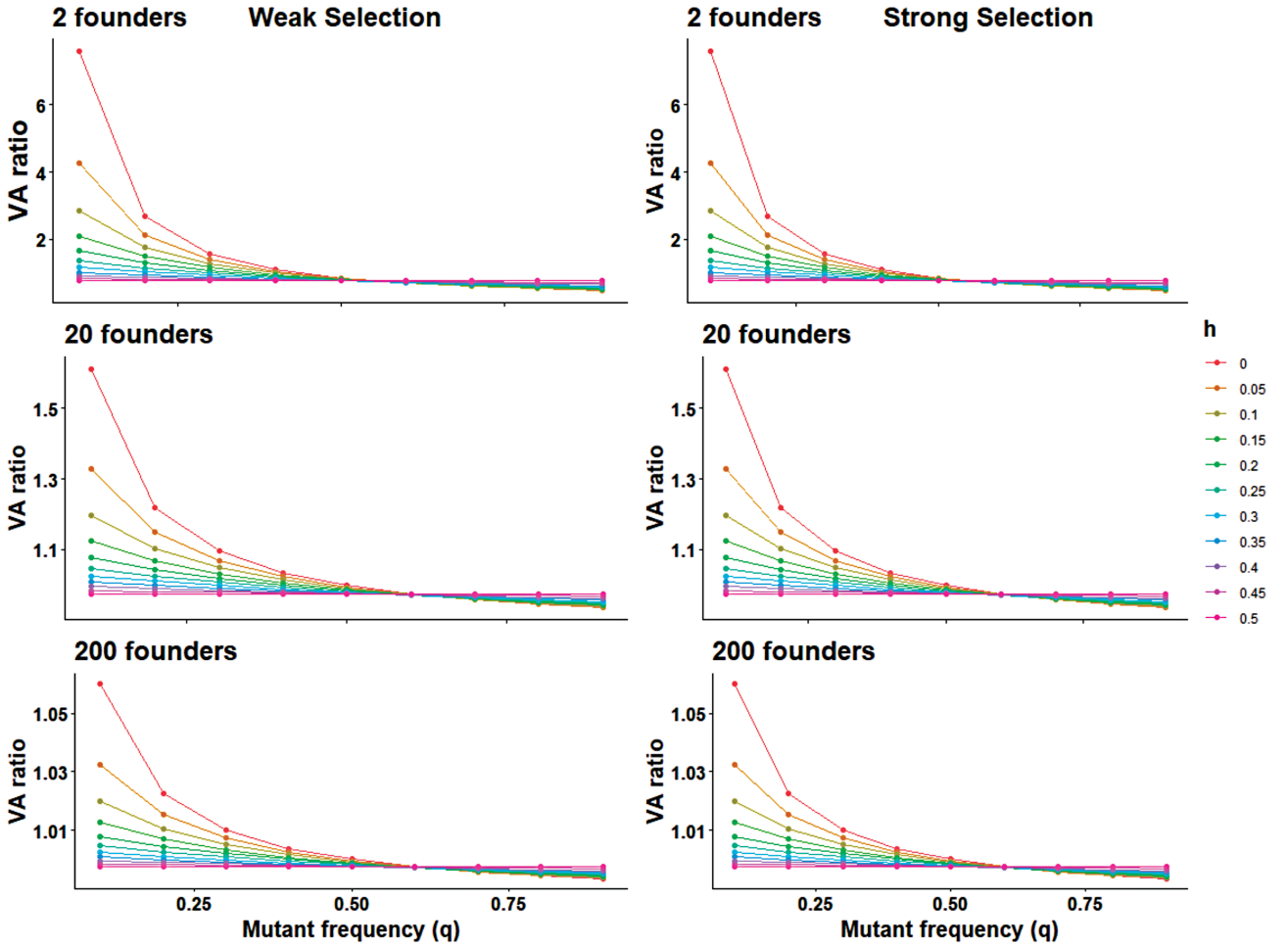

Figure 4. Ratio of post-bottleneck to pre-bottleneck V_A under weak (s = 0.01) and strong (s = 0.1) selection in the purifying selection model (Zhang et al. 2004). As with the neutral model, no variance can be maintained when q = 0.0 or 1.0, so we focus on 0.1 < q < 0.9. Post-bottleneck V_A exceeds pre-bottleneck V_A across all 3 bottleneck sizes and all selection coefficients when the recessive mutant allele is rare and is highly recessive. Increasing N_f reduces the V_A ratio, resulting in a reduced potential post-bottleneck V_A.

