THE CORRELATION OF SUBSTITUTION EFFECTS ACROSS POPULATIONS AND GENERATIONS IN THE PRESENCE OF NON-ADDITIVE FUNCTIONAL GENE ACTION

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RUNNING TITLE: Correlation of QTL substitution effects

Keywords: QTL, substitution effects, epistasis, dominance, genetic distance

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ABSTRACT

Allele substitution effects at quantitative trait loci (QTL) are part of the basis of quantitative genetics theory and applications such as association analysis and genomic prediction. In the presence of non-additive functional gene action, substitution effects are not constant across populations. We develop an original approach to model the difference in substitution effects across populations as a first order Taylor series expansion from a "focal" population. This expansion involves the difference in allele frequencies and second-order statistical effects (additive by additive and dominance). The change in allele frequencies is a function of relationships (or genetic distances) across populations. As a result, it is possible to estimate the correlation of substitution effects across two populations using three elements: magnitudes of additive, dominance and additive by additive variances; relationships (Nei's minimum distances or Fst indexes); and assumed heterozygosities. Similarly, the theory applies as well to distinct generations in a population, in which case the distance across generations is a function of increase of inbreeding. Simulation results confirmed our derivations. Slight biases were observed, depending on the non-additive mechanism and the reference allele. Our derivations are useful to understand and forecast the possibility of prediction across populations and the similarity of GWAS effects.

INTRODUCTION

One of the aims of quantitative genetics is to provide methods for prediction, for instance genomic prediction (prediction of livestock breeding values or of crop performance) or polygenic risk score (risk of a disease in humans). These predictions would ideally work across a range of populations (different breeds, future generations). Ideally, the prediction goes through a process of identifying causal genes, estimating their effects in some population, and transposing these effects to newly genotyped individuals (Lande and Thompson 1990; Meuwissen *et al.* 2001). These "gene effects" are substitution effects – the regression of the own phenotype (for polygenic risk scores) or expected progeny phenotypes (for estimated breeding values) on gene content at the locus. Being able to use substitution effects at causal genes across populations and generations is a goal of genomic prediction, QTL detection and also of causal mutation finding (Grisart *et al.* 2002).

There are several obstacles for these aims. Finding and validating causal genes and understanding their functional mechanism is extremely difficult (Grobet *et al.* 1997; Bonifati *et al.* 2003; Rupp *et al.* 2015). In practice, predictions are done using SNP markers using statistical genetics techniques. In livestock, use of markers results in very good predictions within populations, but mediocre (at best) predictions across populations, even with very sophisticated techniques (Hayes *et al.* 2009; Karoui *et al.* 2012; Porto-Neto *et al.* 2015; MacLeod *et al.* 2016). Indeed, livestock and human genetics empirical results show decreasing predictive ability with increasing genetic distance across distinct populations or generations (Liu *et al.* 2016; Martin *et al.* 2019). In humans, there is strong correlation between GWAS effect estimates across human populations, with typical values around 0.82 (Marigorta and Navarro 2013; Shi *et al.* 2021). The lack of perfect linkage disequilibrium (LD) across markers

68 and genes has been claimed to be a reason for this decrease in accuracy. Adding extra
69 information (more dense maps, biological prior information) should result in a better choice
70 of markers close to causal genes, and therefore in a boost in predictive abilities across
71 populations (Roos *et al.* 2009; MacLeod *et al.* 2016). However, in practice, the increase in
72 predictive ability across populations is small at best (MacLeod *et al.* 2016; Moghaddar *et al.*
73 2019). This is against results from simulations (Roos *et al.* 2009; MacLeod *et al.* 2016) – but a
74 problem in simulations is that typically gene effects are assumed to be biologically additive
75 and therefore constant across populations.
76
77 We argue that, although imperfect LD is a likely cause for not being able to predict across
78 populations, it is not the only one. In fact, substitution (statistical) additive gene action is not
79 homogeneous across populations, even for exactly the same causal mutation. Examples in
80 livestock genetics include myostatin gene (Aiello *et al.* 2018) or DGAT1 (Gautier *et al.* 2007).
81 For instance, in the latter, the "K" allele had rather different substitution effects across breeds:
82 -611, -142 and -351 kg of milk for the respective breeds Montbéliarde, Normande and
83 Holstein, for a trait with a genetic standard deviation of ~600 kg. Although part of these
84 differences may be due to genotype by environment interactions, it is also plausible that this
85 is due to epistasis or dominance; for instance this is the case in DGAT1 (Streit *et al.* 2011). For
86 instance, in the 5-loci epistatic network in Carlborg et al. (2006) some substitution effects at
87 genes switch signs depending on genetic background. In Drosophila, estimated substitution
88 effects of P-element insertions switched signs depending on the genetic background (Magwire
89 *et al.* 2010; Mackay 2015).
90

There is indeed widespread evidence of biological epistasis (Mackay 2014). Whereas biological epistasis does not impede (on the contrary) large additive variation (Hill *et al.* 2008; Mackay 2014; Mäki-Tanila and Hill 2014), it does imply that substitution effects do vary across genetic backgrounds. Thus, in the presence of functional dominance and epistasis, there is no stability of substitution effects across different genetic backgrounds. Even if in all of these populations, additive variation accounts for most genetic variation, and additive substitution effects are sizable (Hill *et al.* 2008), substitution effects may differ across populations.

Recent simulations (Dai *et al.* 2020; Duenk *et al.* 2020) showed that the difference in substitution effects across populations may be quite large under non-additive biological gene action and increases with divergence of populations. It is relatively easy to derive algebraic expressions for substitution effects α assuming specific hypothesis of biological gene action. For instance, assuming biological additive and dominance effects only (Falconer and Mackay 1996) results in $\alpha = a + (q - p)d$, whereas assuming additive, dominance and additive by additive biological gene effects results, assuming linkage equilibrium (LE), in $\alpha_1 = a_1 + (q_1 - p_1)d_1 + (p_2 - q_2)[aa]_{12}$ (Fuerst *et al.* 1997). Both of the approaches (simulation or analytical) are limited because the hypotheses of specific biological gene actions (*e.g.* 2-loci interaction but not 3-loci interaction) are too restrictive. Classically, these hypotheses are bypassed in quantitative genetics by working on statistical effects (Falconer and Mackay 1996; Lynch and Walsh 1998; Mäki-Tanila and Hill 2014).

The key parameter to describe the resemblance of statistical effects across populations is the correlation of substitution effects across populations. Under certain assumptions (independence of allele frequencies and substitution effects, appropriate coding; (Wientjes *et*

al. 2017)), this correlation can be estimated from SNP markers and data of two populations (Karoui *et al.* 2012; Wientjes *et al.* 2017), and can easily be accommodated into genomic prediction models (Karoui *et al.* 2012; Xiang *et al.* 2017). In human studies, the correlation is estimated through the meta-analysis of GWAS statistics (Marigorta and Navarro 2013; Shi *et al.* 2021). However, in addition to empirical results, some theory to describe the resemblance of substitution effects across different populations would be helpful to (1) better understand and quantify the change in *true* substitution effects (*i.e.* if true genes instead of markers were being used), (2) give upper bounds for genomic prediction across populations/generations, and (3) allow *a priori* planning of genomic predictions *i.e.* to include or not different subpopulations.

The aim of this work is to develop a theory to understand and predict, under a neutral scenario, the extent of change of substitution effects across space (breeds, lines) and across time (generations), without invoking or assuming specific modes of biological gene action. As a result, we obtain explicit estimators that are functions of additive, dominance and additive by additive variances, genetic distances across populations, and distributions of allele frequencies. We check and illustrate our theory using published results and simulations considering dominance and epistasis (additive by additive and complementary) from 5-loci interactions. Main factors affecting correlation of substitution effects across populations are their genetic distance and the extent of additive by additive variation, which is rarely large.

THEORY

Analytical results

138 **General Theory.** Here, we model difference of substitution effects across two populations as
139 Taylor expansions around one of them, the "focal" population. Using Kojima's method (Kojima
140 1959, 1961), we put additive substitution effects as a function of differences in allele
141 frequencies across populations, "focal" additive substitution effects, and second order
142 (dominance, additive by additive epistasis) statistical effects. From here, we show that the
143 correlation of substitution effects across populations is (approximately) a function of their
144 differentiation (or genetic distance), the additive, dominant and additive by additive genetic
145 variances, the average heterozygosities and average squared heterozygosities. All these
146 parameters can be estimated in real populations. In the following, we try to stick to Mäki-
147 Tanila and Hill (2014) notation. Many details are given as Appendix in the Supplementary
148 Material. Main notation is presented in Table 1.
149
150 TABLE 1 HERE
151
152 Note that our procedure is general – it does not invoke any particular mechanism for epistasis
153 or dominance, nor knowledge of individual QTL effects and locations. We assume that the
154 population mean is a (possibly complex) function of QTL allele frequencies $\boldsymbol{p}$ and QTL
155 functional or biological effects. The latter, albeit unknown, are assumed to be constant across
156 populations - we therefore do not consider genotype by environment interactions.
157
158 Consider the correlation $r\left(\alpha_i^b, \alpha_i^{b'}\right)$ of substitution effects α^b and $\alpha^{b'}$ across respective
159 populations (breeds, heterotic groups, lines, or generations) b and b'. For simplicity, the allele
160 to which α refers is random – it can be either the wild or the mutant allele. In this manner the
161 average value of α is 0, even in presence of deleterious mutations. It is known that, in presence

of dominant and epistatic biological interactions, the value of α depends on the allele frequencies and biological effects; for instance, $\alpha_1 = a_1 + (q_1 - p_1)d_1 + (p_2 - q_2)[aa]_{12}$ for 2-loci epistasis (Fuerst *et al.* 1997), for $p_1 = 1 - q_1$ and $p_2 = 1 - q_2$ frequencies at loci 1 and 2, respectively. Inspired by this, we want to write the correlation $r\left(\alpha_i^b, \alpha_i^{b'}\right)$ for a locus i as a function of vectors of respective allele frequencies, $\boldsymbol{p}^b$ and $\boldsymbol{p}^{b'}$, but in a general manner, without defining a particular functional or biological gene action. We use a first order Taylor series expansion to approximate additive substitution effects in a population b', as a function of effects in another "focal" population b and their distance. By doing this, it can be shown that the difference of substitution effects between two populations is (approximately) a function of the genetic distance of the two populations, and the magnitude of dominance and second order epistatic variances in the focal population b.

