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The Impact of Non-additive Effects on the Genetic Correlation Between Populations

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ABSTRACT Average effects of alleles can show considerable differences between populations. The magnitude of these differences can be measured by the additive genetic correlation between populations (r_g). This r_g can be lower than one due to the presence of non-additive genetic effects together with differences in allele frequencies between populations. However, the relationship between the nature of non-additive effects, differences in allele frequencies, and the value of r_g remains unclear, and was therefore the focus of this study. We simulated genotype data of two populations that have diverged under drift only, or under drift and selection, and we simulated traits where the genetic model and magnitude of non-additive effects were varied. Results showed that larger differences in allele frequencies and larger non-additive effects resulted in lower values of r_g. In addition, we found that with epistasis, r_g decreases with an increase of the number of interactions per locus. For both dominance and epistasis, we found that, when non-additive effects became extremely large, r_g had a lower bound that was determined by the type of inter-allelic interaction, and the difference in allele frequencies between populations. Given that dominance variance is usually small, our results show that it is unlikely that true r_g values lower than 0.80 are due to dominance effects alone. With realistic levels of epistasis, r_g dropped as low as 0.45. These results may contribute to the understanding of differences in genetic expression of complex traits between populations, and may help in explaining the inefficiency of genomic trait prediction across populations.

Populations can differ considerably in the average effects of loci (*i.e.*, α, the difference between average effects of the two alleles, Falconer and Mackay (1996)). For a given genotype (*i.e.*, individual), differences in α between two populations lead to differences in the additive genetic values of that genotype, as expressed in both populations. The magnitude of these differences can be measured by the additive genetic correlation between populations (r_g), defined as the correlation between the additive genetic values of a genotype expressed in population 1 and population 2. In reality, a single genotype cannot

belong to two populations at the same time. This means that a trait expressed in two populations can be seen as a pair of traits that cannot be measured on the same individual, analogous to *e.g.*, age at sexual maturity in males and females (Falconer and Mackay 1996). Although no phenotypic correlation exists between such pairs of traits, they can nevertheless be genetically correlated.

The r_g can be lower than one due to genotype by environment interaction (GxE) (Falconer 1952), or due to non-additive genetic effects (GxG-interaction) together with differences in allele frequencies between populations (Fisher 1918). Knowledge of this correlation contributes to the understanding of the genetic architectures of polygenic traits (de Candia *et al.* 2013; Brown *et al.* 2016). Such understanding may lead to improved knowledge of genetics and can facilitate accurate prediction of traits, such as disease risk in humans and yield traits in crops (Forsberg *et al.* 2017). Furthermore, understanding the genetic mechanisms that determine r_g may help in explaining the inefficiency of trait prediction across populations (Wientjes *et al.* 2015).

Following Falconer (1952), we can interpret a metric trait expressed in two populations as two different, genetically correlated traits.

■ **Table 1 Overview of scenarios with the genetic architecture of the trait, and their parameters for distributions of sampled dominance coefficients and epistatic coefficients**

| | | Parameters for distributions of non-additive effects | | |
	Configuration	Small	Intermediate	Large
D	Dominance	$\mu_\delta = 0.2, \sigma_\delta = 0.30$	$\mu_\delta = 0.2, \sigma_\delta = 0.70$	$\mu_\delta = 0.2, \sigma_\delta = 1.50$
E_{AA}	A*A	$\mu_\gamma = 0.0, \sigma_\gamma = 0.16$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.33$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.68$
E_{DD}	D*D	$\mu_\gamma = 0.0, \sigma_\gamma = 0.16$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.33$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.68$
E_C	Complementary	$\mu_\gamma = 0.0, \sigma_\gamma = 0.16$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.33$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.68$
E_M	Multiplicative	$\mu_\gamma = 0.0, \sigma_\gamma = 0.16$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.33$	$\mu_\gamma = 0.0, \sigma_\gamma = 0.68$

The additive genetic value of individual i for the trait expressed in the population that i belongs to (say, population 1) is

$$v_i^{P1} = \mathbf{h}'_{a,i} \boldsymbol{\alpha}^{P1},$$

where $\mathbf{h}_{a,i}$ is a column vector of additive genotypes (measured as allele counts, minus the mean allele count in the population) of individual i at quantitative trait loci (QTL), and $\boldsymbol{\alpha}^{P1}$ is a column vector of average effects at those QTL in population 1. The additive genetic value of individual i for another population (say, population 2) is

$$v_i^{P2} = \mathbf{h}'_{a,i} \boldsymbol{\alpha}^{P2},$$

where $\boldsymbol{\alpha}^{P2}$ is a column vector of average effects in population 2. Conceptually, this v_i^{P2} can be thought of as the additive genetic value for an individual in population 2 that has the same genotype as individual i. Here we define the additive genetic correlation between population 1 and population 2 (r_g) as the correlation between both additive genetic values for the individuals in population 1,

$$r_g = cor\left(v_i^{P1}, v_i^{P2}\right) = cor\left(\mathbf{h}'_{a,i} \boldsymbol{\alpha}^{P1}, \mathbf{h}'_{a,i} \boldsymbol{\alpha}^{P2}\right). \tag{1}$$

In other words, the r_g is defined for individuals coming from population 1, which may be different from the r_g defined for individuals coming from population 2 (See Discussion).

Equation (1) illustrates that the value of r_g depends on the differences in average effects between populations. With non-additive effects, average effects depend on the allele frequencies in the population, and, therefore, larger differences in allele frequencies between populations are expected to result in lower values of r_g.

Note that r_g is the correlation between the additive genetic values, not the genotypic values (i.e., additive plus non-additive genetic values). In the absence of GxE-interaction, the genotypic correlation between both populations is equal to one irrespective of the presence of GxG-interactions, because the genotypic value of a genotype (i.e., individual) is the same in both populations. The additive genetic correlation (r_g) may, however, be smaller than one because the partitioning of genotypic values into additive genetic values, dominance deviations and epistatic deviations depends on the allele frequencies (Fisher 1918; Cockerham 1954; Kempthorne 1954).

A deeper understanding of the relationship between non-additive genetic effects, allele frequencies and r_g may help geneticists to predict the value of r_g based on the importance of dominance and epistasis in the expression of the trait, and the genetic distance between populations. Wei *et al.* (1991) studied the impact of dominance on the additive genetic correlation between a purebred and crossbred population, known as r_{pc}. Using a two-locus model, they showed that r_{pc} indeed depends on both the magnitude of the dominance effect (d), and on the difference in allele frequencies between the populations. We are not aware of any theoretical studies that investigated the

relationship between the importance of dominance and r_g between two purebred populations.

With epistasis, r_g is also expected to depend on the magnitude of epistatic effects and on the difference in allele frequencies between populations. Epistasis in the functional (i.e., biological) sense means that the genotypic values of individuals depend on interactions between alleles or genotypes at different loci (Bateson and Mendel 1909), and there is substantial evidence for the existence of functional epistasis across species (Carlborg *et al.* 2003; Le Rouzic *et al.* 2008; Pettersson *et al.* 2011; Mackay 2015). Epistasis in the statistical sense is measured as the deviation of multi-locus genotypic values from the sum of the marginal effects (i.e., average and dominance effects) of the individual loci (Fisher 1918; Cockerham 1954). Although functional epistatic interactions do not necessarily lead to substantial statistical epistasis (Cheverud and Routman 1995; Hill *et al.* 2008; Mäki-Tanila and Hill 2014), epistasis can contribute significantly to the additive genetic variance because average effects of individual loci may capture a substantial part of the functional epistasis (Hill *et al.* 2008; Mäki-Tanila and Hill 2014; Monnahan and Kelly 2015). Furthermore, epistatic variance may be 'converted' into additive genetic variance due to genetic drift or due to selection (Cheverud and Routman 1996; Hill 2017). Thus, epistatic interactions modify average effects of individual loci when allele frequencies change, and may therefore play an important role in the value of r_g and its change over time.

In summary, the r_g between populations is affected by non-additive effects in combination with differences in allele frequencies between populations. For populations in the same environment (i.e., in the absence of GxE), r_g is equal to 1 in the absence of non-additive effects or in the absence of allele frequency differences. So far, the relationship between the nature and magnitude of non-additive effects, differences in allele frequencies, and the value of r_g remains unclear. Our objective was therefore to investigate the impact of non-additive effects on r_g for populations that have diverged either under drift only, or under both drift and selection.

METHODS

We aimed to investigate the relationship between non-additive effects and the additive genetic correlation between populations (r_g) with small effective size, as observed in livestock. For this purpose, we simulated genotypes of quantitative trait loci (QTL) for two populations that have diverged for a number of generations under either pure drift, or under drift and selection. The populations were assumed to be kept in the same environment, so there was no GxE. We simulated traits following several scenarios that differed in the type (i.e., genetic model) and the magnitude of non-additive effects (Table 1).