levels of purifying selection (s = 0.001, 0.01, 0.1, 0.5), we can see at larger selection coefficients, there is more possible V_A than at low-selection coefficients (Figure 5). Even if generally unrealistic, the highest level of additive variance possible in a post-bottleneck population occurs when a deleterious mutant is at high frequencies, is highly recessive, and has a large amount of selective pressure against it. Thus, we again sought to determine V_{Amax} as a function of the mutant frequency, dominance coefficient, and selection coefficient.

The derivative of $E[f_{VA}]$ is calculated as:

$$dE[f_VA]/(dN_f) = \frac{s^2}{4{N_f}^4} q(1-q)((2h-1)^2(2q^2(12N_f^2 - 22N_f + 9) - 2q(12{N_f}^2 - 22N_f + 9) + 5{N_f}^2 - 8N_f + 3) + 2(2h-1)N_f(q(4-6N_f) + 3N_f - 2) + {N_f}^2) \quad (9)$$

A visual depiction of this 4th-degree polynomial and the point of V_{Amax} across a variety of parameter combinations is shown in Supplementary Figure S6. We took the root of the derivative of the additive variance function to find the maximum N_f value for each post-bottleneck variance parameter. Figure 6 illustrates the variance in V_{Amax} following a bottleneck, depending on N_f. Under reasonable values of s (0.01–0.1, according to Zhang et al. 2004), and rare recessive allele frequencies, this model predicts that fewer individuals (N_f = 3–25) are required to maximize V_A compared to the neutral model. We see that under extremely low levels of purifying selection (s = 0.001), only 1 founder is expected to achieve V_{Amax}. As the level of purifying selection increases, the number of founders required for V_{Amax} increases, with extreme levels of selection (s = 0.5) requiring 50–60 founders (Figure 6 and Supplementary Figure S7). Consistent with the neutral model, we observe that common mutant alleles (q > 0.6) with a high degree of recessivity (h << 0) require more founders for V_{Amax} than those that are rare and additive. Overall, our analyses indicate that when purifying selection is considered, fewer founders are required to maximize V_A than predicted under the neutral model. Thus, post-bottleneck V_A is maximized under high selection against rare, highly recessive deleterious mutations. Of course, a deleterious mutation (s > 0.1) is unlikely to reach high frequency due to the effects of purging (Mathur and DeWoody 2021) and the true value of V_{Amax} in natural populations likely depends on allele frequencies (a function of N_e), on s (which depends on the environment), and on zygosity (which depends on the breeding system).

We sought to determine if an increase in V_A due to dominance after a bottleneck is also associated with an increase

