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# The correlation of substitution effects across populations and generations in the presence of nonadditive functional gene action

Andres Legarra <sup>1,\*</sup> Carolina A. Garcia-Baccino,<sup>1,2,3</sup> Yvonne C. J. Wientjes <sup>4</sup>, and Zulma G. Vitezica<sup>1</sup>

<sup>1</sup>INRAE/INP, UMR 1388 GenPhySE, Castanet-Tolosan 31326, France,

<sup>2</sup>Departamento de Producción Animal, Facultad de Agronomía, Universidad de Buenos Aires, Buenos Aires C1417DSQ, Argentina,

<sup>3</sup>SAS NUCLEUS, Le Rheu 35650, France, and

<sup>4</sup>Wageningen University & Research, Animal Breeding and Genomics, Wageningen 6700 AH, the Netherlands

\*Corresponding author: INRAE, UMR1388 GenPhySE, CS 52627, 31326 Castanet Tolosan, France. Email: andres.legarra@inrae.fr

## 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 nonadditive 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  $F_{st}$  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 nonadditive 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.

**Keywords:** QTL; substitution effects; epistasis; dominance; genetic distance

## 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 and 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 a 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 and genes has been claimed to be a reason for this decrease in accuracy. Adding extra information (more dense maps and biological prior information) should result in a better choice of markers close to causal genes, and therefore in a boost in predictive abilities across populations (Roos et al. 2009; MacLeod et al. 2016). However, in practice, the increase in predictive ability across populations is small at best (MacLeod et al. 2016; Moghaddar et al. 2019). This is against results from simulations (Roos et al. 2009; MacLeod et al. 2016)—but a problem in simulations is that typically gene effects are assumed

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to be biologically additive and therefore constant across populations.

We argue that, although imperfect LD is a likely cause for not being able to predict across populations, it is not the only one. In fact, substitution (statistical) additive gene action is not homogeneous across populations, even for exactly the same causal mutation. Examples in livestock genetics include myostatin gene (Aiello *et al.* 2018) or DGAT1 (Gautier *et al.* 2007). For instance, in the latter, the “K” allele had rather different substitution effects across breeds:  $-611$ ,  $-142$ , and  $-351$  kg of milk for the respective breeds Montbéliarde, Normande, and Holstein, for a trait with a genetic standard deviation of  $\sim 600$  kg. Although part of these differences may be due to genotype-by-environment interactions, it is also plausible that this is due to epistasis or dominance; for instance this is the case in DGAT1 (Streit *et al.* 2011). For instance, in the 5-loci epistatic network in Carlborg *et al.* (2006) some substitution effects at genes switch signs depending on genetic background. In *Drosophila*, estimated substitution effects of P-element insertions switched signs depending on the genetic background (Magwire *et al.* 2010; Mackay 2015).

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 nonadditive biological gene action and increases with divergence of populations. It is relatively easy to derive algebraic expressions for substitution effects  $\alpha$  assuming a 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 theories 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.

This study aims to develop a theory to understand and predict, under a neutral scenario, the extent of change of substitution effects across space (breeds and 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. The main factors affecting the 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

#### General theory

Here, we model difference of substitution effects across two populations as Taylor expansions around one of them, the “focal” population. Using Kojima’s method (Kojima 1959, 1961), we put additive substitution effects as a function of differences in allele frequencies across populations, “focal” additive substitution effects, and second-order (dominance, additive by additive epistasis) statistical effects. From here, we show that the correlation of substitution effects across populations is (approximately) a function of their differentiation (or genetic distance), the additive, dominant and additive by additive genetic variances, the average heterozygosities, and average squared heterozygosities. All these parameters can be estimated in real populations. In the following, we try to stick to Mäki-Tanila and Hill (2014) notation. Many details are given as Supplementary File S1. Main notation is presented in Table 1.

Note that our procedure is general—it does not invoke any particular mechanism for epistasis or dominance, nor knowledge of individual QTL effects and locations. We assume that the population mean is a (possibly complex) function of QTL allele frequencies  $\mathbf{p}$  and QTL functional or biological effects. The latter, albeit unknown, are assumed to be constant across populations—we, therefore, do not consider genotype by environment interactions.

Consider the correlation  $r(\alpha_i^b, \alpha_i^{b'})$  of substitution effects  $\alpha^b$  and  $\alpha^{b'}$  across respective populations (breeds, heterotic groups, lines, or generations)  $b$  and  $b'$ . For simplicity, the allele to which  $\alpha$  refers is random—it can be either the wild or the mutant allele. In this manner, the average value of  $\alpha$  is 0, even in presence of deleterious mutations. It is known that, in presence of dominant and epistatic biological interactions, the value of  $\alpha$  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  $r(\alpha_i^b, \alpha_i^{b'})$  for a locus  $i$  as a function of vectors of respective allele frequencies,  $\mathbf{p}^b$  and  $\mathbf{p}^{b'}$ , 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