We considered six genetic models; a basic model with additive effects only (A), which served as a basis for comparison, and five alternative models with non-additive effects: one with only dominance effects (D), and four with only epistatic effects. With epistasis, we simulated interactions between pairs of loci that followed one of the configurations
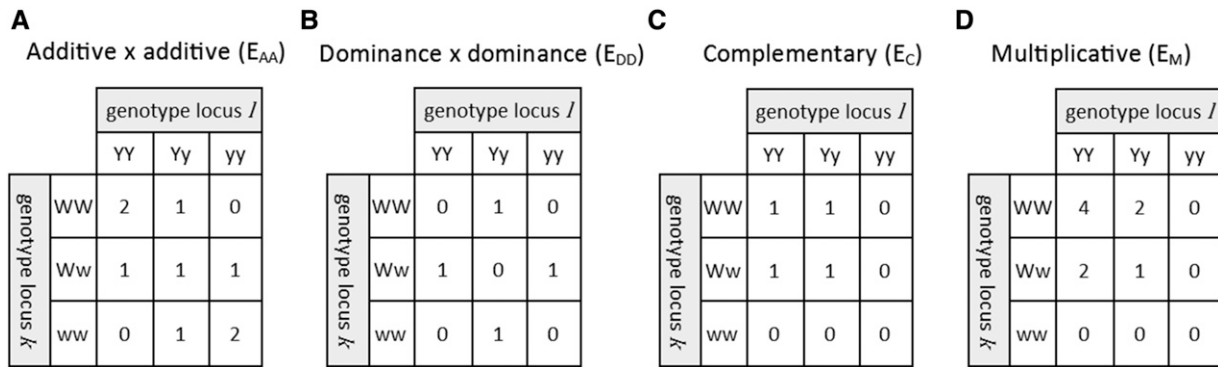
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A Additive x additive (E_{AA})

		genotype locus *l*		
		YY	Yy	yy
genotype locus *k*	WW	2	1	0
	Ww	1	1	1
	ww	0	1	2

B Dominance x dominance (E_{DD})

		genotype locus *l*		
		YY	Yy	yy
genotype locus *k*	WW	0	1	0
	Ww	1	0	1
	ww	0	1	0

C Complementary (E_C)

		genotype locus *l*		
		YY	Yy	yy
genotype locus *k*	WW	1	1	0
	Ww	1	1	0
	ww	0	0	0

D Multiplicative (E_M)

		genotype locus *l*		
		YY	Yy	yy
genotype locus *k*	WW	4	2	0
	Ww	2	1	0
	ww	0	0	0

Figure 1 Epistatic contrasts for four biological epistatic configurations.

presented in Figure 1. We chose these genetic models so that there were scenarios with only dominance variance (D), scenarios with only additive by additive epistatic variance (E_{AA} and E_M), and scenarios with all types of non-additive variance (E_C and E_{DD}). For each genetic model, we considered three magnitudes of non-additive effects, labeled as small, intermediate, and large.

Simulation

We simulated genotypes of two livestock populations (1 and 2) that diverged for 50 generations (Figure 2). For divergence, we considered two situations: one where the populations diverged due to drift only, and one where the populations diverged also due to selection in population 1 and drift in population 2.

Populations: We simulated a historical population with QMSim (Sargolzaei and Schenkel 2009) by randomly mating 100 males and 500 females starting in generation -3001. From generation -3000 to generation -2501, we simulated a bottleneck by gradually decreasing population size to 150 (25 males and 125 females) to create initial linkage disequilibrium (LD), and population size was gradually increased again to 600 during the next 100 generations. The population size remained constant from generation -2400 until -1 to allow for the development of mutation-drift equilibrium. To provide a sufficient number of individuals for the development of populations 1 and 2, we doubled the number of individuals in the last historical generation (generation 0) to 200 males and 1,000 females. This simulation resulted in an average effective population size (N_e) of $\sim$285 generation 0, calculated as the harmonic mean of $\frac{4N_m N_f}{N_m + N_f}$ in each preceding generation, where N_m is the number of males and N_f is the number of females that become parents in a generation (Falconer and Mackay 1996).

After simulating the historical population, we simulated two current populations (1 and 2). We randomly sampled 100 males and 500 females from the last historical generation to become founders of population 1. The remaining 100 males and 500 females were the founders of population 2. We will refer to the generation of founders as generation 0. Within each population, simulation continued for 50 generations by randomly mating 100 selected males with 500 selected females. Each mating resulted in 5 offspring, resulting in a total of 2,500 offspring (exactly 1,250 males and 1,250 females) in each generation. Generations were non-overlapping, meaning that in each generation, the parents were selected from the previous generation only. In the drift scenario, animals in both populations were randomly selected to become parents of the next generation. Effective population size (N_e) in the drift scenario was $\sim$285 in the two

populations. In the selection-drift scenario, animals in population 1 were selected based on their own phenotype (mass selection), while in population 2, selection was random. In this scenario, effective population size (N_e) in population 1 was $\sim$250, which was calculated as $1/(2\Delta F)$, where ΔF is the inbreeding rate estimated from the pedigree (Falconer and Mackay 1996). We simulated selection only in population 1 to reduce computation time.

Genome: The simulated genome consisted of 10 chromosomes of 1 Morgan that each had 200 randomly positioned bi-allelic loci. In the first historical generation (generation -3001), we randomly sampled the allele frequencies of loci from a uniform distribution. Mutation rate was $2.5*10^{-5}$ during the historical generations. In generation 0, the distribution of allele frequencies had evolved to a U-shape, and we randomly selected 500 segregating loci to become QTL, which resulted in low linkage disequilibrium between QTL. There was no mutation from generation 0 to 50, because the QMSim software does not allow for mutation after the last historical generation.

Functional genetic effects: Additive effects (a) of all 500 QTL were sampled from $\sim N(0, 1)$. We assumed that the size of the dominance and epistatic effects were proportional to the additive effects of the QTL involved in the interaction (Wellmann and Bennewitz 2011). We therefore sampled dominance coefficients (δ) for all QTL from $\sim N(\mu_\delta, \sigma_\delta^2)$, from which dominance effects (d) were computed as $\delta|a|$. Similarly, we sampled epistatic coefficients (γ) for all pairwise epistatic interactions from $\sim N(\mu_\gamma, \sigma_\gamma^2)$, from which functional epistatic effects (ϵ) were computed as $\gamma_{kl}\sqrt{|a_k a_l|}$ where k and l denote the QTL involved in the interaction. Each QTL had an epistatic interaction with 5 randomly sampled other QTL, resulting in a total of 1250 pairwise interactions.