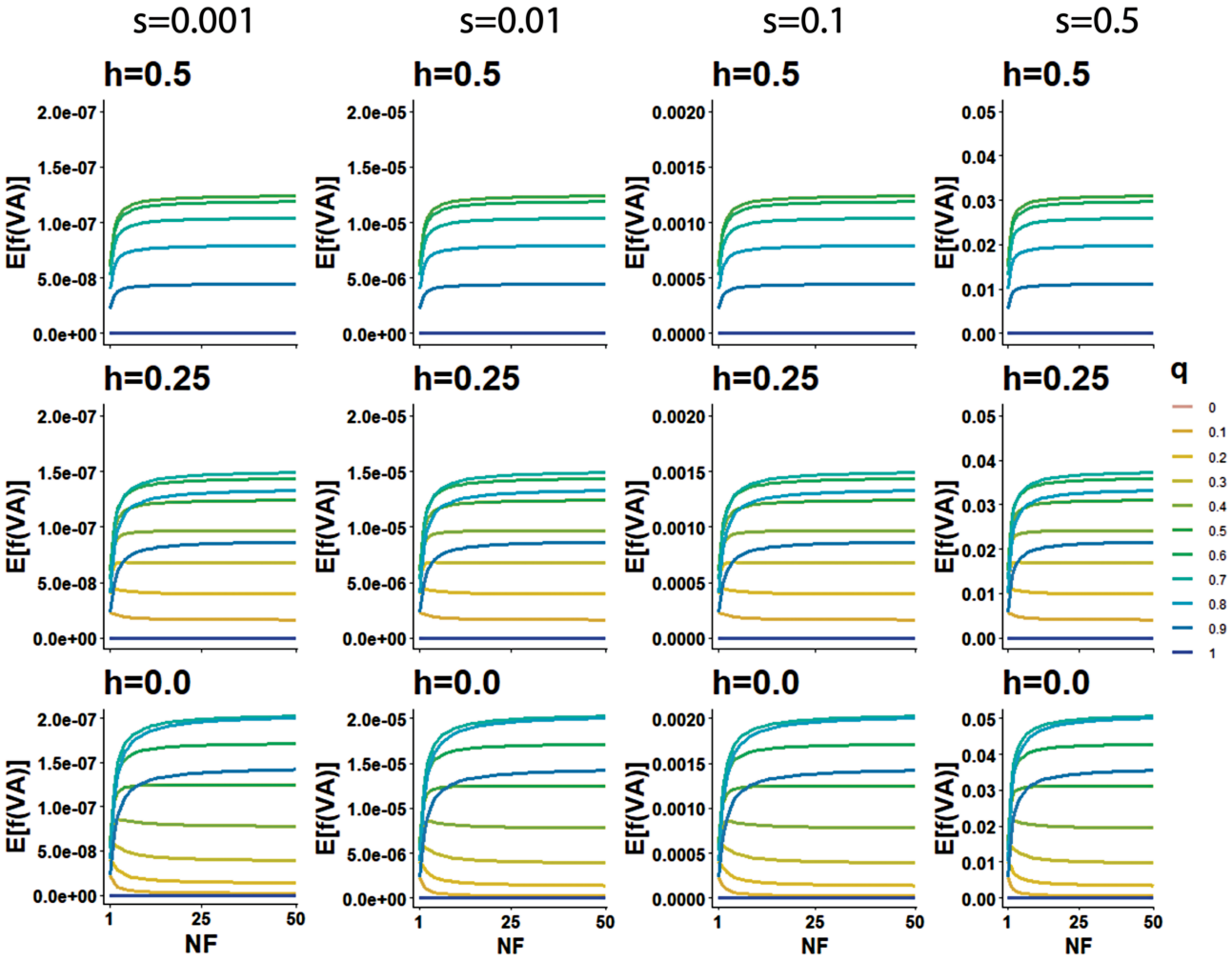

Figure 5. Analytical results of expected V_A in the post-bottleneck population as a function of the varying founder numbers (N_f), recessive allele frequencies (q), and dominance coefficients (h), and selection coefficients (s = 0.001, 0.01, 0.1, 0.5) in the purifying selection model. V_A increases with q and is inversely proportional to h. In addition, increasing selection against the deleterious mutation increases the overall range of possible post-bottleneck V_A.