To derive additive substitution effects α as function of allelic frequencies $\boldsymbol{p}$, we use Kojima's definition of statistical effects as first, second… derivatives of the mean of the population (μ) as a function of p . We don't invoke any explicit function – we just presume that there is one, in other words, change in allele frequencies of the population implies change in the total average genotypic value. Using Kojima's method, the additive substitution effect at the *i*-th locus is the first derivative (Kojima 1959, 1961):

$$\alpha_i = \frac{1}{2}\frac{\partial \mu}{\partial p_i}$$

Higher order statistical effects implying locus *i* (i.e. dominance deviations and epistatic interactions) can be represented by higher order partial derivatives of μ or equivalently as

derivatives of α_i. The dominance deviation at the *i*-th locus (that we denote as d^* to distinguish from the biological or functional effect d (Falconer and Mackay 1996)) is:

$$d_i^* = -\frac{1}{4}\frac{\partial^2 \mu}{\partial p_i^2} = -\frac{1}{2}\frac{\partial \alpha_i}{\partial p_i}$$

The negative sign comes because the dominance deviation is usually understood as a feature of *heterozygosity,* in other words, it is of opposite sign than the increase of homozygosity in ∂p_i^2. Last, the epistatic pairwise deviation of locus i with j is

$$(\alpha\alpha)_{ij} = \frac{1}{4}\frac{\partial^2 \mu}{\partial p_i \partial p_j} = \frac{1}{2}\frac{\partial \alpha_i}{\partial p_j}$$

This is positive because it is the effect of increasing both p_i and p_j. Note that interaction of order k implies k-ith order derivative with scaling factor $1/2^k$.

Kojima's method shows, therefore, that higher order effects of one locus are derivatives of lower order effects. With these elements we can make a Taylor order expansion of α_i around frequencies in the "focal" population, $\boldsymbol{p}^b$, so that $\boldsymbol{p}^{b'} = \boldsymbol{p}^b + \boldsymbol{\epsilon}$, such that from values of α in b and changes in allele frequencies $\boldsymbol{\epsilon} = \boldsymbol{p}^{b'} - \boldsymbol{p}^b$ we create a function $\alpha_i^{b'} \approx f\left(\alpha_i^b, \boldsymbol{\epsilon}\right)$. In the Appendix (section 1.1), we show that the Taylor linear approximation of the substitution effects of population b': $\alpha_i^{b'}$, from effects from populations $b, \alpha_i^b, d_i^{*b}, (\boldsymbol{\alpha\alpha})_i^b$ is:

$$\alpha_i^{b'} \approx \alpha_i^b + 2\epsilon_i\left(-d_i^{*b}\right) + 2\boldsymbol{\epsilon}'(\boldsymbol{\alpha\alpha})_i^b \qquad (1)$$

where we use differences in allele frequencies $\boldsymbol{\epsilon}$, d_i^{*b} is the statistical dominance deviation at the locus i and $(\boldsymbol{\alpha\alpha})_i^b$ is a vector containing epistatic substitution effects of locus i with the rest of loci. By convention we assign $(\alpha\alpha)_{ii}^b = 0$.

From equation 1, the covariance across two populations b and b' of the two substitution effects α_i^b and $\alpha_i^{b'}$ of the locus i is:

$$Cov\left(\alpha_i^b, \alpha_i^{b'}\right) \approx Cov\left(\alpha_i^b, \alpha_i^b + 2\epsilon_i(-d_i^*) + 2\boldsymbol{\epsilon}'(\boldsymbol{\alpha\alpha})_i^b\right) = Var\left(\alpha_i^b\right) \qquad (2)$$

The equality holds because terms $Cov\left(\alpha_i^b, 2\epsilon_i\left(-d_i^{*b}\right)\right)$ and $Cov\left(\alpha_i^b, 2\boldsymbol{\epsilon}'(\boldsymbol{\alpha\alpha})_i^b\right)$ are null, given that the different statistical effects (α_i^b, d_i^{*b} and $(\boldsymbol{\alpha\alpha})_i^b$) are mutually orthogonal by construction.

Thus $r\left(\alpha_i^b, \alpha_i^{b'}\right) = \sqrt{\frac{Var(\alpha_i^b)}{Var(\alpha_i^b)Var\left(\alpha_i^{b'}\right)}}$, and now we need the variance of $\alpha_i^{b'}$ as a function of effects in population b, this is (see the Appendix, section 1.2 for details):

$$\begin{aligned} Var\left(\alpha_i^{b'}\right) &\approx Var\left(\alpha_i^b + 2\epsilon_i\left(-d_i^{*b}\right) + 2\boldsymbol{\epsilon}'(\boldsymbol{\alpha\alpha})_i^b\right) \qquad (3) \\ &= Var\left(\alpha_i^b\right) + 4Var(\epsilon_i)\left(Var\left(d_i^{*b}\right) + E^2\left(d_i^{*b}\right)\right) \\ &+ 4tr\left(Var(\boldsymbol{\epsilon}')Var\left((\boldsymbol{\alpha\alpha})_i^b\right)\right) \end{aligned}$$

This expression is unsymmetric and seems to imply that by construction $Var\left(\alpha_i^{b'}\right) > Var\left(\alpha_i^b\right)$; the reason for this is that for the "focal" population b the variance (or at least its estimators) is better known than for the "approximated" population b'. An alternative derivation in the Appendix (section 1.4) shows that, if the "focal" population is a third one (*f*) a set of expressions analogous to (2) and (3) is:

$$Var(\alpha_i^{b'}) \approx Var(\alpha_i^f) + 4Var\left(\epsilon_i^{(b')} d_i^{*f}\right) + 4Var\left(\boldsymbol{\epsilon}^{(b')'}(\boldsymbol{\alpha\alpha})_i^f\right)$$

$$Var(\alpha_i^b) \approx Var(\alpha_i^f) + 4Var\left(\epsilon_i^{(b)} d_i^{*f}\right) + 4Var\left(\boldsymbol{\epsilon}^{(b)'}(\boldsymbol{\alpha\alpha})_i^f\right)$$

$$Cov(\alpha_i^{b'}, \alpha_i^b) \approx Var(\alpha_i^f) + Cov\left(\epsilon_i^{(b')}, \epsilon_i^{(b)}\right)\left(Var(d_i^{*b}) + E^2(d_i^{*b})\right)$$

$$+ Cov\left(\boldsymbol{\epsilon}^{(b')'}(\boldsymbol{\alpha\alpha})_i^f, \boldsymbol{\epsilon}^{(b)'}(\boldsymbol{\alpha\alpha})_i^f\right)$$

Where $\epsilon_i^{(b')} = p_i^{b'} - p_i^f$ and $\epsilon_i^{(b)} = p_i^b - p_i^f$. From these expressions, we obtain (2) and (3) as a particular case if the focal population is *b*.

In the expression (3), $Var(\boldsymbol{\epsilon}')$ and $Var\left((\boldsymbol{\alpha\alpha})_i^b\right)$ are matrices. The first one describes the variability of differences in allele frequencies:

$$Var(\boldsymbol{\epsilon}') = \begin{pmatrix} Var(\epsilon_1) & Cov(\epsilon_1, \epsilon_2) & & Cov(\epsilon_1, \epsilon_n) \\ Cov(\epsilon_2, \epsilon_1) & Var(\epsilon_2) & & Cov(\epsilon_2, \epsilon_n) \\ & & \dots & \\ Cov(\epsilon_n, \epsilon_1) & & & Var(\epsilon_n) \end{pmatrix}$$

A locus that may diverge a lot (for instance because it is highly polymorphic) has high $Var(\epsilon)$; two loci in strong linkage will show non-zero $Cov(\epsilon_1, \epsilon_2)$. The second matrix contains (co)variances of the epistatic effects across all pairs marker *i* – other markers:

$$Var\left((\boldsymbol{\alpha\alpha})_i^b\right) = \begin{pmatrix} Var\left((\alpha\alpha)_1^b\right) & Cov\left((\alpha\alpha)_1^b, (\alpha\alpha)_2^b\right) & & Cov\left((\alpha\alpha)_1^b, (\alpha\alpha)_n^b\right) \\ Cov\left((\alpha\alpha)_2^b, (\alpha\alpha)_1^b\right) & Var\left((\alpha\alpha)_2^b\right) & & Cov\left((\alpha\alpha)_2^b, (\alpha\alpha)_n^b\right) \\ & & \dots & \\ Cov\left((\alpha\alpha)_n^b, (\alpha\alpha)_1^b\right) & & & Var\left((\alpha\alpha)_n^b\right) \end{pmatrix}$$

For instance, $Var\left((\alpha\alpha)_1^b\right)$ contains the variance of the epistatic effect of marker i with marker 1, and so on. We assume $Var\left((\boldsymbol{\alpha\alpha})_i^b\right) = \boldsymbol{I}\, \sigma^2_{(\alpha\alpha,b)}$, *i.e.* epistatic terms $(\boldsymbol{\alpha\alpha})_i^b$ can be either positive or negative, with a variance $\sigma^2_{(\alpha\alpha,b)}$ and are a priori uncorrelated to each other. Assuming null off-diagonals for $Var\left((\boldsymbol{\alpha\alpha})_i^b\right)$ results that, in the previous product

$tr\left(Var(\boldsymbol{\epsilon}')Var\left((\boldsymbol{\alpha\alpha})_i^b\right)\right)$, off-diagonal elements of $Var(\boldsymbol{\epsilon}')$ disappear from the result (even if they are not null). Thus, assuming that all diagonal elements of $Var(\boldsymbol{\epsilon}')$ have the same common variance σ_ϵ^2, this results in $4tr\left(Var(\boldsymbol{\epsilon}')Var\left((\boldsymbol{\alpha\alpha})_i^b\right)\right) = 4n\sigma_\epsilon^2\sigma_{(\alpha\alpha,b)}^2$. Note that assuming that all diagonal elements of $Var(\boldsymbol{\epsilon}')$ are equal is an approximation – for instance more polymorphic loci vary more.

The expression $Var\left(\epsilon_i d_i^{*b}\right) = Var(\epsilon_i)\left(Var\left(d_i^{*b}\right) + E^2\left(d_i^{*b}\right)\right)$ is detailed in the Appendix (section 1.2), and it shows that both the variability of dominance deviations $Var\left(d_i^{*b}\right) = \sigma_{d,b}^2$ and its mean $E\left(d_i^{*b}\right) = \mu_{d,b}$ which, if not zero, can be understood as the basis of inbreeding depression, enter into the expression. Also, we assume $\boldsymbol{\epsilon}$ (change in allele frequencies, but not the allele frequencies themselves) and the different non-additive effects d_i^{*b} and $(\boldsymbol{\alpha\alpha})_i^b$ to be independent (uncorrelated). This makes sense as loci may be selected for additive effects but not for non-additive effects.

Our next goal is to relate these results in (3) to quantities that are measured empirically. In particular, we need the variances of the different genetic effects and the variance of changes in allele frequencies. We address these two terms in turn.