Table 1 Notation

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

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  $\alpha$  as function of allelic frequencies  $\mathbf{p}$ , we use Kojima's definition of statistical effects as first, second... derivatives of the mean of the population ( $\mu$ ) as a function of  $p$ . We do not 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  $\mu$  or equivalently as derivatives of  $\alpha_i$ . 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  $\partial p_i^2$ . 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  $k$ -th 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  $\alpha_i$  around frequencies in the "focal" population,  $\mathbf{p}^b$ , so that  $\mathbf{p}^{b'} = \mathbf{p}^b + \boldsymbol{\epsilon}$ , such

that from values of  $\alpha$  in  $b$  and changes in allele frequencies  $\boldsymbol{\epsilon} = \mathbf{p}^{b'} - \mathbf{p}^b$  we create a function  $\alpha_i^{b'} \approx f(\alpha_i^b, \boldsymbol{\epsilon})$ . In the Supplementary File S1 (Section 1.1), we show that the Taylor linear approximation of the substitution effects of population  $b'$ :  $\alpha_i^{b'}$ , from effects from populations  $b$ ,  $\alpha_i^b$ ,  $d_i^{*b}$ ,  $(\alpha\alpha)_i^b$  is:

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

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

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

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

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

Thus  $r(\alpha_i^b, \alpha_i^{b'}) = \sqrt{\frac{\text{Var}(\alpha_i^b)}{\text{Var}(\alpha_i^b)\text{Var}(\alpha_i^{b'})}}$ , and now we need the variance of  $\alpha_i^{b'}$  as a function of effects in population  $b$ , this is (see the Supplementary File S1, Section 1.2 for details):

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

This expression is unsymmetric and seems to imply that by construction  $\text{Var}(\alpha_i^{b'}) > \text{Var}(\alpha_i^b)$ ; 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  $b'$ . In statistical terms, population  $b$  has  $\text{Var}(\alpha_i^b | \sigma_A^2, \sigma_D^2, \sigma_{AA}^2, \mu_{d,b}, \overline{H}_b, \overline{H}_b^2)$  all of them known for population  $b$ , and population  $b'$  has  $\text{Var}(\alpha_i^{b'} | \sigma_A^2, \sigma_D^2, \sigma_{AA}^2, \mu_{d,b}, \overline{H}_b, \overline{H}_b^2)$  where variances and

heterozygosities are still from population  $b$  (and not from  $b'$  itself). So, [3] is  $Var(\alpha_i^b | \text{information on } b)$  versus  $Var(\alpha_i^{b'} | \text{information on } b)$ . The higher variance of  $\alpha_i^b$  than of  $\alpha_i^{b'}$  is due to this extra incertitude.

An alternative derivation in the [Supplementary File S1](#) (Section 1.4) shows that, if the “focal” population is a third one ( $f$ ) a set of expressions analogous to [Equations \(2\)](#) and [\(3\)](#) is:

$$\begin{aligned} Var(\alpha_i^{b'}) &\approx Var(\alpha_i^f) + 4Var(\epsilon_i^{(b)} d_i^{*f}) + 4Var(\epsilon^{(b')}(\alpha\alpha)_i^f) \\ Var(\alpha_i^b) &\approx Var(\alpha_i^f) + 4Var(\epsilon_i^{(b)} d_i^{*f}) + 4Var(\epsilon^{(b)}(\alpha\alpha)_i^f) \\ Cov(\alpha_i^{b'}, \alpha_i^b) &\approx Var(\alpha_i^f) + Cov(\epsilon_i^{(b)}, \epsilon_i^{(b)}) (Var(d_i^{*b}) + E^2(d_i^{*b})) \\ &\quad + Cov(\epsilon^{(b')}(\alpha\alpha)_i^f, \epsilon^{(b)}(\alpha\alpha)_i^f) \end{aligned}$$

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 [Equations \(2\)](#) and [\(3\)](#) as a particular case if the focal population is  $b$ .

In the expression [\(3\)](#),  $Var(\epsilon')$  and  $Var((\alpha\alpha)_i^b)$  are matrices. The first one describes the variability of differences in allele frequencies:

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

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 nonzero  $Cov(\epsilon_1, \epsilon_2)$ . The second matrix contains (co)variances of the epistatic effects across all pairs marker  $i$ —other markers:

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

For instance,  $Var((\alpha\alpha)_1^b)$  contains the variance of the epistatic effect of marker  $i$  with marker 1, and so on. We assume  $Var((\alpha\alpha)_i^b) = \mathbf{I} \sigma_{(\alpha\alpha, b)}^2$ , i.e., epistatic terms  $(\alpha\alpha)_i^b$  can be either positive or negative, with a variance  $\sigma_{(\alpha\alpha, b)}^2$  and are a priori uncorrelated to each other. Assuming null off-diagonals for  $Var((\alpha\alpha)_i^b)$  results that, in the previous product  $tr(Var(\epsilon)Var((\alpha\alpha)_i^b))$ , off-diagonal elements of  $Var(\epsilon')$  disappear from the result (even if they are not null). Thus, assuming that all diagonal elements of  $Var(\epsilon')$  have the same common variance  $\sigma_\epsilon^2$ , this results in  $4tr(Var(\epsilon)Var((\alpha\alpha)_i^b)) = 4n\sigma_\epsilon^2\sigma_{(\alpha\alpha, b)}^2$ . Note that assuming that all diagonal elements of  $Var(\epsilon)$  are equal is an approximation—for instance more polymorphic loci vary more.