For both dominance and epistasis, we considered 3 magnitudes of effects: small, intermediate, and large. For all magnitudes, the mean dominance coefficient (μ_δ) was 0.2, and the mean epistatic coefficient (μ_γ) was 0.0. The magnitude of dominance and epistatic effects were controlled by changing the standard deviation of dominance coefficients (σ_δ) or epistatic coefficients (σ_γ). For dominance, σ_δ was 0.3 with small effects, 0.7 with intermediate effects, and 1.5 with large effects (Table 1). The mean and standard deviation of small dominance coefficients were chosen based on empirical results of Bennewitz and Meuwissen (2010) and Sun and Mumm (2016). For epistasis, σ_γ was scaled such that the total functional epistatic variance was comparable to the total functional dominance variance in
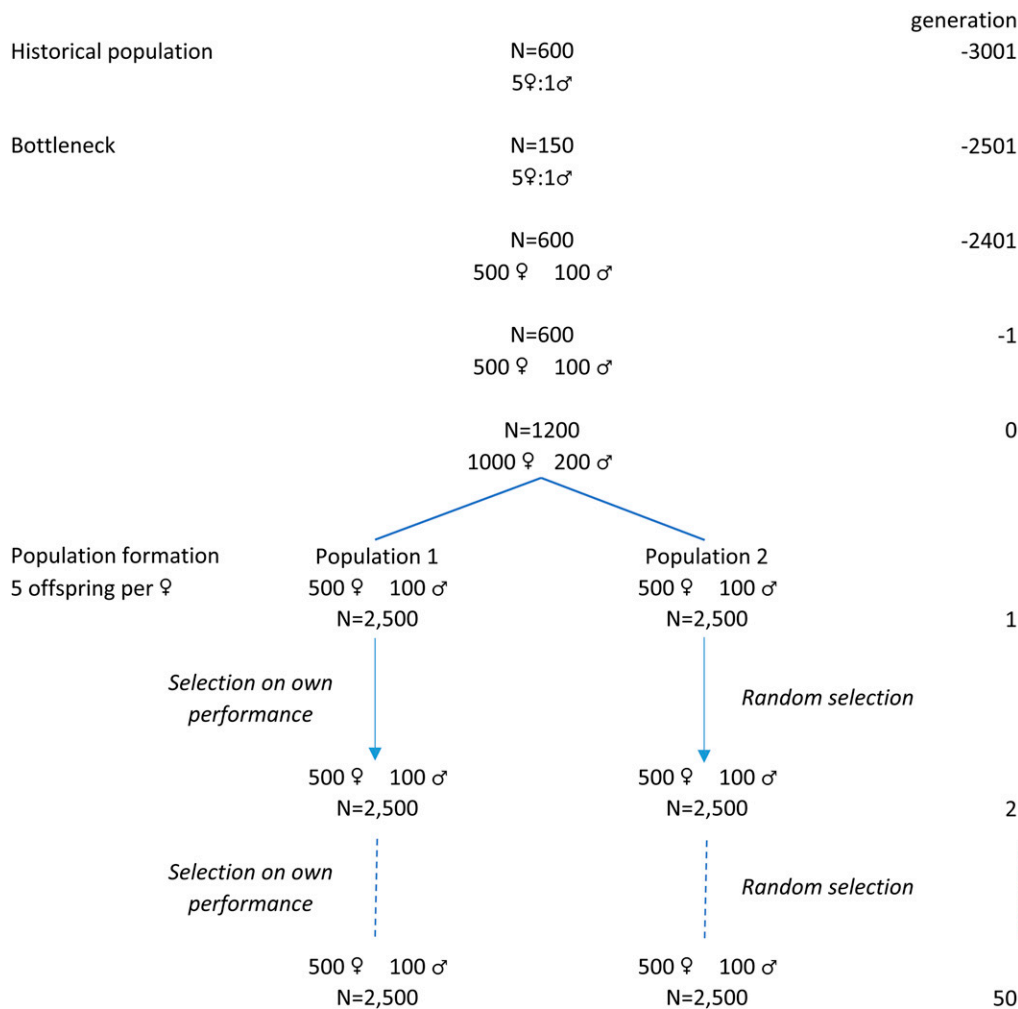
generation

Historical population	N=600	-3001
	5♀:1♂	
Bottleneck	N=150	-2501
	5♀:1♂	
	N=600	-2401
	500 ♀ 100 ♂	
	N=600	-1
	500 ♀ 100 ♂	
	N=1200	0
	1000 ♀ 200 ♂	

Population formation
5 offspring per ♀

Population 1	Population 2	
500 ♀ 100 ♂	500 ♀ 100 ♂	1
N=2,500	N=2,500	

Selection on own performance   *Random selection*

500 ♀ 100 ♂	500 ♀ 100 ♂	2
N=2,500	N=2,500	

Selection on own performance   *Random selection*

500 ♀ 100 ♂	500 ♀ 100 ♂	50
N=2,500	N=2,500	

Figure 2 Overview of the simulated population structure.

the scenario with the same magnitude. To this end, σ_γ was computed as $\sqrt{(\mu_\delta^2 + \sigma_\delta^2)/N_\gamma}$, where N_γ is the number of epistatic interactions per QTL, and μ_δ^2 and σ_δ^2 are the squared mean and variance of dominance effects in the scenario with the corresponding magnitude. For example, with small epistatic effects, σ_γ was computed as $\sqrt{(0.2^2 + 0.3^2)/5} \approx 0.16$ (Table 1).

From functional dominance and epistatic effects to statistically orthogonal effects: We simulated dominance and epistasis by introducing functional dominance and epistatic effects that are independent of allele and genotype frequencies. Our interest, however, is in statistical average, dominance and epistatic effects of QTL, which do depend on genotype frequencies (Fisher 1918; Cheverud and Routman 1995). We will describe the general procedure to obtain these statistical effects, for a general situation where there can be dominance, epistasis, or both. Note, however, that our scenarios had either dominance or epistasis, but never both. After obtaining statistical effects, we describe how we computed the additive genetic value, genotypic value and phenotype for each individual. Although genotypic values themselves are independent of genotype frequencies, the partitioning of these genotypic values into additive, dominance, and epistatic components does depend on genotype frequencies. Additive genetic values of individuals in population 1 were needed to compute r_g, and genotypic values and phenotypes were needed because selection in population 1 was based on own performance. In the following, we describe the procedure to

obtain the average effects and dominance effects in population 1 ($\boldsymbol{\alpha}^{P1}$). The procedure to obtain these effects in population 2 ($\boldsymbol{\alpha}^{P2}$) follows naturally by replacing the genotype and allele frequencies of population 1 with the frequencies in population 2.

The procedure starts by applying the natural and orthogonal interactions (NOIA) model (Álvarez-Castro and Carlborg 2007) for each epistatic interaction between two QTL. First, functional epistatic values for the 9 possible two-locus genotypes at QTL k and l were collected in a vector $\mathbf{c}_{kl} = \mathbf{t}\epsilon_{kl}$, where ϵ_{kl} is a scalar representing the functional epistatic effect between QTL k and l, and $\mathbf{t}$ is a 9×1 vector of epistatic contrasts for the 9 two-locus genotypes, ordered as (WWYY, WwYY, wwYY, WWYy, ..., wwyy). The simulated epistatic contrasts in $\mathbf{t}$ followed one of four configurations: additive x additive (E_{AA}), dominance x dominance (E_{DD}), complementary (E_C), or multiplicative (E_M) (Figure 1). The contrasts in $\mathbf{t}$ were centered and scaled to a standard deviation of one, so that the contrasts were comparable between configurations. We then used genotype frequencies of QTL k and l to partition the functional epistatic values in $\mathbf{c}_{kl}$ into 9 statistical genetic effects (Álvarez-Castro and Carlborg 2007; Vitezica *et al.* 2017)

$$\mathbf{b}_{kl} = \left(\mathbf{W}_{kl}'\mathbf{D}_{kl}\mathbf{W}_{kl}\right)^{-1}\mathbf{W}_{kl}'\mathbf{D}_{kl}\mathbf{c}_{kl},$$

where $\mathbf{D}_{kl}$ is a 9x9 diagonal matrix with each of the nine genotype frequencies in the same order as in $\mathbf{t}$. Matrix $\mathbf{W}_{kl} = \mathbf{W}_k \otimes \mathbf{W}_l$,

where $\otimes$ denotes the Kronecker product, and $\mathbf{W}_k$ and $\mathbf{W}_l$ are constructed as

$$\mathbf{W}_x = \begin{bmatrix} 1 & \mathbf{w}_a & \mathbf{w}_d \end{bmatrix}$$

$$= \begin{bmatrix} 1 & -(-p_{Xx} - 2p_{xx}) & \dfrac{2p_{Xx}p_{xx}}{p_{XX} + p_{xx} - (p_{XX} - p_{xx})^2} \\[2ex] 1 & -(1 - p_{Xx} - 2p_{xx}) & \dfrac{4p_{WW}p_{ww}}{p_{XX} + p_{xx} - (p_{XX} - p_{xx})^2} \\[2ex] 1 & -(2 - p_{Xx} - 2p_{xx}) & \dfrac{2p_{WW}p_{Ww}}{p_{XX} + p_{xx} - (p_{XX} - p_{xx})^2} \end{bmatrix},$$

(1)

where columns relate to orthogonal contrasts for the mean (1), average effect ($\mathbf{w}_a$), and dominance effect ($\mathbf{w}_d$) of QTL X and where p_{Xx}, p_{Xx}, and p_{xx} are the genotype frequencies of QTL X. The resulting vector of statistical genetic effects is

$$\mathbf{b}_{kl} = \begin{bmatrix} \mu, \alpha_{kl}^k, d_{kl}^k, \alpha_{kl}^l, (\alpha\alpha)_{kl}, (d\alpha)_{kl}, d_{kl}^l, (\alpha d)_{kl}, (dd)_{kl} \end{bmatrix}', \quad (2)$$

where α_{kl}^k and α_{kl}^l are the terms that contribute to average effects of QTL k and l. The other terms in $\mathbf{b}_{kl}$ contribute to dominance effects (d_{kl}^k, d_{kl}^l) of individual QTL and to epistatic effects of interacting QTL ($(\alpha\alpha)_{kl}$, $(d\alpha)_{kl}$, $(\alpha d)_{kl}$, $(dd)_{kl}$).