in V_G as a whole. To validate the analytical predictions of both models, we ran forward-time simulations to measure population genetic diversity for various levels of dominance and number of founders. Specifically, we sought to confirm that high degree of recessivity ($h << 0.5$) leads to an increase in post-bottleneck genetic diversity, as measured by nucleotide diversity, and assess if such high levels of diversity are sustained over time. We used SimBit, a recently published forward-time genetic simulator that allows for flexibility with demographic scenarios, mutational and recombination rate, and the level of dominance (Matthey-Doret 2021). Each independent simulation consisted of 1 population containing 10 000 individuals, each with 50 loci (specified in SimBit as biallelic loci [i.e., wild vs. mutant]), a uniform mutation rate of 1×10^{-4} (to help ensure genetic variation was produced and could be illustrated in a timeframe of conservation relevance) for each locus, and a recombination rate of 1×10^{-6}. For each simulation, we varied the average dominance coefficient (H = 0.0, 0.125, 0.25, 0.375, 0.5), the number of founders (N_f = 2, 20, 50, 100, 150, 200, 250, 300), and the fitness effects of the homozygous mutant alleles (0.9 and 1.0 for average selection coefficients of 0.1 and 0.0, respectively) for a total of 80 independent simulations with different combinations of H, N_f, and S. Starting with a uniform state of 0 mutations at generation 0 for all loci, we allowed the population to accumulate genetic variation for 99 999 generations before reducing the population to the specific N_f value at generation 100 000. We allowed immediate recovery to 10 000 individuals in generation 100 001, as assumed in both theoretical models (Willis and Orr 1993; Zhang et al. 2004), and then allowed the population to persist uninterrupted for 99 999 more generations. We obtained VCF output files every 10 000 generations, as well as for generation 2 (population infancy) and 100 001 (immediately following the bottleneck). We used VCFTools (Danecek et al. 2011) to measure nucleotide diversity for each locus for each specified generation using the (- - site-pi) function.

We observed no appreciable increase in nucleotide diversity from pre-bottleneck levels when there was no selection (S = 0.0, Figure 7; Supplementary Figure S8). All loci appeared to maximize genetic diversity within the first 99 999 generations, with a maximum nucleotide diversity value of 0.5, regardless of the level of dominance. However, we observed that under extreme bottlenecks (N_f = 2), post-bottleneck