The expression  $Var(\epsilon_i d_i^{*b}) = Var(\epsilon_i) (Var(d_i^{*b}) + E^2(d_i^{*b}))$  is detailed in the [Supplementary File S1](#) (Section 1.2), and it shows that both the variability of dominance deviations  $Var(d_i^{*b}) = \sigma_{d, b}^2$  and its mean  $E(d_i^{*b}) = \mu_{d, b}$  which, if not zero, can be understood as the basis of inbreeding depression, enter into the expression. Also, we assume  $\epsilon$  (change in allele frequencies, but not the allele frequencies themselves) and the different non-additive effects  $d_i^{*b}$  and  $(\alpha\alpha)_i^b$  to be independent (uncorrelated). This makes sense as loci may be selected for additive effects but not for nonadditive effects.

Our next goal is to relate these results in [Equation \(3\)](#) 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](#)):

$$\begin{aligned} Var(\alpha_i^b) &= \sigma_{\alpha, b}^2 = \frac{\sigma_A^2}{nH_b} \\ Var(d_i^{*b}) + E^2(d_i^{*b}) &= \sigma_{d, b}^2 + \mu_{d, b}^2 = \frac{\sigma_D^2}{nH_b^2} \end{aligned}$$

(the latter is shown in the [Supplementary File S1](#), Section 1.5) and

$$Var((\alpha\alpha)_{i,j>i}^b) = \sigma_{(\alpha\alpha, b)}^2 = \frac{\sigma_{AA}^2}{n(n-1)H_b H_b} \approx 2 \frac{\sigma_{AA}^2}{n^2 H_b H_b}$$

for  $n$  the number of QTL loci and using functions of heterozygosities (more details in the [Supplementary File S1](#), Section 1.6):

$$\begin{aligned} \overline{H}_b &= E(2p_i^b(1-p_i^b)) \\ \overline{H}_b^2 &= E(4p_i^b(1-p_i^b)p_i^b(1-p_i^b)) \\ \overline{HH}_b &= E_{i>j}(2p_i^b(1-p_i^b)2p_j^b(1-p_j^b)) \approx \frac{1}{2} \overline{H}_b \overline{H}_b \end{aligned}$$

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  $\alpha^b$ . Note that we assume HWE and LE within both  $b$  and  $b'$ . Of course, we do not 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  $\sigma_\epsilon^2$ , the variance of differences of allele frequency. In fact,  $\sigma_\epsilon^2 = Var(p^{b'} - p^b) = E((p^{b'} - p^b)^2) - E(p^{b'} - p^b)^2 = E((p^{b'} - p^b)^2)$  because  $E(p^{b'} - p^b) = 0$  when averaged across loci.

Therefore,  $\sigma_\epsilon^2 = E((p^{b'} - p^b)^2)$  which corresponds to Nei’s “minimum genetic distance” ([Nei 1987](#); [Caballero and Toro 2002](#)), and, accordingly, will be called  $D_{b, b'}$  or  $\sigma_\epsilon^2$ . The value of  $D_{b, b'}$  can be estimated from marker data as  $\hat{D}_{b, b'} = \frac{1}{n} \sum (p_i^{b'} - p_i^b)^2$ , 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 \(1992\)](#)  $F_{ST} = \frac{E((p_i^{b'} - p_i^b)^2)}{E(p_i^{b'}(1-p_i^{b'}) + p_i^b(1-p_i^b))}$  with an estimator

$\hat{F}_{ST} = \frac{\frac{1}{n} \sum_i (p_i^{b'} - p_i^b)^2}{\frac{1}{n} \sum_i (p_i^{b'}(1-p_i^{b'}) + p_i^b(1-p_i^b))}$  ([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

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

Combining expressions above, [Equation \(3\)](#) becomes

$$\begin{aligned} \text{Var}(\alpha_i^{b'}) &= \frac{\sigma_A^2}{n\bar{H}_b} + 4D_{b,b'} \frac{\sigma_D^2}{n\bar{H}_b^2} + 4nD_{b,b'} \frac{2\sigma_{AA}^2}{n^2\bar{H}_b\bar{H}_b} \\ &= \frac{1}{n} \left( \frac{\sigma_A^2}{\bar{H}_b} + 4D_{b,b'} \frac{\sigma_D^2}{\bar{H}_b^2} + 8D_{b,b'} \frac{\sigma_{AA}^2}{\bar{H}_b\bar{H}_b} \right) \end{aligned} \quad (4)$$