We repeated this procedure of partitioning functional epistatic effects into statistical genetic effects for all pairwise interactions between QTL. Each QTL was involved in 5 epistatic interactions and therefore has 5 terms that contribute to its average effect. Following this reasoning, the average effect of QTL k in population 1 with epistasis is

$$\alpha_k^{P1} = a_k + \left(1 - 2p_k^{P1}\right)d_k + \sum_{l \in \mathbb{Z}}^{N_\gamma} \alpha_{kl}^k,$$

where p_k^{P1} is the frequency of the counted allele of QTL k in population 1, $\mathbb{Z}$ is the set of loci that QTL k interacts with, and $N_\gamma = 5$. Note the difference between "additive effect" (a) and "average effect" (α); the additive effect a is half the difference in genotypic value between both opposing homozygotes, whereas the average effect (α) is the (statistical) marginal effect of the QTL. Throughout this manuscript, we will use the term "functional additive effect" to refer to a, and "average effect" (i.e., statistical substitution effect) to refer to α.

In our simulations, we needed to compute phenotypes of selection candidates in each generation, for which we needed the statistical dominance effect (d^*) of each QTL as well. The dominance effect of QTL k in population 1 with epistasis is

$$d_k^{P1*} = d_k + \sum_{l \in \mathbb{Z}}^{N_\gamma} d_{kl}^k$$

Additive genetic values and phenotypes: We computed additive genetic values ($\mathbf{v}$) of selection candidates in population 1 for the trait expressed in both population 1 and 2. Their genotypic values ($\mathbf{g}$) and phenotypes were only computed for the trait expressed in population 1. The additive genetic value of individual i for the trait expressed in population 1 (2) were computed as $v_i^{P1} = \mathbf{h}_{a,i}'\boldsymbol{\alpha}^{P1}$ ($v_i^{P2} = \mathbf{h}_{a,i}'\boldsymbol{\alpha}^{P2}$), and genotypic values for the trait expressed in population 1 were computed as

$$g_i^{P1} = v_i^{P1} + \mathbf{h}_{d,i}'\mathbf{d}^{P1*} + \mathbf{h}_{a,i}'\otimes\mathbf{h}_{a,i}'(\boldsymbol{\alpha\alpha})^{P1} + \mathbf{h}_{a,i}'\otimes\mathbf{h}_{d,i}'(\boldsymbol{\alpha d})^{P1}$$
$$+ \mathbf{h}_{d,i}'\otimes\mathbf{h}_{a,i}'(\mathbf{d\alpha})^{P1} + \mathbf{h}_{d,i}'\otimes\mathbf{h}_{d,i}'(\mathbf{dd})^{P1},$$

where $\mathbf{h}_{a,i}$ is a column vector of additive genotype indicators for individual i, and $\mathbf{h}_{d,i}$ is column a vector of dominance genotype indicators for individual i. These indicators were coded following the NOIA parameterization as denoted in the rows of $\mathbf{w}_a$ and $\mathbf{w}_d$ (Equation 1) for genotypes XX, Xx, and xx, respectively. Phenotypes with a broad sense heritability of 0.5 were computed as $\mathbf{y}^{P1} = \mathbf{g}^{P1} + \mathbf{e}^{P1}$, where $\mathbf{e}^{P1} \sim N(0, \sigma_e^2)$, and σ_e^2 was equal to the variance of genotypic values (σ_g^2).

Computing parameters of interest

The parameters of interest were (1) the genetic correlation between the trait in population 1 and the trait in population 2 (r_g), and (2) the average absolute difference in allele frequencies between populations ($\overline{\Delta p}$). For each generation, we computed r_g as the Pearson correlation between the additive genetic values of individuals in population 1 for the trait expressed in the two populations (equation (1)). Effectively, this r_g is a weighted correlation between $\boldsymbol{\alpha}^{P1}$ and $\boldsymbol{\alpha}^{P2}$, where the weights depend on the allele frequencies in population 1. Hence, the r_g computed as the correlation of additive genetic values of individuals in population 2 may give different results because the genotypes sampled from population 2 result in different weights than those sampled from population 1 (see Discussion). For each generation, we computed $\overline{\Delta p}$ as $\sum \left(|p_k^A - p_k^B| \right)/500$. We chose this parameter as a measure for population divergence, because we expect that there is a linear relationship between $\overline{\Delta p}$ and r_g. These parameters were computed for generation 1 to 5, and for every 5th generation after generation 5, to limit computation time.

Replicates

We ran the simulation with drift 50 times, resulting in 50 sets of genotypes (i.e., replicates). For each of those replicates, we computed $\overline{\Delta p}$ and r_g for each of the scenarios (i.e., genetic model and magnitude). We ran the simulations with both selection and drift for each scenario separately, because the selection of parents in population 1 depended on the genetic model. To limit computation time, we used 20 replicates for each scenario with selection.

Data availability

The data used in this study can be reproduced with the files and seeds in the following GitHub repository: https://git.wageningenur.nl/duenk002/rg-and-non-additive-effects. Supplemental material available at figshare: https://doi.org/10.25387/g3.10252856.

RESULTS

First, for each scenario with selection, we show the change in mean genotypic value ($\bar{g}$) and the change of additive genetic variance (V_A) in population 1 across generations, to illustrate how population 1 evolved over time. Second, we report realized fractions of additive, dominance and epistatic variance in generation 1 and 50. Third, for scenarios with small non-additive effects, we show the effects of the genetic model and of applying selection on the additive genetic correlation (r_g) and the difference in allele frequency ($\overline{\Delta p}$) between populations. Fourth, for each genetic model with selection, we investigate the impact of the magnitude of non-additive effects and the number of generations since divergence. Finally, we investigate the relationship between r_g and $\overline{\Delta p}$ across genetic models and within genetic models. All results presented

Table 2 Fractions of additive (V_A), dominance (V_D), and epistatic (V_I) variances with respect to the total genetic variance in generation 1 and generation 50 with selection. Reported values are averages of 20 replicates

Scenario	Effect size	Generation 1			Generation 50		
		V_A	V_D	V_I	V_A	V_D	V_I
D	Small	0.961	0.039	0.000	0.924	0.076	0.000
	Intermediate	0.871	0.129	0.000	0.511	0.489	0.000
	Large	0.702	0.298	0.000	0.198	0.802	0.000
E_{AA}	Small	0.992	0.000	0.008	0.997	0.000	0.003
	Intermediate	0.976	0.000	0.024	0.988	0.000	0.012
	Large	0.952	0.000	0.048	0.969	0.000	0.031
E_{DD}	Small	0.910	0.064	0.026	0.703	0.289	0.008
	Intermediate	0.751	0.173	0.076	0.358	0.602	0.040
	Large	0.528	0.333	0.139	0.146	0.752	0.101
E_C	Small	0.985	0.012	0.003	0.947	0.051	0.001
	Intermediate	0.947	0.044	0.009	0.737	0.250	0.013
	Large	0.871	0.105	0.024	0.471	0.511	0.017
E_M	Small	0.998	0.000	0.002	0.999	0.000	0.001
	Intermediate	0.993	0.000	0.007	0.995	0.000	0.005
	Large	0.983	0.000	0.017	0.989	0.000	0.011

refer to generation 50 and to scenarios with small non-additive effects, unless otherwise stated.

Mean genotypic value and variance components

With all scenarios, the mean genotypic value expressed in genetic standard deviations ($\bar{g}$) in population 1 increased due to selection (Figure S 1). With all genetic models, the increase in $\bar{g}$ was smaller when the magnitude of non-additive effects was larger. This result was expected, because the marginal effects of alleles may change over time in the presence of non-additive effects, reducing the effectiveness of selection. The increase in $\bar{g}$ was largest with model A, and it was smallest with model E_{DD} and large non-additive effects. There were only small differences in $\bar{g}$ between models D, E_{AA}, E_C, and E_M.

The additive genetic variance in population 1 (V_A) decreased due to selection with all scenarios (Table 2 and Figure S 2). With genetic model A, E_{AA}, E_C and E_M, about 95–98% of V_A was lost after 50 generations of selection, whereas with D and E_{DD}, 88–95% of V_A was lost. A change in magnitude of non-additive effects did not substantially affect the decrease in V_A, except with genetic models D and E_{DD}, where more additive genetic variance was preserved with larger non-additive effects. In the drift scenario, the average loss of V_A was about 7% for all scenarios (results not shown).

In generation 1, scenarios that had only additive genetic (V_A) and epistatic variance (V_I), V_A accounted for the largest, and V_I for the smallest fraction of the total genetic variation (Table 2). The largest fraction of V_I was realized with genetic model E_{AA} (max. 0.048), followed by E_{DD} (max. 0.033), E_C (max. 0.024) and E_M (max. 0.017). The largest fraction of dominance variance (V_D) was realized with model E_{DD} (max. 0.364), followed by D (max. 0.298) and E_C (max. 0.105). With genetic models D, E_{DD} and E_C, the fraction V_D increased and V_A decreased across generations, especially with intermediate or large effects (Table 2, generation 50). The fraction V_I remained relatively constant across generations with all scenarios.