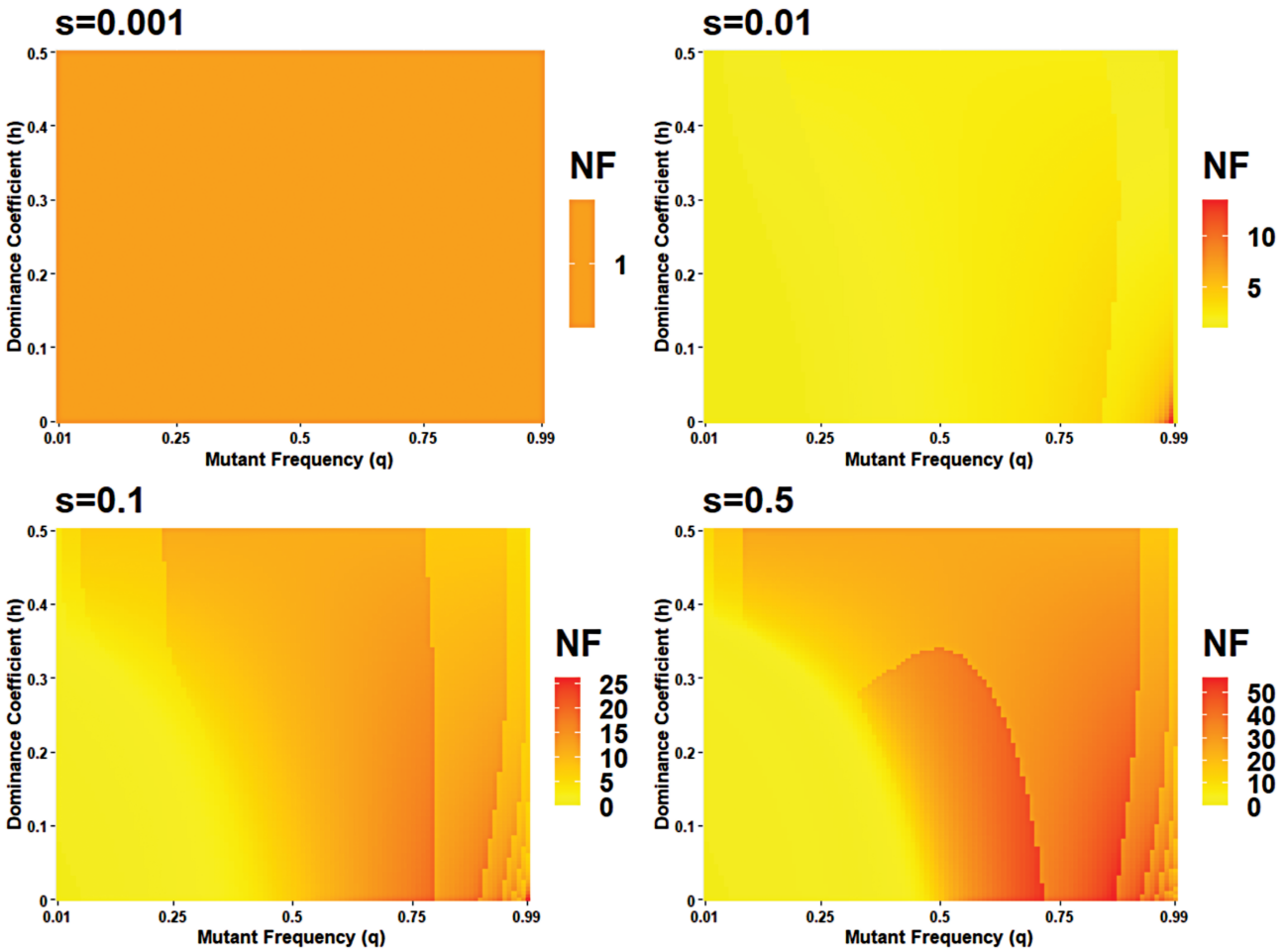

Figure 6. The number of founders required to maintain the maximum amount of additive variance (V_{Amax}) under various combinations of dominance coefficents and recessive allele frequencies with differing selection intensities (s = 0.001, 0.01, 0.1, 0.5) under a model of purifying selection (Zhang et al. 2004). The number of founders needed to reach V_{Amax} is highest under common recessive allele frequencies and a high level of dominance. The number of founders increases as the intensity of selection increases. Rare recessive alleles require fewer founders for V_{Amax}, consistent with the neutral model.

genetic diversity was unpredictable whereas larger founding population sizes (N_f = 200, 250, 300) reduced fluctuations between pre- and post-bottleneck genetic diversity. When selection was incorporated into the simulations, we consistently observed that a high level of recessivity between alleles (H = 0.0) yielded the highest level of nucleotide diversity in both pre- and post-bottleneck populations (Figure 7). For an N_f of 20, 50, and 100, the highest nucleotide diversity was generated at loci where H = 0. Loci having an intermediate to high level of dominance (H = 0.25, 0.375, 0.5) also increased in diversity when compared to the pre-bottleneck levels (Figure 7 and Supplementary Figure S8). These findings differ from the analytical predictions that low to intermediate dominance levels do not lead to an increase in $E(V_A)$. This difference could be because our population was not in equilibrium before the bottleneck, or because V_D exerts a stronger effect on genetic diversity than V_A. Overall, our analyses showed that populations generally reestablished pre-bottleneck levels of genetic diversity.

Our forward-time population genetic simulations confirm that non-neutral loci with high levels of recessivity (H << 0.5) produce the highest level of nucleotide diversity when compared to other dominance levels. Furthermore, simulations including selective pressures confirmed an instantaneous increase in post-bottleneck genetic variation under certain conditions, but they also illustrate that such increases in nucleotide diversity are relatively rare and unsustainable in the post-bottleneck population. When founding size was large, changes in nucleotide diversity generally did not occur. However, under neutrality, dominance had no influence on nucleotide diversity in the post-bottleneck populations.

