Quantitative genetics theory for genomic selection and efficiency of genotypic value prediction in open-pollinated populations

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ABSTRACT: Quantitative genetics theory for genomic selection has mainly focused on additive effects. This study presents quantitative genetics theory applied to genomic selection aiming to prove that prediction of genotypic value based on thousands of single nucleotide polymorphisms (SNPs) depends on linkage disequilibrium (LD) between markers and QTLs, assuming dominance and epistasis. Based on simulated data, we provided information on dominance and genotypic value prediction accuracy, assuming mass selection in an open-pollinated population, all quantitative trait loci (QTLs) of lower effect, and reduced sample size. We show that the predictor of dominance value is proportional to the square of the LD value and to the dominance deviation for each QTL that is in LD with each marker. The weighted (by the SNP frequencies) dominance value predictor has greater accuracy than the unweighted predictor. The linear × linear, linear × quadratic, quadratic × linear, and quadratic × quadratic SNP effects are proportional to the corresponding linear combinations of epistatic effects for QTLs and the LD values. LD between two markers with a common QTL causes a bias in the prediction of epistatic values. Compared to phenotypic selection, the efficiency of genomic selection for genotypic value prediction increases as trait heritability decreases. The degree of dominance did not affect the genotypic value prediction accuracy and the approach to maximum accuracy is asymptotic with increases in SNP density. The decrease in the sample size from 500 to 200 did not markedly reduce the genotypic value prediction accuracy.

Keywords: genome-wide selection, dominance value prediction, prediction accuracy

Introduction

The statistical problem of breeding value prediction when there are a very large number of markers and few observations has been addressed thorough various genomic selection models, most of which provide similar prediction accuracy levels [De Los Campos et al., 2013; Daetwyler et al., 2013]. A current focus of genomic selection research is on fitting non-additive effects to predicting genotypic values [Wang et al., 2010; Zhao et al., 2013]. For maize, where the main objective in commercial breeding programs is to develop hybrids, predicting genotypic value is as important as predicting breeding value aimed at exploring heterosis [Technow et al., 2012; Massman et al., 2013].

Toro and Varona (2010) analyzed simulated data and concluded that the inclusion of dominance effects increased the accuracy of breeding value prediction and made it possible to obtain an extra response to selection using mate allocation techniques. Wittenburg et al. (2011) included dominance and epistasis in simulated datasets. The analyses showed that only the inclusion of dominance effects improved breeding value prediction accuracy. Using simulated data and assuming one additive and three additive-dominance models, Wellmann and Bennewitz (2012) analyzed the prediction accuracy of additive, dominance, and genotypic values. The inclusion of dominance effects increased the accuracy of genotypic value prediction by approximately 17% and the accuracy of breeding value prediction by 2%. Denis and Bouvet (2013) assessed the prediction accuracy of additive and genotypic values fitting an additive-dominance model. Including the dominance effect improved the accuracy of genotypic value prediction in the clone population but not the accuracy of additive value prediction in the breeding population.

Quantitative genetics theory including non-additive effects does not seem to have been fully developed in the context of genomic prediction [Goddard, 2009; Gianola et al., 2009; Vitezica et al., 2013]. Furthermore, efficient genome-wide prediction of the genotypic value of non-assessed single-crosses and pure lines, and of vegetative propagated plants in a recurrent breeding program, depends on the prediction accuracy of non-additive gene effects [ultimately, on the genotypic value prediction accuracy]. Thus, we presented quantitative genetics theory applied to genomic selection aiming to prove that prediction of genotypic value based on thousands of single nucleotide polymorphisms (SNPs) depends on linkage disequilibrium (LD) between markers and quantitative trait loci (QTLs), assuming dominance and epistasis. Additionally, we provided information on dominance and genotypic values prediction accuracy based on simulated data, assuming mass selection in open-pollinated populations, QTLs of lower effect, and reduced sample size.