Effect of genetic model and of selection on r_g

For all genetic models and small non-additive effects, r_g was lower with selection than with drift only (Figure 3). With drift only, r_g was between 0.99 and 1 for all genetic models. After 50 generations of selection, average r_g was lowest with genetic model E_{DD} (0.65), followed by E_{AA} (0.75), D (0.83), E_C (0.83) and finally E_M (0.94). There was a tendency that scenarios with the largest non-additive variance in generation 1 had the smallest r_g in generation 50 (Figure S 3). Note that the r_g was always equal to 1 with the additive model (A) (results not shown).

As expected, $\overline{\Delta p}$ was larger with selection than with drift, and was the same across all genetic models with drift (0.05; Figure 4). With selection, $\overline{\Delta p}$ with non-additive models was very similar (around 0.20) to the value with an additive model.
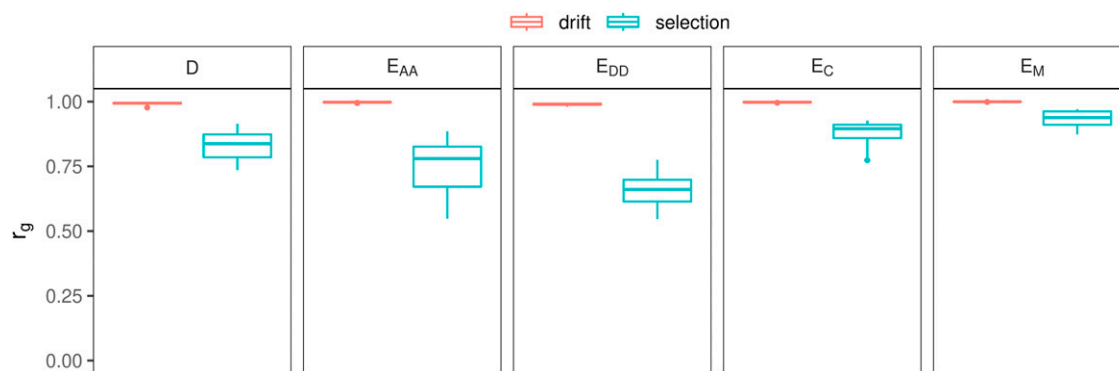

Figure 3 Effect of genetic model on r_g with small non-additive effects, under drift only, or under drift and selection.
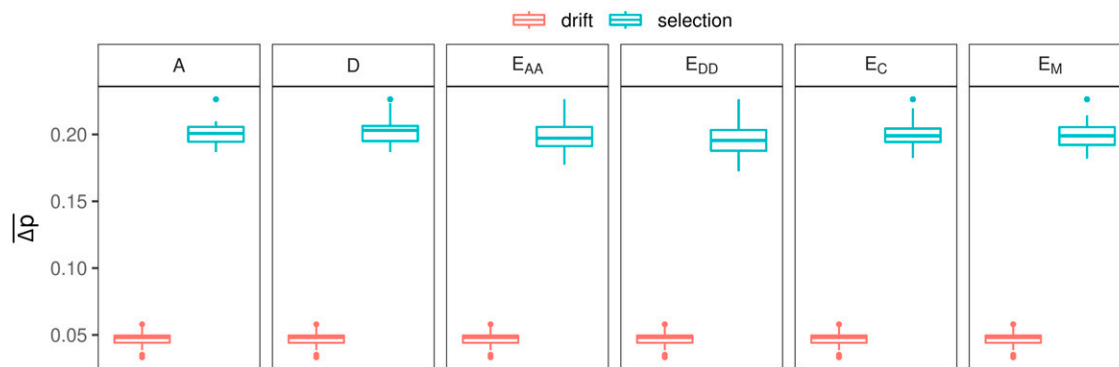
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Figure 4 Effect of genetic model on the difference in allele frequencies between populations, under drift only, or under drift and selection.

Effect of the magnitude of non-additive effects

For all genetic models and with selection, r_g decreased with increasing magnitude of non-additive effects (Figure 5). With genetic model D, r_g dropped about 31% from small to intermediate, and about 27% from intermediate to large dominance effects. With all epistatic models, the drop in r_g with increasing magnitude was smaller (16–23%) than with D.

For all genetic models with selection, the average absolute difference in allele frequency between lines ($\overline{\Delta p}$) decreased with increasing magnitude of non-additive effects, especially with D and E_{DD} (Figure 6). With model D, $\overline{\Delta p}$ was 0.18 with intermediate dominance effects, and 0.141 with large effects. With E_{DD}, $\overline{\Delta p}$ was 0.162 with intermediate epistatic effects, and 0.130 with large effects. With the other epistatic models (E_{AA}, E_C and E_M), the effect of an increase in magnitude on $\overline{\Delta p}$ was much smaller (~0.19 with intermediate and ~0.18 with large effects).

Effect of number of generations since divergence

With all scenarios, r_g decreased with the number of generations since divergence, and the rate of decrease was relatively small during the first five generations ($r_g > 0.94$), especially when the non-additive effects were small ($r_g > 0.98$) (Figure 7). After the first five generations, the

rate of decrease in r_g differed across genetic models. There was a considerable difference between genetic models, the E_M model showed the smallest decline of r_g over time, and the E_{DD} model showed the largest decline. With large non-additive effects, models E_M and E_{AA} tended to show an accelerated decrease in r_g across generations, whereas models D, E_C and E_{DD} tended to show a decelerated decrease in r_g (Figure 7).

With all scenarios, the average absolute difference in allele frequency between lines ($\overline{\Delta p}$) increased with the number of generations since divergence (Figure 8). In contrast to the result of the genetic correlation with small non-additive effects (Figure 7), $\overline{\Delta p}$ was remarkably similar between the genetic models (Figure 8). With large effects, models D and E_{DD} showed a smaller $\overline{\Delta p}$ than models E_M, E_{AA}, and E_C.

In summary, for each genetic model, r_g was smallest with selection, large non-additive effects and many generations since divergence. Overall, the smallest realized value of r_g after 50 generations of divergence was achieved with genetic model D or E_{DD} ($r_g \approx 0.41$ for both).

Relationship Between r_g and $\overline{\Delta p}$

For all genetic models, there was a clear negative relationship between $\overline{\Delta p}$ and r_g (Figure 9), and the relationship was strongest for genetic models showing the strongest decline of r_g with time (Figure 7).
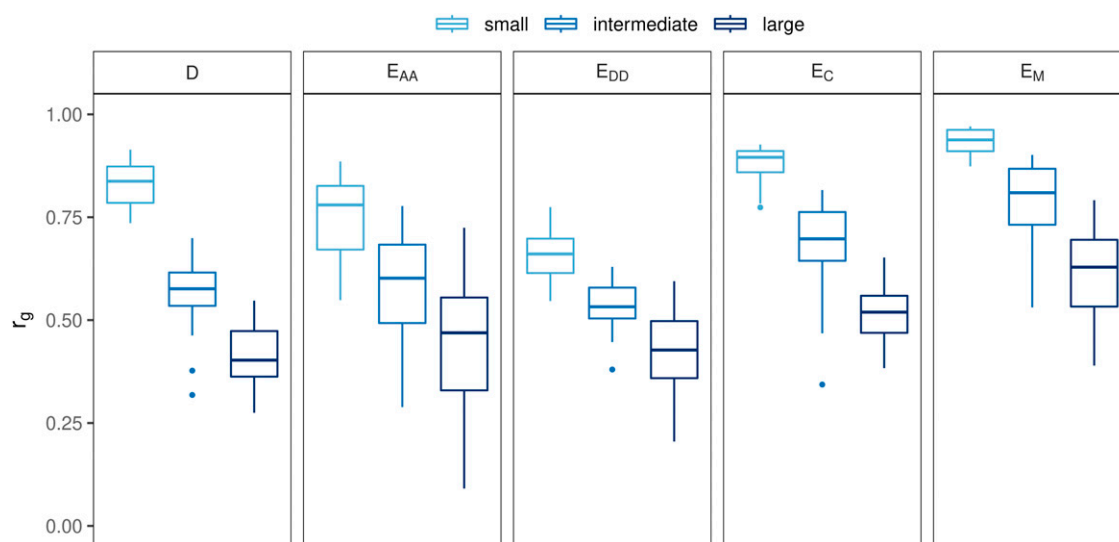