We factorize the variance of statistical additive, dominant and additive by additive effects as follows (Mäki-Tanila and Hill 2014; Vitezica *et al.* 2017):

$$Var\left(\alpha_i^b\right) = \sigma_{\alpha,b}^2 = \frac{\sigma_A^2}{n\overline{H}_b}$$

$$Var\left(d_i^{*b}\right) + E^2\left(d_i^{*b}\right) = \sigma_{d,b}^2 + \mu_{d,b}^2 = \frac{\sigma_D^2}{n\overline{H}_b^2}$$

(the latter is shown in the Appendix, section 1.5) and

$$Var\left((\alpha\alpha)^{b}_{i,j,j>i}\right) = \sigma^2_{(\alpha\alpha,b)} = \frac{\sigma^2_{AA}}{n(n-1)\overline{H_b H_b}} \approx 2\frac{\sigma^2_{AA}}{n^2\overline{H}_b\,\overline{H_b}}$$

for n the number of QTL loci and using functions of heterozygosities (more details in the Appendix, section 1.6):

$$\overline{H_b} = E\left(2p_i^b\left(1-p_i^b\right)\right)$$

$$\overline{H_b^2} = E\left(4p_i^b\left(1-p_i^b\right)p_i^b\left(1-p_i^b\right)\right)$$

$$\overline{HH_b} = E_{i>j}\left(2p_i^b\left(1-p_i^b\right)2p_j^b\left(1-p_j^b\right)\right) \approx \frac{1}{2}\overline{H_b}\,\overline{H_b}$$

Here we have assumed independence of QTL allele frequencies and QTL effects. All variances and effects, as well as heterozygosities H_b, refer to the focal population b with allele frequencies p^b and effects α^b. Note that we assume HWE and LE within both b and b'. Of course, we don't know allele frequencies or even numbers of true causal genes, but the first can be prudently guessed and the latter cancel out in the following.

Consider the scalar σ_ϵ^2, the variance of differences of allele frequency. In fact, $\sigma_\epsilon^2 = Var\left(p^{b'} - p^b\right) = E\left(\left(p^{b'} - p^b\right)^2\right) - E\left(p^{b'} - p^b\right)^2 = E\left(\left(p^{b'} - p^b\right)^2\right)$ because $E\left(p^{b'} - p^b\right) = 0$ when averaged across loci. Therefore, $\sigma_\epsilon^2 = E\left(\left(p^{b'} - p^b\right)^2\right)$ which corresponds to Nei's "minimum genetic distance" (Nei 1987; Caballero and Toro 2002), and, accordingly, will be called $D_{b,b'} = \sigma_\epsilon^2$. The value of $D_{b,b'}$ can be estimated from marker data as $\widehat{D}_{b,b'} = \frac{1}{n}\sum\left(p_i^{b'} - p_i^b\right)^2$, although it is sensitive to the spectra of polymorphisms (e.g. SNP chips vs sequencing). In addition, $D_{b,b'}$ is also the numerator of the F_{ST} fixation index, e.g.

Hudson's(1992) $F_{ST} = \frac{\mathrm{E}\left(\left(p_i^{b'} - p_i^b\right)^2\right)}{\mathrm{E}\left(p_i^{b'}\left(1-p_i^b\right)+p_i^b\left(1-p_i^{b'}\right)\right)}$ with an estimator $\hat{F}_{ST} = \frac{\frac{1}{n}\sum_i\left(\left(p_i^{b'} - p_i^b\right)^2\right)}{\frac{1}{n}\sum_i\left(p_i^{b'}\left(1-p_i^b\right)+p_i^b\left(1-p_i^{b'}\right)\right)}$ (Hudson *et al.* 1992; Bhatia *et al.* 2013). In principle, $D_{b,b'}$ and F_{ST} can be estimated from markers, but also from evolutionary distances and effective population size, or both (Weir and Hill 2002; Bonhomme *et al.* 2010). Now we can rewrite the last term of equation (3) as

$$4tr\left(Var(\boldsymbol{\epsilon}')Var\left((\boldsymbol{\alpha}\boldsymbol{\alpha})_i^b\right)\right) = 4n\left(\sigma_\epsilon^2\sigma_{(\alpha\alpha,b)}^2\right) = 4nD_{b,b'}\frac{2\sigma_{AA}^2}{n^2\,\bar{H}_b\,\bar{H}_b}$$

Combining expressions above, equation (3) becomes

$$Var\left(\alpha_i^{b'}\right) = \tag{4}$$

$$\frac{\sigma_A^2}{n\bar{H}_b} + 4D_{b,b'}\frac{\sigma_D^2}{n\overline{H_b^2}} + 4nD_{b,b'}2\frac{\sigma_{AA}^2}{n^2\bar{H}_b\,\bar{H}_b} =$$

$$\frac{1}{n}\left(\frac{\sigma_A^2}{\bar{H}_b} + 4D_{b,b'}\frac{\sigma_D^2}{\overline{H_b^2}} + 8D_{b,b'}\frac{\sigma_{AA}^2}{\bar{H}_b\,\bar{H}_b}\right)$$

From here the correlation of α across populations is (factorizing out $\frac{1}{n}$)

$$r\left(\alpha_i^b, \alpha_i^{b'}\right) \approx \frac{Cov\left(\alpha_i^b, \alpha_i^{b'}\right)}{\sqrt{\left(Var\left(\alpha_i^b\right)\right)\left(Var\left(\alpha_i^{b'}\right)\right)}} = \tag{5}$$

$$\frac{Var\left(\alpha_i^b\right)}{\sqrt{\left(Var\left(\alpha_i^b\right)\right)\left(Var\left(\alpha_i^{b'}\right)\right)}} = \frac{\sqrt{Var\left(\alpha_i^b\right)}}{\sqrt{Var\left(\alpha_i^{b'}\right)}} =$$

$$\frac{\sqrt{\frac{\sigma_A^2}{\overline{H}_b}}}{\sqrt{\frac{\sigma_A^2}{\overline{H}_b} + 4D_{b,b'}\frac{\sigma_D^2}{\overline{H}_b^2} + 8D_{b,b'}\frac{\sigma_{AA}^2}{\overline{H}_b\,\overline{H}_b}}}$$

Expression [5] can also be obtained if we start the Taylor expansion from a third focal population that is neither *b* nor *b'*, as shown in the Appendix, section 1.4. Factorizing out $\overline{H_b}$ we arrive to the slightly clearer expression

$$r\left(\alpha_i^b, \alpha_i^{b'}\right) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + D_{b,b'}\left(4\frac{\overline{H}_b}{\overline{H}_b^2}\,\sigma_D^2 + 8\frac{1}{\overline{H}_b}\sigma_{AA}^2\right)}} \tag{6}$$

which shows well that the correlation is a function of distance across populations $\left(D_{b,b'}\right)$ and weights of additive *vs.* non-additive variances. Note that $D_{b,b'}$ is always positive, which implies that $0 < r\left(\alpha_i^b, \alpha_i^{b'}\right) < 1$ as expected.

The quantities involved in equation (6) are (1) Nei's "minimum genetic distance" $D_{b,b'}$, which describes the similarity of populations b and b', (2) the variance of statistical additive, dominant and additive by additive effects at the individual level σ_A^2, σ_D^2, σ_{AA}^2 in population b (3) first and second moments of heterozygosities $\overline{H}_b$, $\overline{H_b^2}$. All these values can be, in principle, estimated from data or "prudently guessed". For the particular case of heterozygosities, SNP markers are a poor choice and it is likely better to use a guess based on sequence or evolutionary processes (coalescence).

From the definition of F_{ST} and assuming $\overline{H}_b \approx \overline{H}_{b'}$, $D_{b,b'} \approx \frac{F_{ST}}{1-F_{ST}}\overline{H}_b$ (detailed in the Appendix, section 1.7), leading to

$$r(\alpha_i^b, \alpha_i^{b'}) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + \frac{F_{ST}}{1-F_{ST}}\left(4\frac{(\overline{H}_b)^2}{\overline{H_b^2}}\,\sigma_D^2 + 8\sigma_{AA}^2\right)}} \tag{7}$$

The advantage of the F_{ST} is that it is more robust to the spectra of allele frequencies used to estimate it (Bhatia *et al.* 2013). If we further assume that dominance variance σ_D^2 is negligible, we can write a neat expression of the correlation in terms of F_{ST}:

$$r(\alpha_i^b, \alpha_i^{b'}) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + \frac{8F_{ST}}{1-F_{ST}}\sigma_{AA}^2}} \approx \sqrt{1 - \frac{8F_{ST}}{1-F_{ST}}\frac{\sigma_{AA}^2}{\sigma_A^2}} \tag{8}$$

The second approximation involving $\frac{1}{1+x} \approx 1 - x$. This expression (8) plainly tells that the squared correlation of gene substitution effects across two population is (to a few degrees of approximation) a linear function of the similarity of populations and the additive by additive variance. To our knowledge, these results showing the importance of the different factors on the difference between substitution effects had been shown before only through simulations. Thus, the algorithm to estimate *a priori* the correlation of α across populations b and b', $r(\alpha_i^b, \alpha_i^{b'})$, is:

1. Estimate in population b
    a. additive, dominance, and additive by additive variances
    b. average heterozygosity $\overline{H_b}$ and average squared heterozygosity $\overline{H_b^2}$
2. Estimate Nei's distance $D_{b,b'}$ and/or F_{ST} of the two populations
3. Apply equation (6) or (7).

Consideration of directionality of substitution effects In Plant and Animal Breeding the origin of the allele is often overlooked, as a mutation may be evolutionary harmful but of interest for farming, and also because many traits selected for do not have a close relationship to fitness in the wild. However, in Evolutionary Genetics it is reasonable to think that most mutations are deleterious, thus with a negative effect of the mutant allele. In Medical Genetics reports of estimated substitution effects are also often done in terms of "susceptible" alleles. In both cases $E(\alpha) \neq 0$ or even $\alpha > 0$ for all loci. In both cases α is "oriented" and has no zero mean. In the theory above we have considered that α is the effect of a randomly drawn allele, which leads to $E(\alpha) = 0$ and enormously simplifies the algebra. In order to consider oriented α, we propose to transform the estimate of $r(\alpha_i^b, \alpha_i^{b'})$ into $r(|\alpha_i^b|, |\alpha_i^{b'}|)$, the correlation of the absolute values. Assuming that α follows a normal distribution, $|\alpha|$ follows a so-called folded normal distribution. From here, $r(|\alpha_i^b|, |\alpha_i^{b'}|)$ is obtained from $r(\alpha_i^b, \alpha_i^{b'})$ using expressions (not detailed here) in Kan and Robotti (2017), conveniently programmed in the R package MomTrunc (Galarza *et al.* 2020). The specific R function is in the Appendix, section 1.8, and we will call it r2rabs().