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

$$\begin{aligned} r(\alpha_i^b, \alpha_i^{b'}) &\approx \frac{\text{Cov}(\alpha_i^b, \alpha_i^{b'})}{\sqrt{(\text{Var}(\alpha_i^b))(\text{Var}(\alpha_i^{b'}))}} \\ &= \frac{\text{Var}(\alpha_i^b)}{\sqrt{(\text{Var}(\alpha_i^b))(\text{Var}(\alpha_i^{b'}))}} = \frac{\sqrt{\text{Var}(\alpha_i^b)}}{\sqrt{\text{Var}(\alpha_i^{b'})}} \quad (5) \\ &= \frac{\sqrt{\frac{\sigma_A^2}{\bar{H}_b}}}{\sqrt{\frac{\sigma_A^2}{\bar{H}_b} + 4D_{b,b'} \frac{\sigma_D^2}{\bar{H}_b^2} + 8D_{b,b'} \frac{\sigma_{AA}^2}{\bar{H}_b\bar{H}_b}}} \end{aligned}$$

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 [Supplementary File S1](#), Section 1.4. Factorizing out  $\bar{H}_b$  we arrive to the slightly clearer expression

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

which shows well that the correlation is a function of distance across populations ( $D_{b,b'}$ ) and weights of additive vs nonadditive variances. Note that  $D_{b,b'}$  is always positive, which implies that  $0 < r(\alpha_i^b, \alpha_i^{b'}) < 1$  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  $\sigma_A^2$ ,  $\sigma_D^2$ ,  $\sigma_{AA}^2$  in population  $b$  (3) first and second moments of heterozygosities  $\bar{H}_b$ ,  $\bar{H}_b^2$ . 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  $\bar{H}_b \approx \bar{H}_{b'}$ ,  $D_{b,b'} \approx \frac{F_{ST}}{1-F_{ST}} \bar{H}_b$  (detailed in the [Supplementary File S1](#), Section 1.7), leading to

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

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  $\sigma_D^2$  is negligible, we can write a neat expression of the correlation in terms of  $F_{ST}$ :

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

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 populations 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  $\alpha$  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  $\bar{H}_b$  and average squared heterozygosity  $\bar{H}_b^2$
- 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  $\alpha$  is "oriented" and has no zero mean. In the theory, above we have considered that  $\alpha$  is the effect of a randomly drawn allele, which leads to  $E(\alpha) = 0$  and enormously simplifies the algebra. In order to consider oriented  $\alpha$ , 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  $\alpha$  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 [Supplementary File S1](#), 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

$$r(\alpha_i^{t_1}, \alpha_i^{t_2}) \approx \frac{\sqrt{\sigma_A^2}}{\sqrt{\sigma_A^2 + \frac{F_{ST}}{1-F_{ST}} \left( 4 \frac{(\bar{H}_{t_1})^2}{\bar{H}_{t_1}^2} \sigma_D^2 + 8\sigma_{AA}^2 \right)}}. \text{ In pedigree-based context,}$$

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  $\Delta F$  and steady increase of inbreeding. Thus,  $F_{ST} \approx \frac{(t_2 - t_1)\Delta F}{2}$  to obtain

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

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

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

Thus, the correlation of substitution effects decreases when there is large drift, reflected in high values of  $\Delta F$ . 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.

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

## Simulations

### Description of the simulations

The objective of the simulation is to verify our results considering different kinds of nonadditive biological gene action, and not to infer the values of the correlation of substitution effects across populations as this requires realistic presumptions of the forms and magnitudes of epistatic interactions, something that is largely unknown.

We used *macs* (Chen et al. 2009) to simulate a “cattle” scenario of two domestic cattle breeds which diverged from a common ancestral population, in the lines of (Pérez-Enciso 2014; Pérez-Enciso et al. 2015), where a large population had a 10-fold reduction bottleneck (domestication) 2000 generations ago and a split into two populations  $t$  generations ago, where we made  $t$  oscillate between 0 and 100 by steps of 10. Parameters in the simulation were tailored (Pérez-Enciso 2014; Pérez-Enciso et al. 2015) to mimic observed levels of diversity in cattle (Gibbs et al. 2009) and lead to  $F_{ST}$  values between 0 and 0.15. We considered 100 DNA stretches of 300 Kb each. We simulated 200 individuals per population, from which we obtained allele frequencies per population. Details are provided in the Supplementary File S1, Section 1.9. This provided  $\sim 400,000$  segregating loci with realistic allele frequencies (L-shaped distribution of allele frequencies).

To simulate nonadditive biological gene action, we considered three scenarios. All of them involved 5000 single marker polymorphisms drawn at random from the simulated ones with no particular restriction. First scenario was Complete Dominance (within locus); second one was 1000 networks of 5 loci in Complementary Epistasis, and the third one 1000 networks of 5 loci with Multiplicative Epistasis (additive by additive). We also simulated networks of 2 and of 10 loci with similar results (not shown). These scenarios are similar to Hill et al. (2008) but instead of considering 2 loci we consider 5. We use these forms of epistasis, as the first two ones may be interpreted as biologically meaningful gene actions, and the third one is an extreme case for the

change in substitution effect across populations. In addition, all three scenarios are analytically tractable. Complete dominance has the genotypic value of the heterozygote equal to one of the homozygotes, e.g., the presence of a single copy of the “good” allele is enough to, say, avoid the disease. Complementary epistasis can be seen as a multi-loci dominance, e.g., disease happens when there is a recessive deleterious genotype at any of the loci. Additive by additive epistasis can be understood as a pure multiplication of gene contents and has no good biological interpretation. Networks contribute additively to the total phenotype. Note that, by definition, functional gene action is the same across all populations. From the description of the nonadditive gene action and some algebra in the Supplementary File S1, we are able to derive analytically the values of  $\alpha$ ,  $d^*$  and  $(\alpha\alpha)$  in each population and variances  $\sigma_A^2$ ,  $\sigma_D^2$ , and  $\sigma_{AA}^2$ . Details are given in the Supplementary File S1, Section 1.10. For each value of  $t$ , we made 10 replicates and averaged the results.