Figure 5 Effect of magnitude of non-additive effects on r_g for all genetic models, where population 1 was selected and population 2 was not selected.
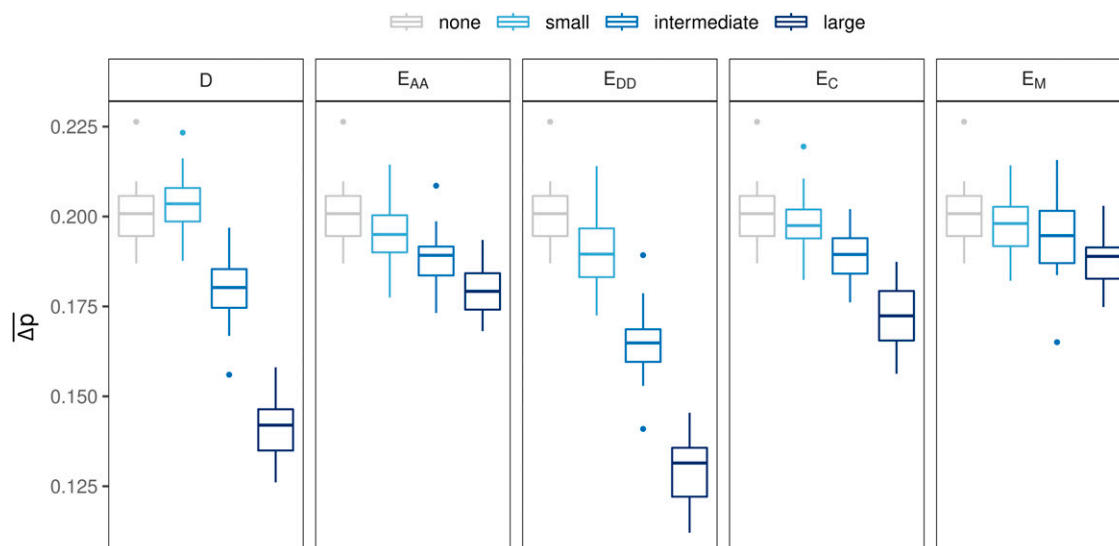
Figure 6 Effect of magnitude of non-additive effects on the difference in allele frequencies between populations under selection. In each subplot, the additive scenario (A) was included for reference (*i.e.*, magnitude "none").

This result suggests that differences between genetic models in the decline of r_g over time originate from different impacts of $\overline{\Delta p}$ on r_g, and not from differences in $\overline{\Delta p}$ *per se*. For example, with small non-additive effects and after 50 generations of divergence, the value of r_g was different between genetic models, whereas the realized $\overline{\Delta p}$ was very similar (Figure 9). In other words, r_g is a function of $\overline{\Delta p}$ and of genetic architecture.

DISCUSSION

Our objective was to investigate the relationship between non-additive effects, differences in allele frequencies between populations ($\overline{\Delta p}$), and the genetic correlation between populations (r_g). We simulated genotype data of two populations that have diverged for a number of generations under drift only, or drift and selection, and we simulated traits where the genetic model and magnitude of non-additive effects were varied.

We computed r_g as the correlation between additive genetic values of individuals in population 1, for the trait expressed in population 1 and 2. Effectively, this r_g is a weighted correlation

between average effects in population 1 ($\boldsymbol{\alpha}^1$) and 2 ($\boldsymbol{\alpha}^2$), where the weights depend on the sample of genotypes that were used to compute the additive genetic values. This suggests that different values of r_g could have been obtained when using the additive genetic values of individuals in population 2, because of differences in genotype frequencies between populations. We chose, however, to focus on population 1 because we were also interested in the change of allele frequencies over time due to selection. This approach leads to values of r_g that indicate whether information from an unselected population (population 2) can be used to predict additive genetic values in a selected population (population 1).

Realized variance components

Because little is known about the quantity and magnitude of dominance and epistatic effects in reality, we considered a range of functional non-additive effect sizes and epistatic configurations. Realized proportions in our simulations (Table 2) did not always match with those observed in real data. For example, with large dominance effects, the fraction of dominance variance was 30%, which is uncommon in real data (Ertl *et al.* 2014; Lopes *et al.* 2016; Moghaddar and van der Werf 2017;
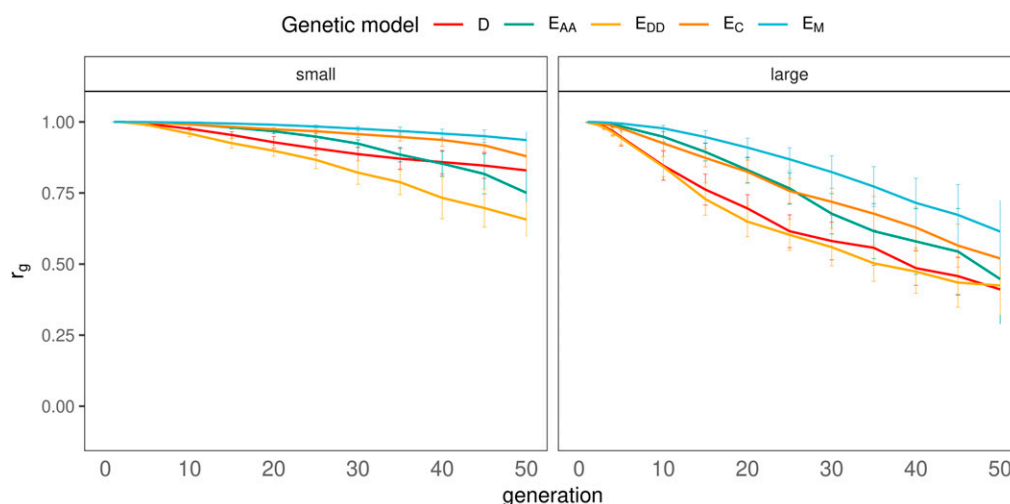

Figure 7 Effect of number of generations since divergence on r_g for all genetic models with small (left) or large (right) non-additive effects.

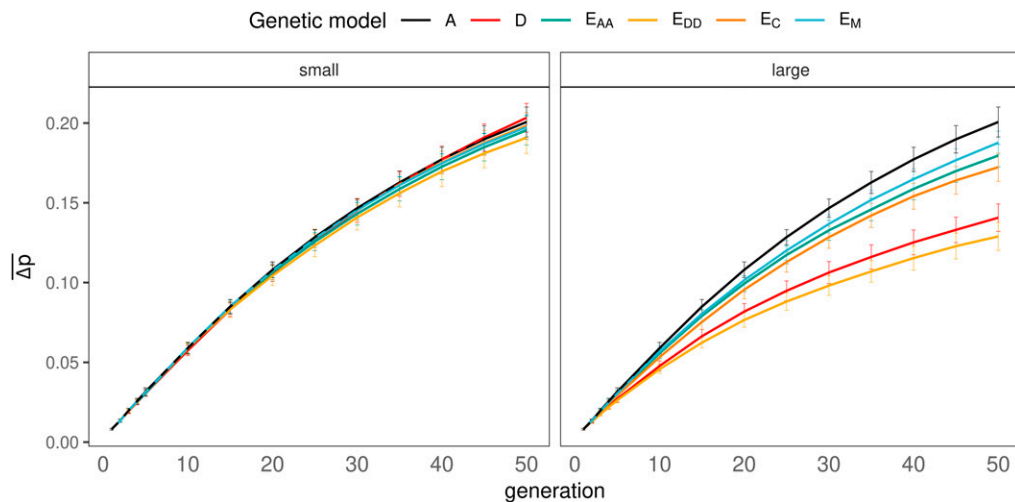G3·Genes | Genomes | Genetics

Figure 8 Effect of number of generations since divergence on the difference in allele frequencies between populations, for all genetic models and small (left) or large (right) non-additive effects. Dotted line represents additive trait.

Joshi *et al.* 2018). Similarly, scenario E_{DD} also resulted in more dominance variance than expected in real populations, especially with large epistatic effects (33%). Empirical studies on livestock (Bennewitz and Meuwissen 2010) and crops (Sun and Mumm 2016) found that approximately 0.3% of loci show overdominance, which is comparable to our scenario with small dominance effects (0.5% overdominance). Furthermore, the scenario with small dominance effects resulted in a small proportion of dominance variance, and might therefore be most realistic for actual populations.

In contrast to our realized proportions of dominance variance, proportions of epistatic variance were lower (max. 5%) than estimates from an empirical study on litter size in pigs (about 26%) (Vitezica *et al.* 2018), though the standard error of that estimate was large (about 22%). Further evidence of statistical epistatic effects is scarce, probably because methods used for the detection of statistical epistasis are frequently underpowered (Wei *et al.* 2014). Furthermore, it has been suggested that incomplete LD between genomic markers and QTL may create the illusion of epistasis, making inference about the importance of epistasis from genome-wide regression studies difficult (Wei *et al.* 2014; Zan *et al.* 2018; de los Campos *et al.* 2019). In contrast to the

lack of evidence of statistical epistasis, there is substantial evidence that physiological epistasis is abundant in several classes of organisms (Carlborg *et al.* 2003; Le Rouzic *et al.* 2008; Pettersson *et al.* 2011; Mackay 2015). Nevertheless, large epistatic effects between pairs of loci are believed to be unlikely (Wei *et al.* 2014), and the contribution of epistatic variance to the total genetic variance is expected to be small (Hill *et al.* 2008).