Materials and Methods

Theory

Linkage disequilibrium measure

It was assumed that the population was a Hardy-Weinberg equilibrium population [generation –1]. It
was further assumed that B and b are the alleles of a QTL (QTL 1) and that C and c are the alleles of an SNP (SNP 1). B is the allele that increases the trait expression and let b be the allele that decreases the trait expression. Assuming linkage, the probabilities of the gametes BC, Bc, bC, and bc in the gametic pool produced by the population are, respectively:

\[
\begin{align*}
P_{BC}^{k,i} &= p_ip_k + \Delta_{bc}^{k,i} \\
P_{Bc}^{k,i} &= p_kq_i - \Delta_{bc}^{k,i} \\
P_{bC}^{k,i} &= q_ip_k - \Delta_{bc}^{k,i} \\
P_{bc}^{k,i} &= q_iq_k + \Delta_{bc}^{k,i}
\end{align*}
\]

where \(p\) is the frequency of the major allele (B or C), \(q = 1 - p\) is the frequency of the minor allele (b or c), and \(\Delta_{bc}^{k,i} = P_c^{k,i}P_{bc}^{k,i} - P_{bc}^{k,i}P_{c}^{k,i}\) is the measure of linkage disequilibrium (Kempthorne, 1957). The LD measure can also be expressed as \(\Delta_{bc}^{k,i} = \sum_{p} p_i p_k P_{BC}^{k,i} P_{Bc}^{k,i} \), where \(P_{BC}^{k,i}\) is the correlation between the values of the alleles at the two loci (one for B and C, and zero for b and c) in the gametic pool of generation –1 (Hill and Robertson, 1968).

**Genetic model**

It was assumed that E and e are the alleles of a second QTL (QTL 2), where E and e increase and decrease the trait expression, respectively. The genotypic value of an individual for the two QTLs in generation 2 (for simplicity, the superscript (0) – for generation 0 – was omitted in all parameters) is the product of the genotypes relative to QTL 1 and SNP 2. The parametric values of the regression coefficients in a whole-genome analysis are derived by regression analysis that relates the genotypic value (G) conditional on the SNP genotype to the number of copies of one allele of each SNP. The additive-dominance with epistasis model is:

\[
G = \beta_1 + \beta_2 b + \beta_3 c + \beta_4 bc + \beta_{12} b c + \beta_{13} b c + \beta_{23} b c + \beta_{123} b c + \text{error}
\]

where \(x_1\) and \(x_2\) are the numbers of copies of one allele of each SNP. The model can be expressed as \(y_{(81 \times 1)} = X_{(81 \times 9)} \beta + \text{error}\), where \(y\) is the vector of the genotypic values conditional on the SNP genotypes, \(X\) is the incidence matrix, and \(\beta\) is the parameter vector. Notice that assuming biallelic QTLs, there are 3 \times 3 \times 3 \times 81 = 81 genotypes for QTLs and markers (for example, BbCCeeFf). Because the genotypes have different probabilities, we defined the matrix of genotype probabilities as \(P_{(81 \times 81)}\) (for example, BBbCCceEF). Because the genotypes have different probabilities, we defined the matrix of genotype probabilities as \(P_{(81 \times 81)} = \text{diagonal} \{f_{i,j}^{\alpha,\beta}\} \), where \(f_{i,j}^{\alpha,\beta}\) is the probability of the individual with \(i\) and \(j\) copies of allele B of the QTL 1 and allele C of the SNP 1, and \(f_{i,j}^{\alpha,\beta}\) is the probability of the individual with \(k\) and \(l\) copies of allele E of the QTL 2 and allele F of the SNP 2 (i, j, k, l = 2, 1, or 0).

The genotype probabilities relative to QTL 1 and SNP 1 in generation 0 are (for simplicity, the superscript (0) – for generation 0 – was omitted in all parameters that depend on the LD measure of generation –1):