From the true substitution effects  $\alpha^b$  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,  $\alpha$  are negative by construction (i.e., the mutant allele is deleterious). To conciliate this fact with our derivations, that assume that  $\alpha$  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  $\alpha$  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  $r_{\text{mutant}}(\alpha^b, \alpha^{b'})$  (which corresponds e.g., to typical use in Evolutionary and Medical Genetics) and the correlation for the “random allele” effect  $r_{\text{random}}(\alpha^b, \alpha^{b'})$  (which corresponds, e.g., to genomic selection and some GWAS). We observed that  $r_{\text{mutant}}(\alpha^b, \alpha^{b'}) < r_{\text{random}}(\alpha^b, \alpha^{b'})$ . For instance, in one of the scenarios  $r_{\text{mutant}}(\alpha^b, \alpha^{b'}) = 0.67$  and  $r_{\text{random}}(\alpha^b, \alpha^{b'}) = 0.85$ .

Now we describe the estimators. We considered either the use of “all” polymorphisms, or of a “SNP” selection in which  $\text{MAF} > 0.01$  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  $D_{b,b'}$ ,  $\bar{H}_b$ , and  $\bar{H}_b^2$ . 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  $\bar{H}_b = 0.107$ , and  $\bar{H}_b^2 = 0.018$  from a U-shaped distribution (Hill et al. 2008) detailed later. 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”  $r_{\text{random}}(\alpha^b, \alpha^{b'})$ :  $\hat{r}_{\text{all}}$ ,  $\hat{r}_{\text{SNP}}$ , and  $\hat{r}_{\text{SNPFst}}$ , and also the three corresponding estimators for “mutant allele”  $r_{\text{mutant}}(\alpha^b, \alpha^{b'})$  applying function `r2rabs()` to  $\hat{r}_{\text{all}}$ ,  $\hat{r}_{\text{SNP}}$ , and  $\hat{r}_{\text{SNPFst}}$ .

### Results of the simulations

Simulated variance components are shown in Table 2. All scenarios yield high additive genetic variances, as expected.

True simulated values of correlation across substitution effects  $r_{\text{random}}(\alpha^b, \alpha^{b'})$  and their estimates  $\hat{r}_{\text{all}}$ ,  $\hat{r}_{\text{SNP}}$ , and  $\hat{r}_{\text{SNPFst}}$ , are presented in Figure 1 (for  $\alpha$  defined for random alleles) and Figure 2 (for  $\alpha$  defined for mutant alleles). Generally speaking, Figure 1 applies to nonfitness related traits (for “random”) and Figure 2 to fitness-related traits (for “mutant”). As predicted by our derivations, there is a clear and almost linear decrease of  $r(\alpha^b, \alpha^{b'})$  with increasing values of  $F_{ST}$ .

In Figure 1 (for  $\alpha$  defined for random alleles) it can be observed that our expressions (equations 6 and 7) tend to slightly overestimate  $r_{\text{random}}(\alpha^b, \alpha^{b'})$  for Complete Dominance, and Complementary Epistasis. The estimates are quite good for Multiplicative Epistasis. Estimators using SNP markers are slightly less accurate than using the complete polymorphism spectra, and using  $F_{ST}$  from SNP markers, coupled with a guess of heterozygosities, is similar to using SNP alone to infer both distances and heterozygosities.