Our analytical prediction that no more that 130–140 founders should maximize V_A under neutral conditions is also a reasonable assumption for maximizing nucleotide diversity. Furthermore, our simulation results of nucleotide diversity under strong selection align with the predictions made by the purifying selection model. This is especially evident for bottlenecks of 2–100 individuals, which led to an increase in nucleotide diversity that was highest for loci with high recessivity (H << 0.5). There are caveats to these simulations, as SimBit models neutral loci with fully equilibrated populations using a coalescent approach. Measurements of nucleotide diversity in early generations may represent a non-equilibrated population, but after 99 999 generations our simulations likely represented pre-bottleneck populations near equilibrium. Broadly, we conclude that dominance exerts an appreciable influence on the level of nucleotide diversity under scenarios when selection is present, with the highest level of

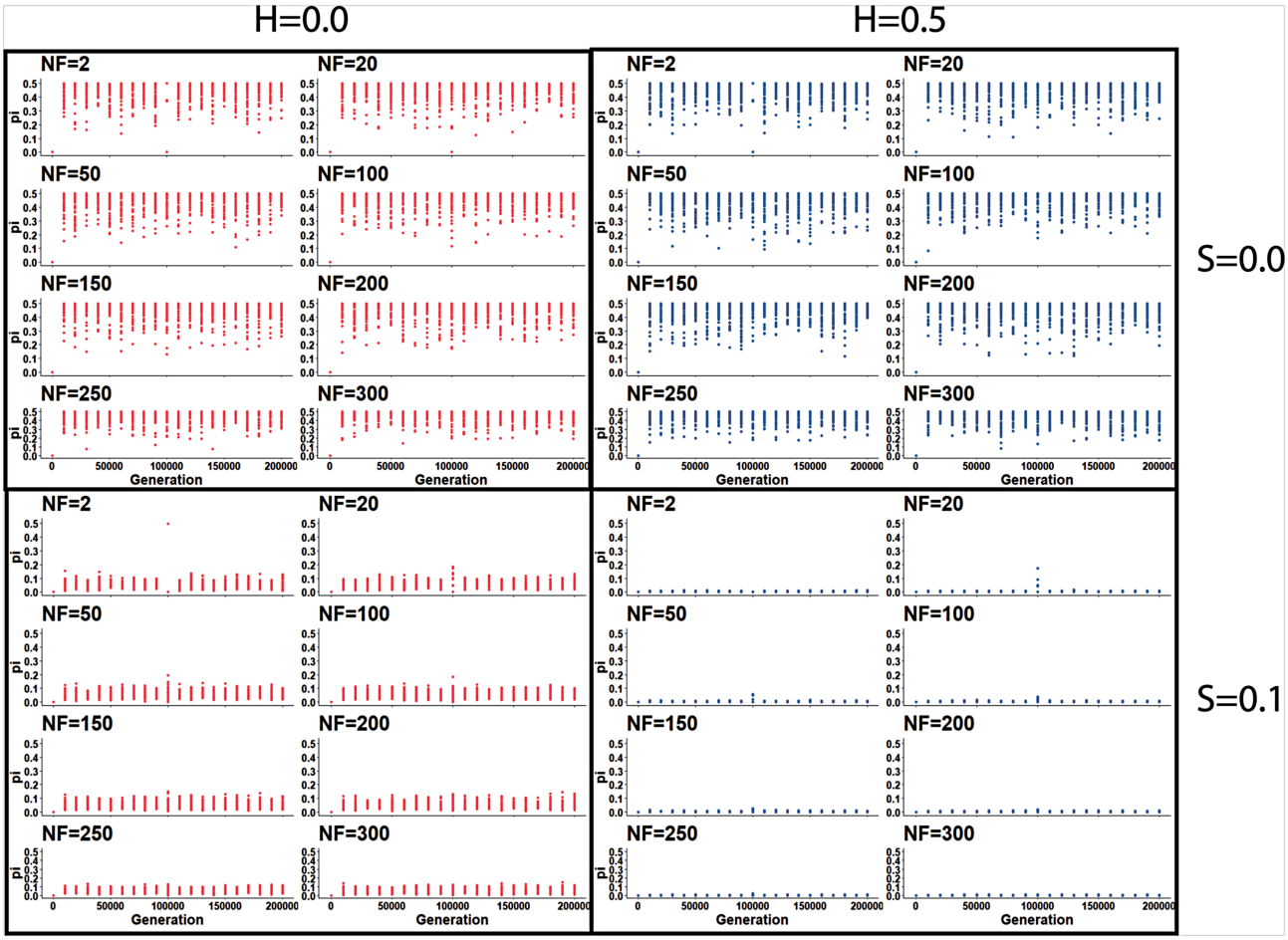

Figure 7. SimBit (Matthey-Doret 2021) forward-time simulations under various numbers of founders with high recessivity (H=0.0) and additivity (H=0.5), under neutrality (S=0.0) and strong selection (S=0.1). Each simulation tracked 50 loci within a single population for 200,000 generations, where in generation 100,000 the population was subjected to a bottleneck of the corresponding number of founders. Under neutrality, genetic variation is always maximized, regardless of dominance. Under selection, loci that had high recessivity (H = 0) produced the highest nucleotide diversity, while traits that were additive (H = 0.5) consistently produced the lowest levels of nucleotide diversity.

dominance producing the highest level of nucleotide diversity. These data also suggest that a population of ~150–300 founders is sufficient to match pre-bottleneck genetic diversity levels for all dominance coefficients.

Discussion

Although both models synthesized in this paper produce different quantitative predictions for V_{Amax}, several conclusions on how dominance influences V_A following a population bottleneck emerge. Both models indicate that V_A can increase for a population bottleneck when deleterious recessive mutations are rare and dominance is strong ($h << 0$). Overall, we see that the neutral model requires ~4× more founders to achieve V_{Amax} than the model of purifying selection. For populations that have undergone sharp declines in N_e, a founding population of ~50–100 individuals will allow for the short-term recovery of genetic variability (i.e., heterozygosity) of most populations (reviewed in Jamieson and Allendorf 2012; Frankham et al. 2014). Our synthesis of the models developed by Willis and Orr (1993) and Zhang et al. (2004) suggests that post-bottleneck populations of ~100–150 individuals should generally approach V_{Amax} and could even generate an increase of additive variance relative to pre-bottleneck levels. However, one must approach these results with caution, as forward-time genetic simulations suggest that increases in post-bottleneck genetic diversity may only be temporary artifacts of an extreme genetic drift event. Nevertheless, simulations illustrate that no more than 150–300 founders are required to match pre-bottleneck levels of additive genetic diversity.