Covariance across generations within one population. The definition above of two populations is general enough that we can consider any two populations, *e.g.* two breeds (Angus and Hereford), two strains (New Zealand Holstein and US Holstein) or two generations or time frames (*e.g.* animals born in 2000 vs. animals born in 2005, or animals born in 2000 vs. their descendants). There is evidence that across-generations genetic correlation decreases with (many) generations to values as low as 0.6 (Tsuruta *et al.* 2004; Haile-Mariam and Pryce 2015). Part of this is likely due to genotype by environment interactions. Anyway,

part of the across-generation genetic correlation could be due to changes in the allele frequency due to drift, and therefore it can be accounted for by our model, based on the evolution of average coancestry in the breed. We develop this next.

We will talk about "generations" but ideas apply to pedigrees with overlapping generations as well. Consider that what we previously called populations b and b' are animals born at time t_1 and t_2, with $t_2 > t_1$. Equation (7) becomes $r\left(\alpha_i^{t_1}, \alpha_i^{t_2}\right) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + \frac{F_{ST}}{1-F_{ST}}\left(4\frac{\left(\bar{H}_{t_1}\right)^2}{\overline{H_{t_1}^2}}\sigma_D^2 + 8\sigma_{AA}^2\right)}}$. In pedigree-based context, the F_{ST} is simply half the increase in average relationship from t_1 to t_2 (Powell *et al.* 2010) which is approximately equal to the increase in inbreeding from $t_1 + 1$ to $t_2 + 1$, which in turn is approximately $(t_2 - t_1)\Delta F$ for small values of ΔF and steady increase of inbreeding. Thus, $F_{ST} \approx \frac{(t_2 - t_1)\Delta F}{2}$ to obtain

$$r\left(\alpha_i^{t_1}, \alpha_i^{t_2}\right) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + \frac{\frac{(t_2 - t_1)\Delta F}{2}}{1 - \frac{(t_2 - t_1)\Delta F}{2}}\left(4\frac{\left(\bar{H}_{t_1}\right)^2}{\overline{H_{t_1}^2}}\sigma_D^2 + 8\sigma_{AA}^2\right)}} \quad (9)$$

Assuming, like in (8), small values of dominance variance and of F_{ST}, we obtain

$$r\left(\alpha_i^{b}, \alpha_i^{b'}\right) \approx \sqrt{1 - 4(t_2 - t_1)\Delta F\frac{\sigma_{AA}^2}{\sigma_A^2}}$$

Thus, the correlation of substitution effects decreases when there is large drift, reflected in high values of ΔF. This is the case for instance if parents of the next generation are very highly selected without restrictions in future inbreeding, resulting in a considerable change in allele frequencies over the generations.

369

370 This agrees with classical theory (Falconer and Mackay 1996): the variance in change of allele
371 frequencies from one generation to the next is simply ΔF. Typical values of ΔF in livestock
372 (rabbits, pigs, cattle or sheep) are at most 0.01 per generation (Welsh *et al.* 2010; García-Ruiz
373 *et al.* 2016; Fernández *et al.* 2017; Rodríguez-Ramilo *et al.* 2019), although this is potentially
374 changing with genomic selection.

375

376 **Simulations**

377

378 **Description of the simulations.** The objective of the simulation is to verify our results
379 considering different kinds of non-additive biological gene action, and not to infer the values
380 of the correlation of substitution effects across populations as this requires realistic
381 presumptions of the forms and magnitudes of epistatic interactions, something that is largely
382 unknown.

383

384 We used *macs* (Chen *et al.* 2009) to simulate a "cattle" scenario of two domestic cattle breeds
385 which diverged from a common ancestral population, in the lines of (Pérez-Enciso 2014; Pérez-
386 Enciso *et al.* 2015), where a large population had a 10-fold reduction bottleneck
387 (domestication) 2000 generations ago and a split into two populations t generations ago,
388 where we made t oscillate between 0 and 100 by steps of 10. Parameters in the simulation
389 were tailored (Pérez-Enciso 2014; Pérez-Enciso *et al.* 2015) to mimic observed levels of
390 diversity in cattle (Gibbs *et al.* 2009) and lead to F_{ST} values between 0 and 0.15. We considered
391 100 DNA stretches of 300 Kb each. We simulated 200 individuals per population, from which
392 we obtained allele frequencies per population. Details are provided in the Appendix, section

393 1.9. This provided ~400,000 segregating loci with realistic allele frequencies (L-shaped
394 distribution of allele frequencies).
395
396 To simulate non-additive biological gene action, we considered three scenarios. All of them
397 involved 5000 single marker polymorphisms drawn at random from the simulated ones with
398 no particular restriction. First scenario was Complete Dominance (within locus); second one
399 was 1000 networks of 5 loci in Complementary Epistasis, and the third one 1000 networks of
400 5 loci with Multiplicative Epistasis (additive by additive). We also simulated networks of 2 and
401 of 10 loci with similar results (not shown). These scenarios are similar to Hill *et al.* (2008) but
402 instead of considering 2 loci we consider 5. We use these forms of epistasis, as the first two
403 ones may be interpreted as biologically meaningful gene actions, and the third one is an
404 extreme case for the change in substitution effect across populations. In addition, all three
405 scenarios are analytically tractable. Complete dominance has the genotypic value of the
406 heterozygote equal to one of the homozygotes, e.g. the presence of a single copy of the "good"
407 allele is enough to, say, avoid the disease. Complementary epistasis can be seen as a multi-loci
408 dominance, e.g. disease happens when there is a recessive deleterious genotype at *any* of the
409 loci. Additive by additive epistasis can be understood as a pure multiplication of gene contents
410 and has no good biological interpretation. Networks contribute additively to the total
411 phenotype. Note that, by definition, functional gene action is the same across all populations.
412 From the description of the non-additive gene action and some algebra in the Appendix, we
413 are able to derive analytically the values of α, d^* and $(\alpha\alpha)$ in each population and variances
414 σ_A^2, σ_D^2 and σ_{AA}^2. Details are given in the Appendix, section 1.10. For each value of t, we made
415 10 replicates and averaged the results.
416

From the true substitution effects α^b and $\alpha^{b'}$ derived above, we obtained the true value $r(\alpha^b, \alpha^{b'})$. Note that because of the coalescent simulation, all reference alleles (i.e. with frequency p) are "mutant" ones, and due to assumed dominance and epistatic actions, α are negative by construction (i.e. the mutant allele is deleterious). To conciliate this fact with our derivations, that assume that α refers to a random allele and has null means, we did two things: (1) compute a "random allele" version of $\alpha^b, \alpha^{b'}$ in which α was changed sign for "odd" loci, and (2) estimate $r(\alpha^b, \alpha^{b'})$ using the transformation of normal distribution into folded normal (Kan and Robotti 2017), i.e. the r2rabs() function mentioned above. Thus, we have two estimands, the correlation for the "mutant allele" effect $r_{mutant}(\alpha^b, \alpha^{b'})$ (which corresponds *e.g.* to typical use in Evolutionary and Medical Genetics) and the correlation for the "random allele" effect $r_{random}(\alpha^b, \alpha^{b'})$ (which corresponds, *e.g.* to genomic selection and some GWAS). We observed that $r_{mutant}(\alpha^b, \alpha^{b'}) < r_{random}(\alpha^b, \alpha^{b'})$. For instance, in one of the scenarios $r_{mutant}(\alpha^b, \alpha^{b'}) = 0.67$ and $r_{random}(\alpha^b, \alpha^{b'}) = 0.85$.

Now we describe the estimators. We considered either the use of "all" polymorphisms, or of a "SNP" selection in which MAF>0.01 across both populations simultaneously (roughly 40,000 polymorphisms), as this corresponds to typical SNP panels in genetic improvement. Then we used the equation (6) either for "all" or for "SNP", using their frequencies to obtain $D_{b,b'}$, $\overline{H}_b$ and $\overline{H_b^2}$. In "all", the spectra of allele frequencies of polymorphisms and of QTL is the same, but not in "SNP". As "SNP" tends to be biased, we also considered the equation (7) using F_{ST} estimated from SNPs and $\overline{H}_b = 0.107$, and $\overline{H_b^2} = 0.018$ from the "Hill" U-shaped distribution mentioned above. Note that F_{ST} is more robust to the spectra of allele frequencies used to estimate it. Thus, we obtained three estimators for "random allele" $r_{random}(\alpha^b, \alpha^{b'})$: $\hat{r}_{all}$,

440 $\hat{r}_{SNP}$ and $\hat{r}_{SNPFst}$, and also the three corresponding estimators for "mutant allele"

441 $r_{mutant}(\alpha^b, \alpha^{b'})$ applying function r2rabs() to $\hat{r}_{all}$, $\hat{r}_{SNP}$ and $\hat{r}_{SNPFst}$.

442

443 **Results of the simulations.** Simulated variance components (expressed as ratios from total

444 genetic variance σ^2) with marker genotypes and with QTL genotypes are shown in Table 2. All

445 scenarios yield high additive genetic variances, as expected.

446

447 TABLE 2 HERE

448

449 True simulated values of correlation across substitution effects $r_{random}(\alpha^b, \alpha^{b'})$ and their

450 estimates $\hat{r}_{all}$, $\hat{r}_{SNP}$ and $\hat{r}_{SNPFst}$, are presented in Figure 1 (for α defined for random alleles)

451 and Figure 2 (for α defined for mutant alleles). Generally speaking, Figure 1 applies to non-

452 fitness related traits (for "random") and Figure 2 to fitness-related traits (for "mutant"). As

453 predicted by our derivations, there is a clear and almost linear decrease of $r(\alpha^b, \alpha^{b'})$ with

454 increasing values of F_{ST}.

455 In Figure 1 (for α defined for random alleles) it can be observed that our expressions (6-7) tend

456 to slightly over-estimate $r_{random}(\alpha^b, \alpha^{b'})$ for Complete Dominance, and Complementary

457 Epistasis. The estimates are quite good for Multiplicative Epistasis. Estimators using SNP

458 markers are slightly less accurate than using the complete polymorphism spectra, and using

459 F_{ST} from SNP markers, coupled with a guess of heterozygosities, is similar to using SNP alone

460 to infer both distances and heterozygosities.