In summary, among the scenario's we studied here, scenarios D and E_{DD} with small effects, and scenarios E_{AA}, E_C and E_M are probably most realistic, because these scenarios always resulted in little dominance (max. 7%) and epistatic (max. 5%) variance.

Effect of genetic model on r_g

For the dominance model (D), we observed that r_g decreased with increasing size of dominance effects and with increasing difference of allele frequencies between populations. In some cases, the r_g can be negative due to dominance alone, as shown for a two-locus model (Wei *et al.* 1991). Such low values of r_g were, however, only obtained with scenarios where both loci showed substantial overdominance, and where the difference in allele frequencies between the two populations
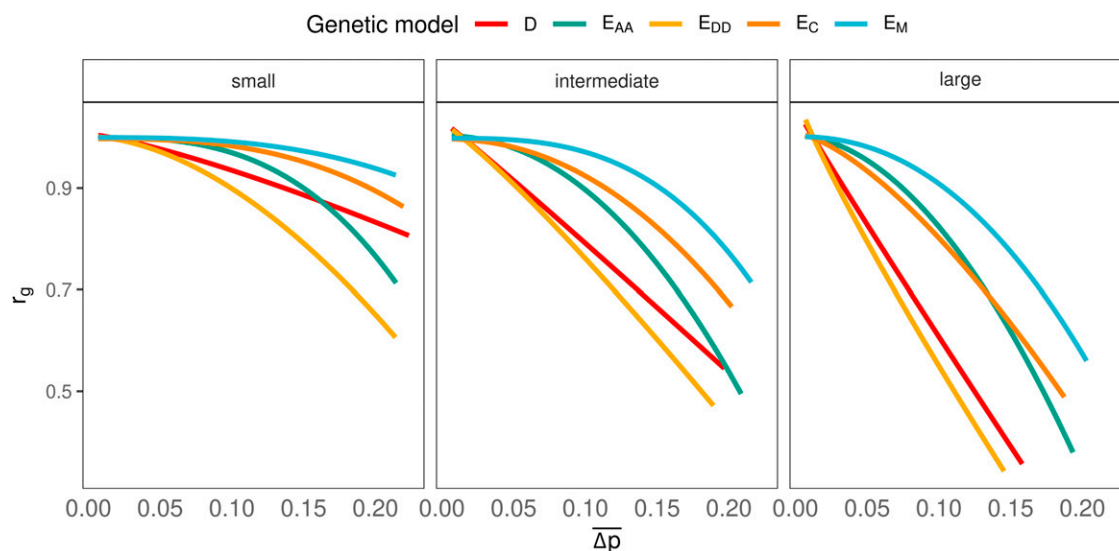

Figure 9 Relationship between r_g and the difference in allele frequencies between populations for all scenarios.

was at least 0.3 for one of the loci. In our study, we considered many loci and the distributions of dominance effects was based on empirical results (Bennewitz and Meuwissen 2010; Sun and Mumm 2016). These distributions resulted in only a fraction of loci showing overdominance (*i.e.*, 0.5% for small effects, 16% for intermediate effects, and 51% for large effects). Furthermore, our simulations resulted in U-shaped distributions of allele frequencies in the last generation of the historical population, which agrees with expectations based on neutral theory (Kimura and Crow 1964; Goddard 2001). After the two populations separated, allele frequency differences between populations were a result of drift and/or selection. We therefore believe that our simulations represent a more realistic model of quantitative traits and population divergence than those in Wei *et al.* (1991). In conclusion, given that dominance variance is usually small and overdominance does not occur frequently, our results show that it is unlikely that true r_g values lower than 0.80 are due to dominance effects alone.

In another simulation study, where the fraction of loci showing overdominance was 12%, realized r_g was 0.78 (Esfandyari *et al.* 2015). Although the fraction of loci showing overdominance in that study was comparable to our scenario with intermediate dominance effects, our realized r_g in that scenario was much lower (0.57). This difference is likely due to the smaller number of generations that populations diverged in the study of Esfandyari *et al.* (2015).

With epistasis, r_g decreased with increasing size of epistatic effects and with increasing difference of allele frequencies between populations, and the value of r_g depended on the nature of the epistatic interaction (*i.e.*, configuration). In addition, there was a tendency for configurations that resulted in large initial non-additive variance to result in smaller values of r_g (Figure S 3). Even though large epistatic effects are unlikely and epistatic variance is expected to be small, r_g could be as low as 0.45 for supposedly realistic epistatic scenarios.

To our knowledge, the relationship between the nature of epistasis and r_g has not been studied before. The mechanism behind differences in r_g between epistatic models can be illustrated with an example of two interacting loci. Suppose that both loci have an additive effect (*a*) of 1, an epistatic coefficient (γ) of 0.5, and the allele frequency at locus 1 (p_1) is the same in both populations (here we use 0.10). Then, we study the effect of allele frequency difference between populations at locus 2 (Δp_2) on the difference in average effects between populations ($\Delta \alpha$) for locus 1 and 2. Results show that E_{AA} and E_M interactions only affect the α of the locus with fixed p (locus 1), whereas E_{DD} and E_C interactions affect the α at both loci (Figure S 4). Note that this result was the same with different values for a, γ, or p_1. This shows that, in general, E_{AA} and E_M interactions create a dependency of α at a locus on the allele frequency of all loci it interacts with, whereas E_{DD} and E_C interactions also create a dependency of α on the allele frequency of the locus itself. These mechanisms may contribute to the differences in r_g between genetic models, because the interplay between differences in allele frequencies and r_g depends on the genetic model.

Effect of magnitude of non-additive effects on r_g

As expected, an increase in magnitude of dominance effects resulted in a lower r_g, which is in line with results from Wei *et al.* (1991). Similarly, an increase in magnitude of epistatic effects also resulted in a lower r_g. An important question is whether this decrease of r_g due to an increase in magnitude continues until the theoretical limit of $r_g = -1$ is reached. Additional analyses revealed that r_g appears to asymptote with increasing magnitude of non-additive effects. In these analyses, we repeated our original simulations of genetic models D and E_{AA}, using non-additive effects that were multiplied by 100 for all magnitudes. Results from those simulations showed that the difference in r_g

between "small", "intermediate", or "large" effects had indeed disappeared (Figure S 5), and that the lower bound of realized values for r_g was ~0.25 with scenario D and ~0.36 with scenario E_{AA}.

To show the mechanism behind this result, we again consider a two-locus model where, like before, both loci have an additive effect (*a*) of 1, the allele frequency of locus 1 (p_1) is 0.10 in both populations and $\Delta p_2 = 0.20$. We studied the effect of the magnitude of the epistatic effect (γ) on the absolute difference in average effects between populations, relative to the absolute value of α in population 1 ($\Delta \alpha / \alpha_A$). We observed that for all epistatic models, especially for larger values of γ, both $\Delta \alpha$ and α_A increase roughly linearly with γ, and that therefore $\Delta \alpha / \alpha_A$ stops increasing with large values of γ (Figure S 6). Note that the same mechanism was observed with dominance when p_2 was the same in both populations and $\Delta p_1 = 0.20$. Hence, a change in magnitude equally affects the variance of α's in the two populations, and the covariance between them. As a result, r_g is unaffected by a change in size of non-additive effects when non-additive effects are already large. In conclusion, when non-additive effects are very large, r_g no longer depends on the magnitude of non-additive effects relative to the magnitude of functional additive effects. At that point, there is a lower bound of r_g that is determined by the nature of the non-additive effects (*i.e.*, type of inter-allelic interaction) and by the difference in allele frequencies between populations.

Number of epistatic interactions

In the epistatic scenarios, we assumed that each locus interacted with 5 other loci. Because little is known about the number of interactions per locus (N_γ) in reality, we tested whether our results were sensitive to a change in N_γ. For that purpose, we repeated all simulations of epistatic scenarios with $N_\gamma = 100$. Note that the total functional epistatic variance with $N_\gamma = 100$ was the same as with $N_\gamma = 5$, because the epistatic coefficients were scaled with N_γ, so that the product $N_\gamma \sigma_\gamma^2$ is constant. This analyses resulted in values of r_g that were very similar to those of our original simulations (results not shown), suggesting that, in our simulations, the value of r_g depends on the level of total functional epistatic variance, which scales similarly with N_γ or σ_γ^2.