**Table 2** Additive, dominance and additive by additive variances in the simulated population 1

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

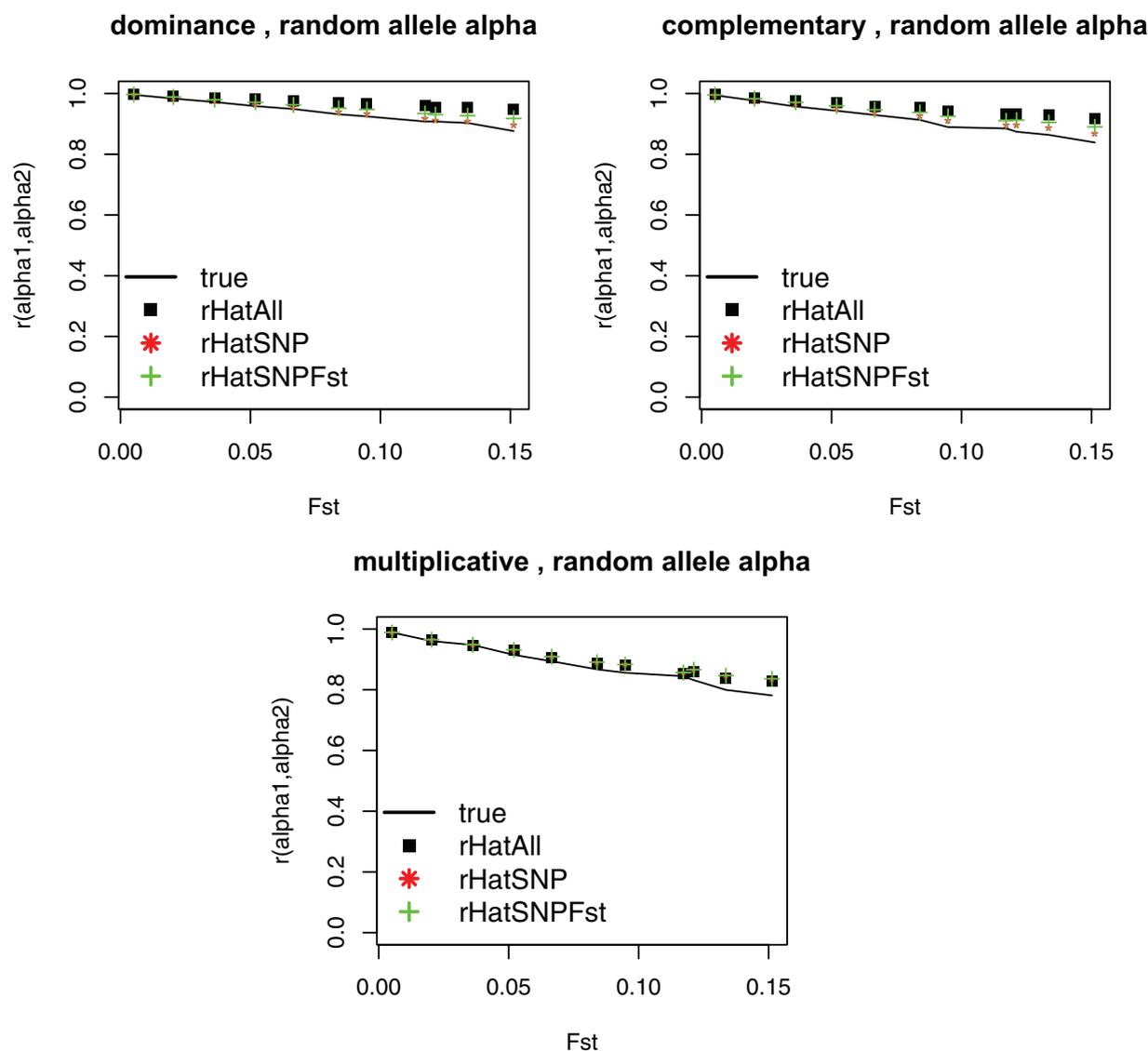
Figure 2 (for  $\alpha$  defined for mutant alleles) presents values of  $r_{\text{mutant}}(\alpha^b, \alpha^{b'})$  and estimates  $\hat{r}_{\text{all}}$ ,  $\hat{r}_{\text{SNP}}$ , and  $\hat{r}_{\text{SNPFst}}$ . Estimating  $r_{\text{mutant}}(\alpha^b, \alpha^{b'})$  is more difficult than estimating  $r_{\text{random}}(\alpha^b, \alpha^{b'})$ : depending on the scenario there is more over- or under-estimation that for  $r_{\text{random}}(\alpha^b, \alpha^{b'})$ . In this case the effect of using all polymorphisms or SNP is more marked. However, overall, we find that our estimators explain well the decay in  $r(\alpha^b, \alpha^{b'})$ . The imperfect disagreement (both in Figures 1 and 2) is probably due to several wrong assumptions; we comment some of them in the Discussion section.