461 Figure 2 (for α defined for mutant alleles) presents values of $r_{mutant}(\alpha^b, \alpha^{b'})$ and estimates

462 $\hat{r}_{all}$, $\hat{r}_{SNP}$ and $\hat{r}_{SNPFst}$. Estimating $r_{mutant}(\alpha^b, \alpha^{b'})$ is more difficult than estimating

463 $r_{random}(\alpha^b, \alpha^{b'})$: depending on the scenario there is more over- or under-estimation that
464 for $r_{random}(\alpha^b, \alpha^{b'})$. In this case the effect of using all polymorphisms or SNP is more marked.
465 However, overall, we find that our estimators explain well the decay in $r(\alpha^b, \alpha^{b'})$. The
466 imperfect disagreement (both in Figures 1 and 2) is probably due to several wrong
467 assumptions; we comment some of them in the Discussion.
468
469 FIGURE 1 HERE
470 FIGURE 2 HERE
471
472 EMPIRICAL EXAMPLES
473
474 **Estimates of correlation across populations using literature values.**
475
476 **Literature values used and assumptions.** From values of the literature, the previous
477 expressions, equations (6) and (7) were applied to obtain guesses of the correlation of
478 substitution effects across different populations and generations within population. Estimates
479 of statistical non-additive variation are scarce, as are estimates of distances across
480 populations in terms of covariance of allele frequencies. The differentiation F_{ST} of Jersey and
481 Holstein breeds of cattle obtained from (VanRaden *et al.* 2011) is 0.06, and among Landrace
482 and Yorkshire is 0.16 (Xiang *et al.* 2017).
483
484 Table 3 includes literature estimates for additive, dominance and epistatic variation. We used
485 estimates for milk yield in Simmental cattle (Fuerst and Sölkner 1994) as if it was Holstein, and
486 for litter size in a commercial pig line (Vitezica *et al.* 2018) as if it was Landrace, because we

could not find estimates in the same populations. These estimates (as most estimates of non-additive variances) are inaccurate and are presented here only as examples. In the particular case of cattle, the estimated value of σ_{AA}^2 is higher than usually expected *a priori* (Hill *et al.* 2008), so we take it as an example of an extreme, but not impossible, case.

TABLE 3 HERE

Then, we assumed three distributions for QTL allele frequencies, following Hill *et al.* (2008): a uniform distribution ("Uniform"), and a U-shaped distributions with $f(p) \propto p^{-1}(1-p)^{-1}$ with effective population size of $Ne = 50$ ("Hill"), bounded at $\left[\frac{1}{2Ne}, 1 - \frac{1}{2Ne}\right]$. We also assumed a Beta(0.04, 0.04) distribution, which is an extreme U-shaped distribution ("Extreme") in which roughly 80% of the QTLs have minor allele frequency lower than 0.01. This results in respective values of $\overline{H_b} = (0.333, 0.107, 0.037)$ and $\overline{H_b^2} = (0.133, 0.018, 0.013)$. Using the values described above, we estimated the correlation of QTL substitution effects across breeds, $r\left(\alpha_i^b, \alpha_i^{b'}\right)$, using equation (7).

Similarly, the correlation of QTL substitution effects a certain number of generations away, $r\left(\alpha_i^{t_2}, \alpha_i^{t_1}\right)$, was obtained applying Equation (9). An increase $\Delta F = 0.01$ per generation was assumed, for the same assumed variances and allele frequency distributions.

Estimates of correlation across populations using literature values. The results for reasonable guesses of the distribution of allele frequencies at QTL are in Table 4. The

510 correlation of QTL substitution effects across breeds was roughly 0.85 across both species
511 (pigs and cattle) and all assumed distributions of gene frequencies. These numbers are higher
512 than scarce estimates of genetic correlations in the literature: 0.4 to 0.8 for production traits
513 (Karoui *et al.* 2012), 0.3 to 0.5 for milk yield (Legarra *et al.* 2014) and 0.6 for body condition
514 (Porto-Neto *et al.* 2015), and we consider that this is because across-breeds genetic
515 correlations also include genotype by environment interactions. It may be argued that these
516 studies used SNPs instead of true QTLs; however, Wientjes et al. (2017) in a simulation study
517 obtained unbiased estimates of correlation across QTLs using SNP markers for a true
518 correlation of 0.5, and (Cuyabano *et al.* 2018) showed analytically that when SNP markers
519 yield correct estimates of true relationships at QTL, estimates of genetic parameters are
520 unbiased.
521
522 TABLE 4 HERE
523
524 Concerning decrease of correlations across generations, results (Table 5) show a slow
525 decrease, and this decrease is, again, not sensitive to the assumed distribution of allelic
526 frequencies. Values in Table 5, quite close to 1, somehow disagree with few existing estimates
527 of across-generation genetic correlations, clearly lower than 1 (Tsuruta *et al.* 2004; Haile-
528 Mariam and Pryce 2015). Again, part of the literature estimates of correlation much lower
529 than 1 is probably due to non-additive gene action, and part due to genotype by environment
530 interactions.
531
532 TABLE 5 HERE
533

DISCUSSION

The fact that most genetic variation is statistically additive is well known. However, this does not imply equality of statistical additive effects across populations, something that is possibly reflected in the difficulty of predicting breeding values or disease risks across (distinct) populations, either in animal or human genetics. Only recently has non-additive biological gene action been identified as playing a role in determining the degree to which prediction across populations is successful (Dai *et al.* 2020; Duenk *et al.* 2020). These authors presented result of simulations, where the problem is that the results are scenario specific and do not allow a good appraisal of the different factors. Having a theory allows to derive more general expressions and understanding factors influencing across-population differences in substitution effects.

In this work, we present a general, formal framework that does not depend on specific hypothesis regarding gene action or order of the epistatic interactions. In our derivation, we approached *high-order functional* epistasis by Taylor expansions, leading to expressions that involve only *low-order statistical* additive epistasis (actually pairwise). Including one extra term in our Taylor expansion would include *three-loci statistical* epistasis and so on, but extra terms would lead to more difficult expressions (covariance of allele frequencies across loci and populations), and it is expected that the magnitude of the statistical effects is smaller and smaller with higher orders of interactions (Mäki-Tanila and Hill 2014). We find reasonable agreement with our simulation and also with values from literature. However, our simulations may not be particularly realistic, something that would require considerable thinking on how to simulate biologically meaningful epistasis mechanisms for a variety of traits. We see them

as building blocks of non-additive architecture. At any rate, the three scenarios generated sizeable non-additive variation which is a challenging case for our expressions.

Three main factors influence the correlation of substitution effects between populations $r(\alpha^b, \alpha^{b'})$: the genetic similarity of the two populations, the magnitudes of additive, dominance and additive by additive variances, and the distribution of allele frequencies at QTL. We consider that showing explicitly these three factors is an achievement, as their role is implicit, yet not explicitly shown, in previous works in simulated and real data (Martin *et al.* 2019; Dai *et al.* 2020; Duenk *et al.* 2020). Now we discuss these three factors.

The distance across populations is summarized by Nei's minimum genetic distances $D_{b,b'}$ or F_{st} indexes. Under pure drift scenarios, these depend on divergence times and effective population sizes (Weir and Hill 2002; Bonhomme *et al.* 2010; Walsh and Lynch 2018).

The factors $\frac{\overline{H_b}}{\overline{H_b^2}}$ and $\frac{1}{\overline{H_b}}$ are weighting factors on dominance and additive by additive variances. If the allele frequencies are modelled using symmetric $Beta(a, a)$ distributions (see Appendix, section 1.11), these become $\frac{\overline{H_b}}{\overline{H_b^2}} = \frac{1}{2\frac{a+1}{a}\left(1+\frac{a+2}{2a+2}\left(\frac{a+3}{2a+3}-2\right)\right)}$ and $\frac{1}{\overline{H_b}} = 2 + \frac{1}{a}$. The first is bounded between 3 (for U-shaped distributions) and 2 (for peaked distributions), so that dominance variation does not play a big role in the difference between substitution effects across populations unless dominance variation is much larger that additive variation, something that seems unlikely based on theory and estimates. However, the second weight, due to epistasis, is not bounded and is large for small values of a (*e.g.* 27 for Beta(0.04,0.04), and in this case functional epistasis plays a strong role in additive variation for U-shaped distributions (Hill *et*

al. 2008). The spectra of allele frequencies of causal mutations is subject to large debate but there seems to be a consensus that low frequency mutations make non-negligible contributions to genetic variance (Eyre-Walker 2010; Gibson 2012). It is unknown if this leads to extreme values of $\frac{1}{H_b}$.

The particular case of purifying selection deserves some attention. For a mutant recessive deleterious allele with fitness $1 - s$, the substitution effect is $\alpha = -ps$ so, in principle, α changes across populations – this is similar to our simulated scenario of Complete Dominance. However, if the locus is truly at equilibrium in all populations, then $p \approx \sqrt{\frac{u}{s}}$ (Crow and Kimura 1970 chap. 6). Provided that s and u are identical across populations, the allele frequency p *and* the substitution effect α should be identical across populations. However, s is not necessarily homogeneous across populations, likely depending on the environment.

The previous result ($\frac{1}{H_b}$ needs to be large for biological dominance to play a role) clarifies the findings of Duenk *et al.* (2020) and Dai *et al.* (2020) that it is mainly biological epistasis that generates changes in additive substitution effects across populations. For instance, when one population drifts, the additive by additive statistical variation enters into additive variation (Hill *et al.* 2006; Walsh and Lynch 2018).

Thus, $r\left(\alpha_i^b, \alpha_i^{b'}\right)$ will be very low only if (1) populations are distinct, (2) there is *statistical* additive by additive variation and (3) QTL allele frequency distributions are U- or L- shaped.

602 As for the magnitudes of non-additive variance, in most conceivable cases σ^2_{AA} and σ^2_D are of
603 magnitudes at most like additive variances, but more often less than half (Fuerst and Sölkner
604 1994; Palucci *et al.* 2007; Hill *et al.* 2008; Mäki-Tanila and Hill 2014; Vitezica *et al.* 2018), so in
605 practice the most limiting factor is distance across breeds. Indeed, there are very few accurate
606 estimates of non-additive variation although more are becoming available. We argue that
607 then, and based also in our results, it will be possible to make theory and data-based choices
608 on the possibilities of using predictions and GWAS results across populations.
609
610 Then, for reasonable assumptions about allele frequency distribution of QTLs, we have shown
611 that the correlation of substitution effects across populations is typically around 0.8 or higher,
612 which is higher than scarce estimates of genetic correlations across populations available in
613 the literature, which range from 0.3 to 0.8 (Karoui *et al.* 2012; Legarra *et al.* 2014; Porto-Neto
614 *et al.* 2015; Xiang *et al.* 2017) the difference being due, probably, to genotype by environment
615 interaction. Our results seem rather robust to different distributions of allele frequencies.
616 These values are high but not 1, which raises the question of how to conceive optimal
617 strategies for across populations predictions (*e.g.* more data within breed or finer locations of
618 causal variants across breed). This is of practical relevance, *e.g.* for genomic predictions in
619 livestock improvement, but also in human genetics *e.g.* for the use of European-based
620 Polygenic Risk Scores in individuals from other ancestries (Martin *et al.* 2019).
621
622 Similar results apply to the same populations across generations, in which case the correlation
623 of substitution effects across generations goes from 0.99 (next 1-2 generations) to 0.80 (10
624 generations). This illustrates that, even if genomic predictions would use QTLs or markers in

very tight LD with QTLs, there would still be, in the long run, a need for a continuous system of data collecting and re-estimation of effects.