Effect of selection on r_g

Non-additive effects and selection create a complex interplay between average effects, the difference in allele frequencies between populations ($\overline{\Delta p}$) over time, and their effects on r_g. For a trait with small dominance effects under selection, we observed that $\overline{\Delta p}$ was almost the same as for an additive trait (Figure 8). We expected, however, that directional dominance would reduce $\overline{\Delta p}$, because the average effect at a locus can become smaller or even switch sign when the frequency of the favorable dominant allele increases (Falconer and Mackay 1996). This change in average effects would affect the change in allele frequencies over time due to selection in population 1, because the selection pressure at loci may change. A reduction in $\overline{\Delta p}$ with small dominance effects was not observed, probably because only a small fraction of loci showed full- or over-dominance. Indeed, with large dominance coefficients (so that the fraction of loci showing over-dominance was much larger compared to with small dominance coefficients) $\overline{\Delta p}$ was smaller (Figure 6). In real data, however, we do not expect a large fraction of loci that show full- or over-dominance (Wellmann and Bennewitz 2011). It is therefore unlikely that dominance significantly affects the change in allele frequencies over time due to selection, compared to a purely additive trait.

For a trait with epistatic effects under selection, we observed that $\overline{\Delta p}$ was a bit smaller than that for a trait with only additive effects

(Figure 8). Similar to the models with only dominance effects, this reduction in $\overline{\Delta p}$ was expected because the average effect at a locus can become smaller or switch sign over time in the presence of epistasis. How epistasis affects the change in allele frequencies due to selection depends on the directionality of the epistatic interaction effect. Theory suggests that, compared to pure additivity, positive interactions (*i.e.*, in the same direction as the additive effects) will promote the selection of favorable alleles, whereas negative interactions (*i.e.*, in the opposite direction from the additive effects) will suppress the selection of favorable alleles (Carter *et al.* 2005; Hansen 2013; Paixão and Barton 2016). We chose to simulate both positive and negative interactions with equal probabilities, because empirical studies suggest that epistatic interactions are not biased in being either positive or negative (*i.e.*, they are non-directional) (Mackay 2014). Our results showed that, for a trait with intermediate epistatic effects, the net effect of having both positive and negative interactions was a decrease in fixation rate of favorable alleles (*i.e.*, with a positive a), and an increase in fixation rate of unfavorable alleles (*i.e.*, with a negative a) compared to an additive trait (Figure S 7). Similar results were found by Esfandyari *et al.* (2017). In conclusion, epistatic effects may affect r_g through two related mechanisms. First, with an epistatic model and when selection takes place in one of the populations, the difference in allele frequencies between populations may be smaller compared to an additive model. This reduction occurs because negative interactions decrease the fixation rates of favorable alleles, and increase those of unfavorable alleles. Second, for given allele frequency differences, the value of r_g depends on the nature of the epistatic interaction.

Loss of additive genetic variance

Selection experiments in Drosophila, maize, and *Escherichia coli* have shown that additive genetic variation (V_A) can be maintained for at least 100 generations (Hill 2016). Some researchers suggested that this preservation of V_A may be due to the conversion of non-additive genetic variance to additive genetic variance (Cheverud and Routman 1996; Hallander and Waldmann 2007; Hill 2017). Simulation studies, however, have failed to show a preservation of V_A due to this conversion (Carter *et al.* 2005; Esfandyari *et al.* 2017). Similarly, our simulations showed little conversion of non-additive genetic variance to V_A with genetic models E_{AA} and E_M, and no conversion with other genetic models (Table 2). As a result, almost all additive genetic variance was lost after 50 generations (Figure S 2).

The large loss of additive genetic variance in our simulations may be due to two reasons. First, there was little epistatic variance in generation one that could be 'converted' to V_A in subsequent generations (Hill *et al.* 2008; Mäki-Tanila and Hill 2014). This was largely because the allele frequency distribution was strongly U-shaped in generation one. Second, mutational variance was zero because there were no mutations simulated after the historical generation. Even though these mechanisms may explain some of the loss of V_A in our simulations, the issue still remains that, to date, simulations have failed to convincingly reproduce the conservation of V_A observed in reality (Johnson and Barton 2005; Walsh and Lynch 2018).

Practical relevance

In our simulations, there was selection in only one of the populations, while the other population was unselected. In reality, populations may have been divergently selected (*e.g.*, Friesian Holstein *vs.* Angus cattle), resulting in larger differences in allele frequencies than simulated here. Hence, r_g between divergently selected populations may be smaller than observed in our simulations.

In this study, we assumed that there were no genotype x environment interactions (GxE), so that r_g values smaller than one were only due to non-additive effects. In reality, both non-additive effects and GxE may contribute to r_g values being smaller than one. The relative importance of non-additive effects and GxE can be inferred from the difference between estimated r_g, from a design where the populations were tested in different environments, and from a design where one of the populations was tested in the environment of the other population. This approach is similar to what was proposed by Wientjes and Calus (2017) to dissect the components of the genetic correlation between purebred and crossbred performance. However, to our knowledge, there are no studies that have used this approach to disentangle the effects of non-additive effects and GxE on r_g. This study shows that, even without GxE, the r_g can be substantially smaller than one, and sometimes even close to zero.

Estimated genetic correlations between two populations ($\hat{r}_g$) may differ across traits (*e.g.*, Lund *et al.* 2011; Karoui *et al.* 2012; Porto-Neto *et al.* 2015). For example, in dairy cattle, $\hat{r}_g$ of fertility traits tended to be lower than those of fat yield and milk production (Karoui *et al.* 2012). The results from the present study suggest that such differences in $\hat{r}_g$ may indicate differences in the underlying genetic model between traits (*i.e.*, in the importance of non-additive effects). Although this may be the case, differences in $\hat{r}_g$ between traits can arise through other mechanisms as well. First, $\hat{r}_g$ often include a component due to GxE interactions. Such GxE interactions may be more important for some traits than for others, resulting in differences in $\hat{r}_g$ between traits. Second, different traits are influenced by (at least partly) different QTL, and some traits may have been under stronger selection than others. As a result, the differences in allele frequencies at QTL between populations may vary across traits. These mechanisms may result in differences in $\hat{r}_g$ between traits, even when the underlying genetic models of those traits are similar. It is therefore questionable whether inferences can be made about differences in genetic model among traits, based on differences in $\hat{r}_g$.

The results in this study may be relevant for the prediction of additive genetic values across populations using genomic information. In this strategy, termed across-population genomic prediction, average effects at markers are estimated in one population, and used to compute additive genetic values in another population (de Roos *et al.* 2009; Hayes *et al.* 2009). It has been suggested that the inefficiency of across-population genomic prediction is partly due to differences in linkage disequilibrium between markers and QTL. This insight has inspired the use of whole-genome sequence (WGS) data, because in WGS data, genotypes of the QTL themselves are included (Iheshiulor *et al.* 2016; Raymond *et al.* 2018a; Raymond *et al.* 2018b). The results of the current study suggest, however, that even when QTL genotypes are known and their average effects are accurately estimated in one population, across-population genomic prediction may be inefficient, because r_g can differ considerably from one, even when genetic variance is mostly additive. This view is supported by the results of Raymond *et al.* (2018b), who reported that although the r_g estimated from putative QTL was higher than the estimate from regular marker data, it was still lower than one.

Similar to across populations, genomic prediction from current to future generations may be inefficient because of changes in allele frequencies, and the subsequent changes in average effects at QTL. In other words, two different generations can be considered as two populations that have a genetic correlation between them that may be lower than unity. The results of this study may therefore partly explain the need for frequent retraining of genomic prediction models to achieve constant accuracy across generations (Sonesson and Meuwissen 2009;

Wolc *et al.* 2011). We expect, however, that the change in allele frequency at a single QTL is relatively small across a few (4-5) generations, especially for traits that are highly polygenic. As a result, r_g may be relatively high across a few generations. Nevertheless, the relative contribution of non-additive effects to the decline of genomic prediction accuracy across generations is currently unknown, and would be an interesting topic for future research.

Conclusion

Our findings show that the genetic correlation between populations (r_g) is partly determined by the difference in allele frequencies between populations and the magnitude of non-additive effects. Large differences in allele frequencies and large non-additive effects resulted in low values of r_g. For both dominance and epistasis, when non-additive effects become extremely large, r_g has a lower bound that is determined by the nature of non-additive effects, and the difference in allele frequencies between populations. In addition, we found that with epistasis, r_g depends on the level of total functional epistatic variance, which is a function of epistatic effect size and the number of interactions per locus. Given that dominance variance is usually small and there is not much overdominance, we expect that it is unlikely that values of r_g below 0.8 are due to dominance alone. With supposedly realistic epistasis, r_g could be as low as 0.45. These results may contribute to the understanding of differences in genetic expression of complex traits between populations, and may help in explaining the inefficiency of genomic prediction across populations.

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