## Empirical examples

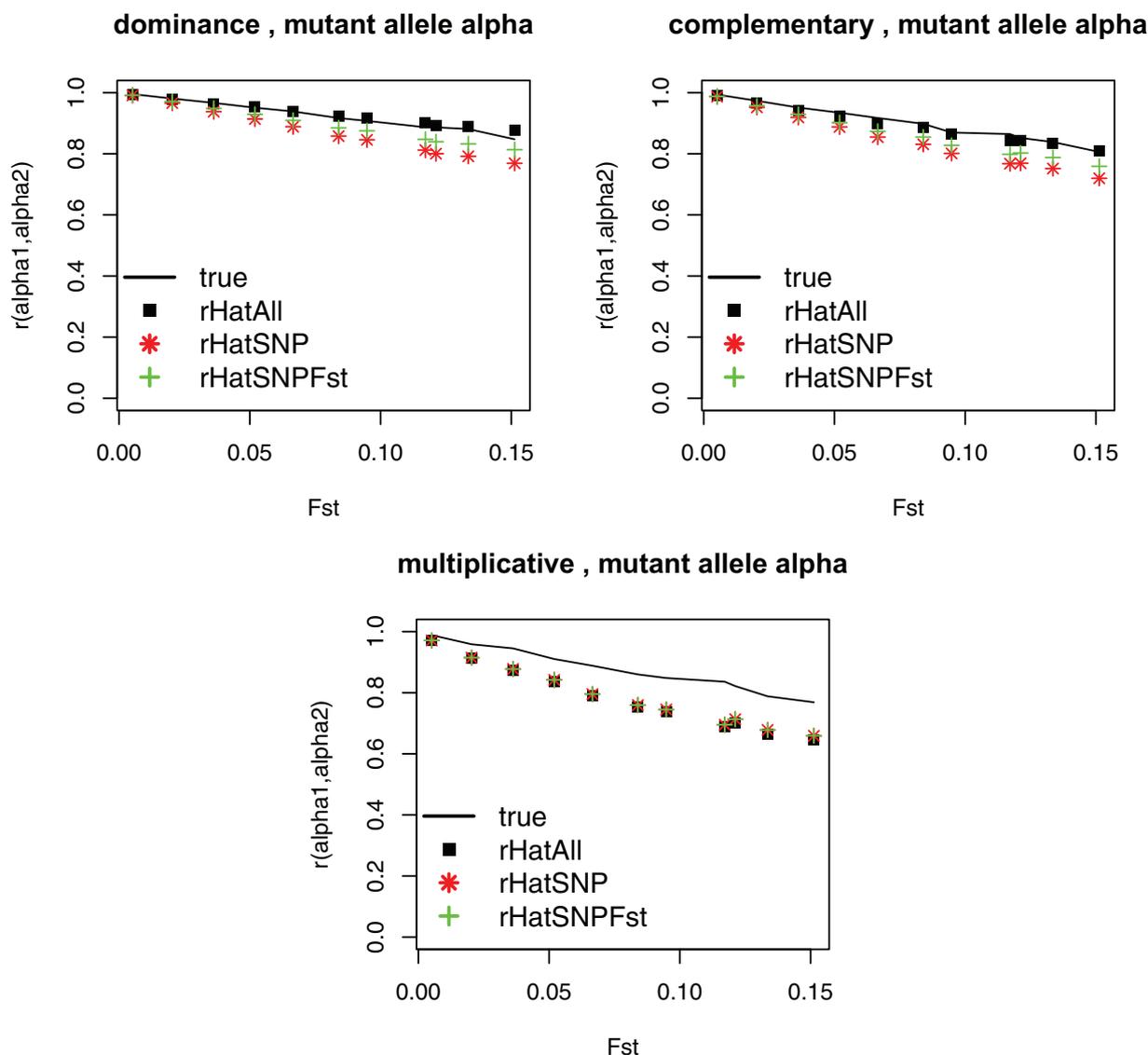
### Estimates of correlation across populations using literature values

#### Literature values used and assumptions

From values of the literature, the previous expressions, Equations (6) and (7) were applied to obtain guesses of the correlation of substitution effects across different populations and generations within population. Estimates of statistical



**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.  $r_{\text{HatAll}}$ : estimates with all polymorphism.  $r_{\text{HatSNP}}$ : estimates using SNP-like loci.  $r_{\text{HatSNPFst}}$ : 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.

nonadditive variation are scarce, as are estimates of distances across populations in terms of covariance of allele frequencies. The differentiation  $F_{ST}$  of Jersey and Holstein breeds of cattle obtained from VanRaden *et al.* (2011) is 0.06, and among Landrace and Yorkshire is 0.16 (Xiang *et al.* 2017).

Table 3 includes literature estimates for additive, dominance and epistatic variation. We used estimates for milk yield in Simmental cattle (Fuerst and Sölkner 1994) as if it was Holstein, and 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  $\sigma_{AA}^2$  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.

Then, we assumed three distributions for QTL allele frequencies, following Hill *et al.* (2008): a uniform distribution (“Uniform”), and a U-shaped distributions with  $f(p) \propto p^{-1}(1-p)^{-1}$

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

Species	$\sigma_A^2$	$\sigma_D^2$	$\sigma_{AA}^2$
Cattle	0.20	0.09	0.15
Pigs	0.092	0.020	0.016

Estimates for milk yield in cattle (Fuerst and Sölkner 1994) and litter size in pigs (Vitezica *et al.* 2018).

with effective population size of  $N_e = 50$  (“Hill”), bounded at  $\left[\frac{1}{2N_e}, 1 - \frac{1}{2N_e}\right]$ . 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,  $r(\alpha_i^b, \alpha_i^{b'})$ , using Equation (7).

Similarly, the correlation of QTL substitution effects a certain number of generations away,  $r(\alpha_i^{t_2}, \alpha_i^{t_1})$ , 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 correlation of QTL substitution effects across breeds was roughly 0.85 across both species (pigs and cattle) and all assumed distributions of gene frequencies. These numbers are higher than scarce estimates of genetic correlations in the literature: 0.4–0.8 for production traits (Karoui et al. 2012), 0.3–0.5 for milk yield (Legarra et al. 2014) and 0.6 for body condition (Porto-Neto et al. 2015), and we consider that this is because across-breeds genetic correlations also include genotype by environment interactions. It may be argued that these studies used SNPs instead of true QTLs; however, Wientjes et al. (2017) in a simulation study obtained unbiased estimates of correlation across QTLs using SNP markers for a true correlation of 0.5, and (Cuyabano et al. 2018) showed analytically that when SNP markers yield correct estimates of true relationships at QTL, estimates of genetic parameters are unbiased.