In the simulations we confirmed that our estimates are reasonably good although not perfect. They are, depending on the scenario and target (random allele or mutant allele), almost unbiased, slightly biased upwards, or biased downwards. There are several reasons for the disagreement. The most obvious one is the inherent approximation of the Taylor series expansion. Secondly, splitting variances such as $Var\left(\epsilon_i d_i^{*b}\right)$ or $Var\left(\boldsymbol{\epsilon}'(\boldsymbol{\alpha}\boldsymbol{\alpha})_i^b\right)$ into basic components implies either a strong assumption of multivariate normality and independence or a less strong one of "expectation and variance-independence" (Bohrnstedt and Goldberger 1969). For instance, it is assumed that the variance of d_i^{*b} is not related to the magnitude of the difference of allele frequencies ϵ_i, but this is not necessarily true. Third, it is further assumed, in the factorization of genetic variances, that QTL effects and allele frequencies are independent. We have also ignored that the change ϵ is proportional to heterozygosity and therefore small at extremes values of allele frequencies.

Another factor that we did not consider is the empirical evidence of an inverse relationship between heterozygosity and absolute effect at the locus (Park *et al.* 2011). It is unclear how this would affect our findings. A (rather extreme) functional gene action that generates larger α at extreme frequencies is overdominance, which is similar to our "dominance" scenario.

As for our estimators of the correlation across "negative" alleles $r_{mutant}\left(\alpha^b, \alpha^{b'}\right)$, they are less robust that the estimators for a "random" allele $r_{random}\left(\alpha^b, \alpha^{b'}\right)$. The reason for this is that obtaining $r_{mutant}\left(\alpha^b, \alpha^{b'}\right)$ from $r_{random}\left(\alpha^b, \alpha^{b'}\right)$ involves a further approximation, the normality of α.

CONCLUSIONS

We presented a coherent, approximate theory, that does not invoke any particular mechanism of gene action, to explain and appraise the change in magnitude of (additive) QTL substitution effects across populations and generations. The theory gives good approximate estimates of this correlation, that needs to be otherwise explicitly estimated. More importantly, the theory shows that the main sources for the change of effects are relationships across populations, magnitudes of additive and first-order non-additive variances (dominance and additive by additive), and spectra of allele frequencies. These findings provide better understanding of the properties of genomic prediction methods and of quantitative genetics in general.

Data Availability Statement. Appendix associated with this manuscript is in https://figshare.com/articles/online_resource/Appendix_to_Genetics_paper/15133947 . Code and files for simulations can also be found in https://figshare.com/articles/software/scripts_zip/14509956 . All other results can be reproduced using equations and figures from the text.

ACKNOWLEDGMENTS

Part of this work was while Y. Wientjes was visiting the GenPhySE unit at INRAE, Toulouse, financed by the Netherlands Organisation of Scientific Research (NWO). Authors thank INRA SelGen metaprograms EpiSel and EpiFun. This project has received funding from the European Unions' Horizon 2020 Research & Innovation programme under grant agreement N°772787 - SMARTER. We are grateful to the Genotoul Bioinformatics Platform Toulouse Midi- Pyrenees

(Bioinfo Genotoul) for providing computing and storage resources. We thank editor and reviewers for very detailed feedback, and MA Toro, A Caballero, S Boitard and M Bonhomme for advice. A.L., Z.G.V. and C.A.G.B. want to dedicate this paper to his friend Eduardo Fernández, who could discuss substitution effects while driving through traffic jams, and who left us too soon.

REFERENCES

Aiello D., K. Patel, and E. Lasagna, 2018 The myostatin gene: an overview of mechanisms of action and its relevance to livestock animals. Anim. Genet. 49: 505–519. https://doi.org/10.1111/age.12696

Bhatia G., N. Patterson, S. Sankararaman, and A. L. Price, 2013 Estimating and interpreting FST: The impact of rare variants. Genome Res. 23: 1514–1521. https://doi.org/10.1101/gr.154831.113

Bohrnstedt G. W., and A. S. Goldberger, 1969 On the Exact Covariance of Products of Random Variables. J. Am. Stat. Assoc. 64: 1439–1442. https://doi.org/10.1080/01621459.1969.10501069

Bonhomme M., C. Chevalet, B. Servin, S. Boitard, J. Abdallah, *et al.*, 2010 Detecting Selection in Population Trees: The Lewontin and Krakauer Test Extended. Genetics 186: 241–262. https://doi.org/10.1534/genetics.110.117275

Bonifati V., P. Rizzu, M. J. van Baren, O. Schaap, G. J. Breedveld, *et al.*, 2003 Mutations in the DJ-1 Gene Associated with Autosomal Recessive Early-Onset Parkinsonism. Science 299: 256–259. https://doi.org/10.1126/science.1077209

Caballero A., and M. A. Toro, 2002 Analysis of genetic diversity for the management of conserved subdivided populations. Conserv. Genet. 3: 289.

Carlborg Ö., L. Jacobsson, P. Åhgren, P. Siegel, and L. Andersson, 2006 Epistasis and the release of genetic variation during long-term selection. Nat. Genet. 38: 418–420. https://doi.org/10.1038/ng1761

Chen G. K., P. Marjoram, and J. D. Wall, 2009 Fast and flexible simulation of DNA sequence data. Genome Res. 19: 136–142. https://doi.org/10.1101/gr.083634.108

Crow J., and M. Kimura, 1970 *An introduction to population genetics theory*. Harper and Row, New York.

Cuyabano B. C. D., A. C. Sørensen, and P. Sørensen, 2018 Understanding the potential bias of variance components estimators when using genomic models. Genet. Sel. Evol. 50: 41. https://doi.org/10.1186/s12711-018-0411-0

Dai Z., N. Long, and W. Huang, 2020 Influence of Genetic Interactions on Polygenic Prediction. G3 Genes Genomes Genet. 10: 109–115. https://doi.org/10.1534/g3.119.400812

Duenk P., P. Bijma, M. P. L. Calus, Y. C. J. Wientjes, and J. H. J. van der Werf, 2020 The Impact of Non-additive Effects on the Genetic Correlation Between Populations. G3 Genes Genomes Genet. 10: 783–795. https://doi.org/10.1534/g3.119.400663

Eyre-Walker A., 2010 Genetic architecture of a complex trait and its implications for fitness and genome-wide association studies. Proc. Natl. Acad. Sci. 107: 1752–1756. https://doi.org/10.1073/pnas.0906182107

Falconer D. S., and T. F. C. Mackay, 1996 *Introduction to quantitative genetics*. Longman New York.

Fernández E., J. Sánchez, R. Martínez, A. Legarra, and M. Baselga, 2017 Role of inbreeding depression, non-inbred dominance deviations and random year-season effect in genetic trends for prolificacy in closed rabbit lines. J. Anim. Breed. Genet. 134: 441–452.

Fuerst C., and J. Sölkner, 1994 Additive and Nonadditive Genetic Variances for Milk Yield, Fertility, and Lifetime Performance Traits of Dairy Cattle. J. Dairy Sci. 77: 1114–1125. https://doi.org/10.3168/jds.S0022-0302(94)77047-8

Fuerst C., J. W. James, J. Sölkner, and A. Essl, 1997 Impact of dominance and epistasis on the genetic make-up of simulated populations under selection: a model development. J. Anim. Breed. Genet. 114: 163–175. https://doi.org/10.1111/j.1439-0388.1997.tb00502.x

Galarza C. E., L. A. Matos, D. K. Dey, and V. H. Lachos, 2020 On moments of folded and doubly truncated multivariate extended skew-normal distributions. ArXiv200913488 Math Stat.

García-Ruiz A., J. B. Cole, P. M. VanRaden, G. R. Wiggans, F. J. Ruiz-López, *et al.*, 2016 Changes in genetic selection differentials and generation intervals in US Holstein dairy cattle as a result of genomic selection. Proc. Natl. Acad. Sci. 113: E3995–E4004.

735 Gautier M., A. Capitan, S. Fritz, A. Eggen, D. Boichard, *et al.*, 2007 Characterization of the
736 DGAT1 K232A and Variable Number of Tandem Repeat Polymorphisms in French
737 Dairy Cattle. J. Dairy Sci. 90: 2980–2988. https://doi.org/10.3168/jds.2006-707

738 Gibbs R. A., J. F. Taylor, C. P. Van Tassell, W. Barendse, K. A. Eversole, *et al.*, 2009 Genome-
739 wide survey of SNP variation uncovers the genetic structure of cattle breeds. Sci. N.
740 Y. NY 324: 528–532.

741 Gibson G., 2012 Rare and common variants: twenty arguments. Nat. Rev. Genet. 13: 135–
742 145. https://doi.org/10.1038/nrg3118

743 Grisart B., W. Coppieters, F. Farnir, L. Karim, C. Ford, *et al.*, 2002 Positional candidate cloning
744 of a QTL in dairy cattle: identification of a missense mutation in the bovine DGAT1
745 gene with major effect on milk yield and composition. Genome Res 12: 222–231.

746 Grobet L., L. J. Royo Martin, D. Poncelet, D. Pirottin, B. Brouwers, *et al.*, 1997 A deletion in
747 the bovine myostatin gene causes the double–muscled phenotype in cattle. Nat.
748 Genet. 17: 71–74. https://doi.org/10.1038/ng0997-71

749 Haile-Mariam M., and J. E. Pryce, 2015 Variances and correlations of milk production,
750 fertility, longevity, and type traits over time in Australian Holstein cattle. J. Dairy Sci.
751 98: 7364–7379. https://doi.org/10.3168/jds.2015-9537

752 Hayes B. J., P. J. Bowman, A. C. Chamberlain, K. Verbyla, and M. E. Goddard, 2009 Accuracy
753 of genomic breeding values in multi-breed dairy cattle populations. Genet Sel Evol
754 41: 51.

Hill W. G., N. H. Barton, and M. Turelli, 2006 Prediction of effects of genetic drift on variance components under a general model of epistasis. Theor. Popul. Biol. 70: 56–62. https://doi.org/10.1016/j.tpb.2005.10.001

Hill W. G., M. E. Goddard, and P. M. Visscher, 2008 Data and Theory Point to Mainly Additive Genetic Variance for Complex Traits. PLOS Genet. 4: e1000008. https://doi.org/10.1371/journal.pgen.1000008

Hudson R. R., M. Slatkin, and W. P. Maddison, 1992 Estimation of levels of gene flow from DNA sequence data. Genetics 132: 583–589.

Kan R., and C. Robotti, 2017 On Moments of Folded and Truncated Multivariate Normal Distributions. J. Comput. Graph. Stat. 26: 930–934. https://doi.org/10.1080/10618600.2017.1322092

Karoui S., M. J. Carabaño, C. Díaz, and A. Legarra, 2012 Joint genomic evaluation of French dairy cattle breeds using multiple-trait models. Genet Sel Evol 44: 39.