Clearly a number of assumptions underlying both models are invalid for most wild populations. The most impractical assumption, instantaneous post-bottleneck growth to infinite size, would have the most profound impact on the predicted V_A. The purging of deleterious alleles is positively correlated with the time (number of generations) required for population expansion (Wang et al. 1999), and thus the mutational load of a post-bottleneck population will steadily decrease (Balick et al. 2015). As mutant allele frequencies decline due to purging following an extended bottleneck, more founding individuals are required to maximize V_A.

Extending the joint-effect model to include different modes of reproduction (e.g., selfing or outcrossing) would no doubt improve our understanding of V_{Amax}. Indeed, different mating systems can influence the V_{Amax} of a system. For example, if all else is equal then a selfing population has a lower N_e and less efficient purging than an outcrossing population so we

expect deleterious allele frequencies to be higher in the selfing population (Charlesworth and Wright 2001; Artieri et al. 2008). Thus, variation in zygosity due to mating systems can influence the number of deleterious variants segregating in the pre-bottleneck population and thus impact the effect of N_f on V_{Amax}. Whereas decreases in narrow-sense heritability are evident for selfing populations (Clo et al. 2019), other studies suggest mating systems contribute little toward V_G (Glémin et al. 2006).

The accumulation of deleterious mutations depends on species-specific factors (e.g., mutation rate, N_e, etc.), making patterns of MA difficult to generalize and conservation outcomes impossible to predict. More broadly, in order for V_{Amax} to be relevant to population viability, we assume a high degree of narrow-sense heritability, where there is high influence of parental genotypes on their progeny phenotypes and thus genetic variance is influenced largely by additive effects. However, narrow-sense heritability has been experimentally shown to be reduced during a bottleneck due to environmental effects (Bryant and Meffert 1996), diminishing the role that additive effects play in the genetic variance of quantitative loci. While V_D is transformed into V_A in both models, V_D can also contribute to genetic variance independently and this may diminish the role that V_A plays in maximizing V_G. V_D may also inflate estimates of narrow-sense heritability if it is not properly measured (Tenesa and Haley 2013), giving false impressions of the role of additive variance in locus-specific genetic variation. Estimates of V_{Amax} can also vary due to environmental heterogeneity, which is context dependent and can skew narrow-sense heritability (Tenesa and Haley 2013).