Concerning decrease of correlations across generations, results (Table 5) show a slow decrease, and this decrease is, again, not sensitive to the assumed distribution of allelic frequencies. Values in Table 5, quite close to 1, somehow disagree with few existing estimates of across-generation genetic correlations, clearly lower than 1 (Tsuruta et al. 2004; Haile-Mariam and Pryce 2015). Again, part of the literature estimates of correlation much lower than 1 is probably due to nonadditive gene action, and part due to genotype by environment interactions.

## 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 nonadditive 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 study, 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

**Table 4** Estimates of correlations of QTL effects across breeds based on values from Table 3 and Equation 7, for different distributions of QTL frequencies

Species	Uniform	Hill <sup>a</sup>	Extreme <sup>b</sup>
Cattle	0.83	0.82	0.84
Pigs	0.87	0.85	0.88

<sup>a</sup>U-shaped distribution with effective population size of 50.

<sup>b</sup>Beta(0.04, 0.04) distribution.

**Table 5** Correlation of QTL effects within breed across time, based on values from Table 3 and Equation 7, for different distributions of QTL frequencies

Species	Distance in generations	Uniform	Hill <sup>a</sup>	Extreme <sup>b</sup>
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

<sup>a</sup>U-shaped distribution with effective population size of 50.

<sup>b</sup>Beta (0.04, 0.04) distribution.

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 nonadditive architecture. At any rate, the three scenarios generated sizeable nonadditive 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  $\frac{H_b}{H_b^0}$  and  $\frac{1}{H_b}$  are weighting factors on dominance and additive by additive variances. If the allele frequencies are modelled using symmetric Beta( $a, a$ ) distributions (see Supplementary File S1, Section 1.11), these become  $\frac{H_b}{H_b^0} = \frac{1}{2^{a+1}(1 + \frac{a+2}{2a+2}(\frac{a+3}{2a+3} - 2))}$  and  $\frac{1}{H_b} = 2 + \frac{1}{a}$ . 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 than 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,  $\alpha$  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  $p \approx \sqrt{\frac{s}{u}}$  (Crow and Kimura 1970, Chapter 6). Provided that  $s$  and  $u$  are identical across populations, the allele frequency  $p$  and the substitution effect  $\alpha$  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,  $r(\alpha_i^p, \alpha_i^b)$  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.

As for the magnitudes of nonadditive variance, in most conceivable cases  $\sigma_{AA}^2$  and  $\sigma_D^2$  are of magnitudes at most like additive variances, but more often less than half (Fuerst and Sölkner 1994; Palucci et al. 2007; Hill et al. 2008; Mäki-Tanila and Hill 2014; Vitezica et al. 2018), so in practice the most limiting factor is distance across breeds. Indeed, there are very few accurate estimates of nonadditive variation although more are becoming available. We argue that then, and based also in our results, it will be possible to make theory and data-based choices on the possibilities of using predictions and GWAS results across populations.

Then, for reasonable assumptions about allele frequency distribution of QTLs, we have shown that the correlation of substitution effects across populations is typically around 0.8 or higher, which is higher than scarce estimates of genetic correlations across populations available in the literature, which range from 0.3 to 0.8 (Karoui et al. 2012; Legarra et al. 2014; Porto-Neto et al. 2015; Xiang et al. 2017) the difference being due, probably, to genotype by environment interaction. Our results seem rather robust to different distributions of allele frequencies. These values are high but not 1, which raises the question of how to conceive optimal strategies for across populations predictions (e.g., more data within breed or finer locations of causal variants across breed). This is of practical relevance, e.g., for genomic predictions in livestock improvement, but also in human genetics e.g., for the use of European-based Polygenic Risk Scores in individuals from other ancestries (Martin et al. 2019).

Similar results apply to the same populations across generations, in which case the correlation of substitution effects across generations goes from 0.99 (next 1–2 generations) to 0.80 (10 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 downward. There are several reasons for the disagreement. The most obvious one is

the inherent approximation of the Taylor series expansion. Second, splitting variances such as  $\text{Var}(\epsilon_i d_i^{*b})$  or  $\text{Var}(\epsilon'(\mathbf{xx})_i^b)$  into basic components implies either a strong assumption of multivariate normality and independence or a less strong one of “expectation and variance-independence” (Bohrstedt 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  $\epsilon_i$ , 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  $\epsilon$  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  $\alpha$  at extreme frequencies is overdominance, which is similar to our “dominance” scenario.

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

## 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 nonadditive 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

Supplementary File S1 associated with this manuscript is in <https://doi.org/10.25386/genetics.13168952>. Code and files for simulations can also be found in [https://figshare.com/articles/software/scripts\\_zip/14509956](https://figshare.com/articles/software/scripts_zip/14509956). All other results can be reproduced using equations and figures from the text.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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