Kojima K., 1959 Role of epistasis and overdominance in stability of equilibria with selection. Proc. Natl. Acad. Sci. U. S. A. 45: 984–989.

Kojima K.-I., 1961 Effects of dominance and size of population on response to mass selection*. Genet. Res. 2: 177–188. https://doi.org/10.1017/S0016672300000689

Lande R., and R. Thompson, 1990 Efficiency of marker-assisted selection in the improvement of quantitative traits. Genetics 124: 743–756.

774 Legarra A., G. Baloche, F. Barillet, J. M. Astruc, C. Soulas, *et al.*, 2014 Within-and across-
775 breed genomic predictions and genomic relationships for Western Pyrenees dairy
776 sheep breeds Latxa, Manech, and Basco-Béarnaise. J. Dairy Sci. 97: 3200–3212.

777 Liu Z., H. Alkhoder, F. Reinhardt, and R. Reents, 2016 Accuracy and bias of genomic
778 prediction for second-generation candidates. Interbull Bull.

779 Lynch M., and B. Walsh, 1998 *Genetics and analysis of quantitative traits*. Sinauer associates.

780 Mackay T. F. C., 2014 Epistasis and Quantitative Traits: Using Model Organisms to Study
781 Gene-Gene Interactions. Nat. Rev. Genet. 15: 22–33.
782 https://doi.org/10.1038/nrg3627

783 Mackay T. F. C., 2015 Epistasis for Quantitative Traits in Drosophila, pp. 47–70 in *Epistasis:*
784 *Methods and Protocols*, Methods in Molecular Biology. edited by Moore J. H.,
785 Williams S. M. Springer, New York, NY.

786 MacLeod I. M., P. J. Bowman, C. J. Vander Jagt, M. Haile-Mariam, K. E. Kemper, *et al.*, 2016
787 Exploiting biological priors and sequence variants enhances QTL discovery and
788 genomic prediction of complex traits. BMC Genomics 17: 144.
789 https://doi.org/10.1186/s12864-016-2443-6

790 Magwire M. M., A. Yamamoto, M. A. Carbone, N. V. Roshina, A. V. Symonenko, *et al.*, 2010
791 Quantitative and Molecular Genetic Analyses of Mutations Increasing Drosophila Life
792 Span. PLOS Genet. 6: e1001037. https://doi.org/10.1371/journal.pgen.1001037

Mäki-Tanila A., and W. G. Hill, 2014 Influence of Gene Interaction on Complex Trait Variation with Multilocus Models. Genetics 198: 355–367. https://doi.org/10.1534/genetics.114.165282

Marigorta U. M., and A. Navarro, 2013 High Trans-ethnic Replicability of GWAS Results Implies Common Causal Variants. PLOS Genet. 9: e1003566. https://doi.org/10.1371/journal.pgen.1003566

Martin A. R., M. Kanai, Y. Kamatani, Y. Okada, B. M. Neale, *et al.*, 2019 Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. 51: 584–591. https://doi.org/10.1038/s41588-019-0379-x

Meuwissen T. H. E., B. J. Hayes, and M. E. Goddard, 2001 Prediction of total genetic value using genome-wide dense marker maps. Genetics 157: 1819–1829.

Moghaddar N., M. Khansefid, J. H. J. van der Werf, S. Bolormaa, N. Duijvesteijn, *et al.*, 2019 Genomic prediction based on selected variants from imputed whole-genome sequence data in Australian sheep populations. Genet. Sel. Evol. 51: 72. https://doi.org/10.1186/s12711-019-0514-2

Nei M., 1987 *Molecular Evolutionary Genetics*. Columbia University Press.

Palucci V., L. R. Schaeffer, F. Miglior, and V. Osborne, 2007 Non-additive genetic effects for fertility traits in Canadian Holstein cattle (Open Access publication). Genet. Sel. Evol. 39: 181. https://doi.org/10.1186/1297-9686-39-2-181

Park J.-H., M. H. Gail, C. R. Weinberg, R. J. Carroll, C. C. Chung, *et al.*, 2011 Distribution of allele frequencies and effect sizes and their interrelationships for common genetic

susceptibility variants. Proc. Natl. Acad. Sci. 108: 18026–18031. https://doi.org/10.1073/pnas.1114759108

Pérez-Enciso M., 2014 Genomic relationships computed from either next-generation sequence or array SNP data. J. Anim. Breed. Genet. Z. Tierzuchtung Zuchtungsbiologie 131: 85–96. https://doi.org/10.1111/jbg.12074

Pérez-Enciso M., J. C. Rincón, and A. Legarra, 2015 Sequence-vs. chip-assisted genomic selection: accurate biological information is advised. Genet. Sel. Evol. 47: 43.

Porto-Neto L. R., W. Barendse, J. M. Henshall, S. M. McWilliam, S. A. Lehnert, *et al.*, 2015 Genomic correlation: harnessing the benefit of combining two unrelated populations for genomic selection. Genet. Sel. Evol. 47: 84. https://doi.org/10.1186/s12711-015-0162-0

Powell J. E., P. M. Visscher, and M. E. Goddard, 2010 Reconciling the analysis of IBD and IBS in complex trait studies. Nat Rev Genet 11: 800–805.

Rodríguez-Ramilo S., J. M. Elsen, and A. Legarra, 2019 Inbreeding and effective population size in French dairy sheep: Comparison between genomic and pedigree estimates. J. Dairy Sci. 102: 4227–4237.

Roos A. P. W. de, B. J. Hayes, and M. E. Goddard, 2009 Reliability of Genomic Predictions Across Multiple Populations. Genetics 183: 1545–1553. https://doi.org/10.1534/genetics.109.104935

Rupp R., P. Senin, J. Sarry, C. Allain, C. Tasca, *et al.*, 2015 A Point Mutation in Suppressor of Cytokine Signalling 2 (Socs2) Increases the Susceptibility to Inflammation of the

Mammary Gland while Associated with Higher Body Weight and Size and Higher Milk Production in a Sheep Model. PLOS Genet. 11: e1005629. https://doi.org/10.1371/journal.pgen.1005629

Shi H., S. Gazal, M. Kanai, E. M. Koch, A. P. Schoech, *et al.*, 2021 Population-specific causal disease effect sizes in functionally important regions impacted by selection. Nat. Commun. 12: 1098. https://doi.org/10.1038/s41467-021-21286-1

Streit M., N. Neugebauer, T. H. E. Meuwissen, and J. Bennewitz, 2011 Short communication: evidence for a major gene by polygene interaction for milk production traits in German Holstein dairy cattle. J. Dairy Sci. 94: 1597–1600. https://doi.org/10.3168/jds.2010-3834

Tsuruta S., I. Misztal, T. J. Lawlor, and L. Klei, 2004 Modeling final scores in US Holsteins as a function of year of classification using a random regression model. Livest. Prod. Sci. 91: 199–207. https://doi.org/10.1016/j.livprodsci.2003.09.016

VanRaden P., K. Olson, G. Wiggans, J. Cole, and M. Tooker, 2011 Genomic inbreeding and relationships among Holsteins, Jerseys, and Brown Swiss. J. Dairy Sci. 94: 5673–5682.

Vitezica Z. G., A. Legarra, M. A. Toro, and L. Varona, 2017 Orthogonal Estimates of Variances for Additive, Dominance and Epistatic Effects in Populations. Genetics genetics.116.199406. https://doi.org/10.1534/genetics.116.199406

Vitezica Z. G., A. Reverter, W. Herring, and A. Legarra, 2018 Dominance and epistatic genetic variances for litter size in pigs using genomic models. Genet. Sel. Evol. 50: 1–8.

Walsh B., and M. Lynch, 2018 *Evolution and Selection of Quantitative Traits*. Oxford University Press.

Weir B. S., and W. G. Hill, 2002 Estimating F-statistics. Annu. Rev. Genet. 36: 721–750. https://doi.org/10.1146/annurev.genet.36.050802.093940

Welsh C. S., T. S. Stewart, C. Schwab, and H. D. Blackburn, 2010 Pedigree analysis of 5 swine breeds in the United States and the implications for genetic conservation. J. Anim. Sci. 88: 1610–1618. https://doi.org/10.2527/jas.2009-2537

Wientjes Y. C. J., P. Bijma, J. Vandenplas, and M. P. L. Calus, 2017 Multi-population Genomic Relationships for Estimating Current Genetic Variances Within and Genetic Correlations Between Populations. Genetics 207: 503–515. https://doi.org/10.1534/genetics.117.300152

Xiang T., O. F. Christensen, and A. Legarra, 2017 Technical note: Genomic evaluation for crossbred performance in a single-step approach with metafounders. J. Anim. Sci. 95: 1472–1480.

Table 1. Notation.

$\alpha_i^b, \alpha_i^{b'}$	Substitution effect of locus i in population b, in population b'	$\sigma^2_{\alpha,b}$	Variance of substitution effects in population b
d_i^{*b}	Dominance deviation at locus i in population b	$\sigma^2_{d,b}, \mu_{d,b}$	Variance and mean of dominance deviations in population b
$(\alpha\alpha)_{ij}^b$	Additive by additive effect of loci i, j at population b	$\sigma^2_{(\alpha\alpha,b)}$	Variance of additive by additive effects in population b
$(\boldsymbol{\alpha\alpha})_i^b$	Vector of additive by additive effects of locus i with all other loci in population b		
$p_i^b, p_i^{b'}$	Allele frequency of locus i in population b, in population b'		
$\boldsymbol{p}^b, \boldsymbol{p}^{b'}$	Vectors of allele frequencies in population b, in population b'		
$\overline{H_b}$	Average heterozygosity at population b, $\overline{H}_b = E\left(2p_i^b\left(1-p_i^b\right)\right)$		
$\overline{H_b^2}$	Average squared heterozygosity at population b, $\overline{H_b^2} = E\left(\left(2p_i^b\left(1-p_i^b\right)\right)^2\right)$		
$\overline{HH_b}$	Average product of heterozygosities at population b, $\overline{HH_b} = E_{i>j}\left(4p_i^b\left(1-p_i^b\right)p_j^b\left(1-p_j^b\right)\right)$		

ϵ_i	Difference in allele frequencies at locus i, $\epsilon_i = p_i^{b'} - p_i^b$	σ_ϵ^2	Variance of the difference in allele frequencies across all loci
$D_{b,b'}$	Nei's minimum genetic distance		
$\sigma_A^2, \sigma_D^2, \sigma_{AA}^2$	Additive, Dominance and Additive by Additive variances (in population b)		

875

876 Table 2. Additive, dominance and additive by additive variances in the simulated population

877 1

	additive	dominance	additive by additive
Complete Dominance	252	113	0
Complementary Epistasis	130	53	12
Multiplicative	219	0	122

878

879

880 Table 3. Variance component estimates, as ratio from phenotypic variance, from literature

Species	σ_A^2	σ_D^2	σ_{AA}^2
Cattle	0.20	0.09	0.15
Pigs	0.092	0.020	0.016

881 Estimates for milk yield in cattle (Fuerst and Sölkner 1994) and litter size in pigs (Vitezica *et al.*

882 2018).