An overarching goal of modern evolutionary and conservation efforts is to evaluate complete genomes in an effort to quantify sources of V_G within populations (e.g., to identify genomic patterns of selection and infer the underlying evolutionary processes; Mathur and DeWoody 2021). Statistical models have been developed to incorporate selection and demography using information from segregating mutations with effective selection strength $N_e s$ to obtain genome-wide estimates of purifying selection against deleterious mutations (Gutenkunst et al. 2010; Johri et al. 2020). Estimates of the allelic SFS, linkage disequilibrium (LD), associated background selection, and chromosomal divergence are integral to determine the distribution of fitness effects (DFE) in demographic contexts (Johri et al. 2020), yet a myriad practical challenges still remain in estimating these parameters in non-model organisms. For example, the inclusion of both common and rare single nucleotide polymorphisms can reduce ascertainment bias (Weiss and Clark 2002), but such efforts are costly, time consuming, and rarely possible in natural systems. Future work should incorporate the extent of LD, the DFE of mutations within populations, and demographic processes for a more complete evaluation of V_G within populations. Furthermore, we hope that future whole-genome assessments will further our understanding of epistasis in the wild, as V_I has historically been a near complete unknown for fitness-related phenotypes in different environments.

Although V_D can strongly influence V_A after bottlenecks, epistatic effects of multiple loci and their effects on V_A deserve further attention. Epistasis is a pivotal process in promoting evolutionary potential (de Visser et al. 2011) and is responsible for variability in many phenotypic traits (e.g., Steiner et al. 2007), and likely inflates estimates of narrow-sense heritability in a way that is similar to the effect of V_D (Zuk et al. 2012). Several models show that the additive variance after a bottleneck is influenced by epistatic effects in addition to single locus dominance effects (Goodnight 1987, 1988; Routman and Cheverud 1997; Cheverud et al. 1999; Barton and Turelli 2004; Turelli and Barton 2006). However, it is important to have a deeper understanding of non-additive effects at a single locus before considering multiple loci, as these effects have downstream effects on epistatic interactions. In particular, dominance interactions impact which allele becomes fixed at all loci involved in epistatic interactions (Cheverud and Routman 1996). Furthermore, pleiotropy (when 1 gene has multiple phenotypic effects), considered one of the main components of the joint-effect model (Zhang et al. 2004), is a precursor of epistatic interactions (de Visser et al. 2011). Thus, our analysis provides an initial synthesis of single locus non-additive effects and their contribution toward the additive component of variance with a hope that this work provides a foundation for considering the non-additive effects of multiple loci on genetic variation in the future.

Conclusions

This review illustrates how the degree of dominance among alleles can play an important role in maintaining V_A. As shown by mathematical modeling, high levels of dominance when the recessive mutant is rare can increase V_A in the post-bottleneck population for both models analyzed, although this effect may be rare and ephemeral. These models complement empirical evidence that allelic dominance can allow for the persistence of deleterious mutant alleles under purifying selection. Furthermore, non-additive effects regarding these mutations promote an increase in V_A for certain quantitative traits. Our synthesis of theoretical models demonstrated that it is possible to extend them to make demographic predictions on the number of founding individuals required to maximize additive genetic variance after a population bottleneck. The number of founders largely depends on the selection coefficient of deleterious mutations, the frequency of deleterious mutations, and the degree of dominance so we encourage attempts to measure these parameters in future empirical studies. These population genetic predictions can be used to quantify the number of individuals that must be established to maximize the initial genetic variance and, thus, the adaptive potential for future generations.

Supplementary Material

Supplementary data are available at *Journal of Heredity* online.

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Data Availability

All scripts that were used for generation of figures and forward time simulations are provided at https://github.com/andrewmularo/DominancePopulationBottleneck

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