883

884

885 Table 4: Estimates of correlations of QTL effects across breeds based on values from Table 3

886 and Equation 7, for different distributions of QTL frequencies

Species	Uniform	Hill[1]	Extreme[2]
Cattle	0.83	0.82	0.84
Pigs	0.87	0.85	0.88

887 [1] U-shaped distribution with effective population size of 50

888 [2] Beta(0.04, 0.04) distribution

889

890 Table 5: Correlation of QTL effects within breed across time, based on values from Table 3 and

891 Equation 7, for different distributions of QTL frequencies

Species	Distance in generations	Uniform	Hill[1]	Extreme[2]
Cattle	1	0.98	0.97	0.98
	2	0.97	0.94	0.97
	5	0.93	0.87	0.93
	10	0.86	0.78	0.87
Pigs	1	1.00	0.99	1.00
	2	0.99	0.98	0.99
	5	0.98	0.96	0.97
	10	0.96	0.93	0.93

892 [1] U-shaped distribution with effective population size of 50

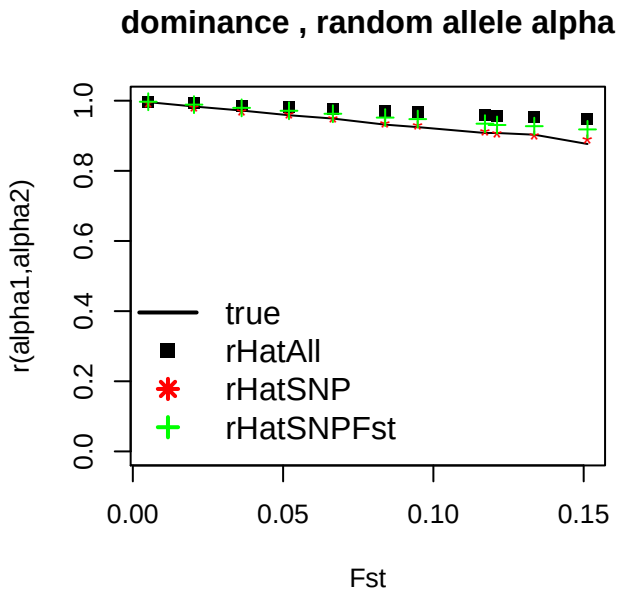
893 [2] Beta(0.04, 0.04) distribution

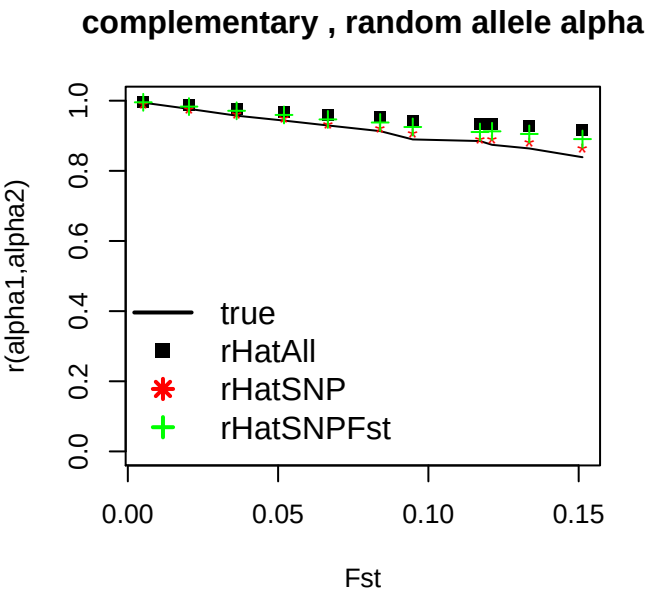
894

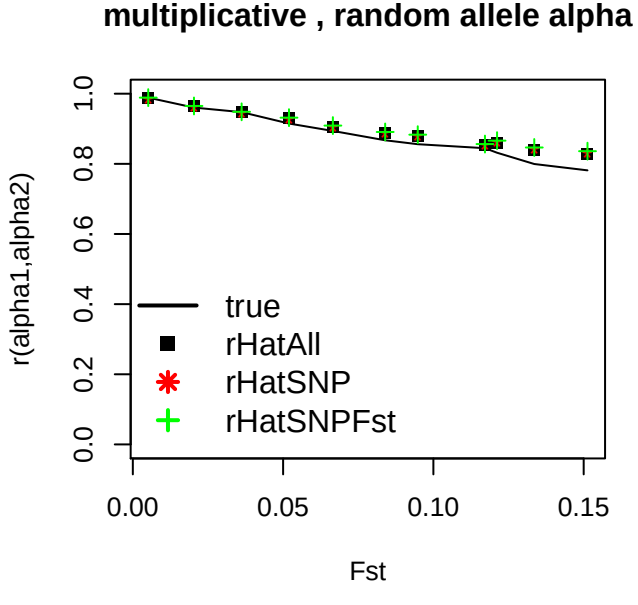
FIGURE LEGENDS

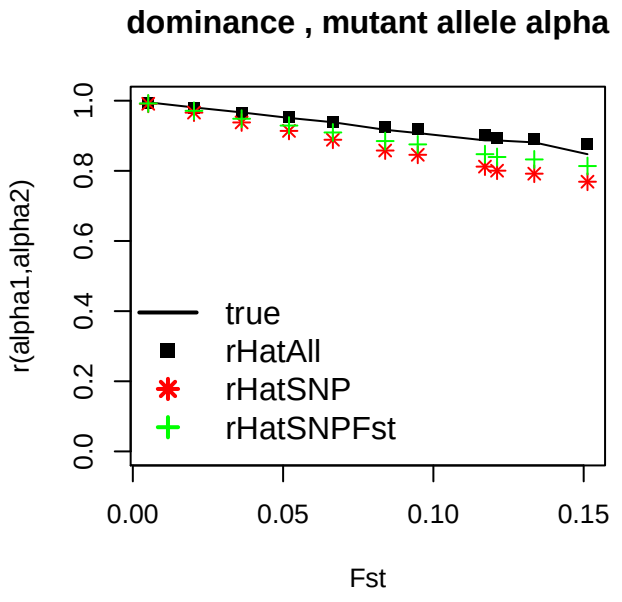
Figure 1. Simulated (straight black line) and estimated (points) correlation across QTL substitution effects of random alleles across two populations as a function of their F_{ST} differentiation coefficient. rHatAll: estimates with all polymorphism. rHatSNP: estimates using SNP-like loci. rHatSNPFst: estimates using SNP-like loci with a correction for heterozygosity. Results of 10 replicates per point with s.e.<0.01.

Figure 2. Simulated (straight black line) and estimated (points) correlation across QTL substitution effects of mutant alleles across two populations as a function of their F_{ST} differentiation coefficient. rHatAll: estimates with all polymorphism. rHatSNP: estimates using SNP-like loci. rHatSNPFst: estimates using SNP-like loci with a correction for heterozygosity. Results of 10 replicates per point with s.e.<0.01.


dominance , random allele alpha
r(alpha1,alpha2)
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.05
0.10
0.15
Fst
true
rHatAll
rHatSNP
rHatSNPFst


complementary , random allele alpha
r(alpha1,alpha2)
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.05
0.10
0.15
Fst
true
rHatAll
rHatSNP
rHatSNPFst


multiplicative , random allele alpha
r(alpha1,alpha2)
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.05
0.10
0.15
Fst
true
rHatAll
rHatSNP
rHatSNPFst


dominance , mutant allele alpha
r(alpha1,alpha2)
0.0
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0.00
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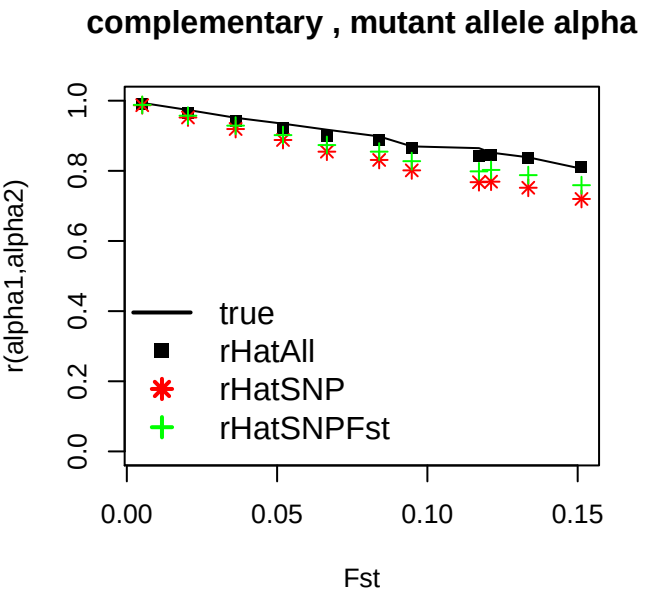
0.10
0.15
Fst
true
rHatAll
rHatSNP
rHatSNPFst


complementary , mutant allele alpha
r(alpha1,alpha2)
0.0
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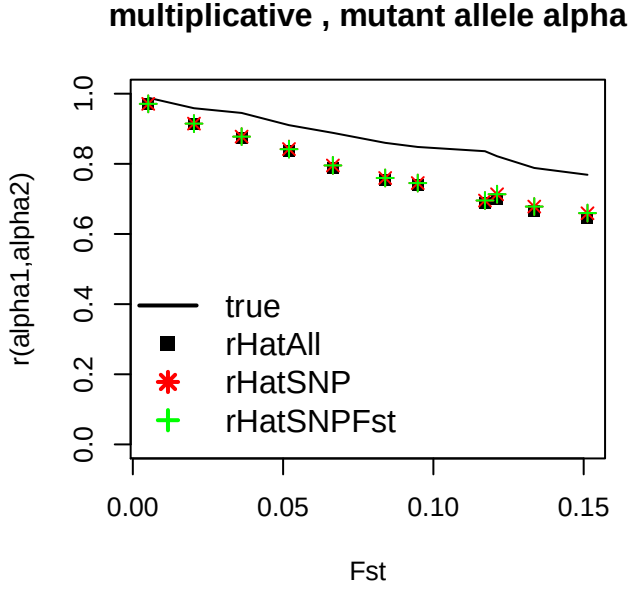
true
rHatAll
rHatSNP
rHatSNPFst


multiplicative , mutant allele alpha
r(alpha1,alpha2)
0.0
0.2
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Fst
true
rHatAll
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rHatSNPFst