\[
\begin{align*}
f_{22} &= p_r^2 q_r^2 + 2p_rq_r\Delta_{bc}^{\alpha,\beta} + \left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{21} &= 2p_r^2 q_r q_i + 2p_r(1 - q_r)\Delta_{bc}^{\alpha,\beta} + 2\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{20} &= p_r^2 q_i^2 - 2p_rq_i\Delta_{bc}^{\alpha,\beta} + \left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{12} &= 2p_rq_r^2 q_i^2 + 2(1 - q_r)p_i\Delta_{bc}^{\alpha,\beta} + 2\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{11} &= f_{11} + f_{10} = 4p_rq_r q_i^2 + 2(1 - q_r)(1 - p_i)\Delta_{bc}^{\alpha,\beta} + 4\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{10} &= 2p_rq_r p_i^2 + 2q_i(1 - p_i)\Delta_{bc}^{\alpha,\beta} - 2\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{00} &= q_r^2 p_r^2 + 2q_i(1 - p_i)\Delta_{bc}^{\alpha,\beta} + \left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{11} &= f_{11} + f_{10} = 4p_rq_r q_i^2 + 2(1 - q_r)(1 - p_i)\Delta_{bc}^{\alpha,\beta} + 4\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{10} &= 2p_rq_r p_i^2 + 2q_i(1 - p_i)\Delta_{bc}^{\alpha,\beta} - 2\left[\Delta_{bc}^{\alpha,\beta}\right]^2 \\
f_{00} &= q_r^2 p_r^2 + 2q_i(1 - p_i)\Delta_{bc}^{\alpha,\beta} + \left[\Delta_{bc}^{\alpha,\beta}\right]^2
\end{align*}
\]
where the indices g and n identify the double heterozygotes in coupling and repulsion phases.

Thus, for the complete model or a reduced model, $\beta = \{X'X\}^{-1}X'Y$ and $R(.) = \beta'X'Y$, where $R(.)$ is the reduction in the total sum of squares due to fitting the model. Finally, after fitting the complete model and eight reduced models, and assuming the same restrictions of Kempthorne [1954], it can be demonstrated that:

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \epsilon$, the reduced model 1)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta + \epsilon$, the reduced model 2)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{1}} + e$, the reduced model 3)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \epsilon$, the reduced model 4)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \epsilon$, the reduced model 5)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \epsilon$, the reduced model 6)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \epsilon$, the reduced model 7)

$$\beta = \frac{\Delta^{-1} \cdot \alpha_{s}}{p_{s}q_{s}}$$ (fitting $G = \beta + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \beta_{x_{2}} + \beta_{x_{1}} + \epsilon$, the reduced model 8)

The alternative model below has been fitted for genomic prediction including dominance and epistatic effects:

$$G = \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \beta_{x_{1}} + \epsilon$$

where $x_{1}, x_{2}, x_{3} = 1, 0, or -1$ if the individual is homozygous for an SNP allele (C or F), heterozygous, or homozygous for the other SNP allele (c or f), respectively, and $x_{1}, x_{2} = 0$ or 1 if the individual is homozygous or heterozygous, respectively. Using the same procedure described, it can be demonstrated that the only differences relative to the previous model is that $\beta_{x_{1}} = d_{SNP}$, $\beta_{x_{1}} = d_{SNP}$, $\beta_{x_{2}} = -[d_{SNP}]_{SNP}$, and $\beta_{x_{2}} = -[d_{SNP}]_{SNP}$. Thus, both models are equivalent. Notice that for this second model, the individual SNP genotypic values are defined as $G_{CC} = m_{C} + \alpha_{C} + \delta_{C}$, $G_{CC} = m_{C} + \delta_{C}$ and $G_{CC} = m_{C} - \alpha_{C}$, where the SNP parameters are $m_C = M + \alpha_{C}$, $m_C = m_{C} + \delta_{C}$, and $G_{CC} = m_{C} - \alpha_{C}$. The SNP parameters are the epistatic effects for the SNP 2 and no QTL in LD with SNP 2.

**SNP effects and variances**

The parameters $M$, $\alpha_{SNP}$, and $d_{SNP}$ are the population mean, the average effect of a SNP substitution, and the dominance deviation at a SNP locus, respectively. The other parameters are the epistatic effects for the SNPs. Notice the relationship between marker effect and marker frequency, LD value, and average effect of QTL substitution, QTL dominance deviation, or QTL epistatic effects. As highlighted by Cockerham [1954], unless all linear combinations of epistatic effects (aa, ad, da, and dd) are zero, there is epistasis between the QTLs. Importantly, these linear combinations of epistatic effects are equivalent to the linear combinations of genotypic values presented by Cockerham [1954] and Viana [2004b].

Thus, a whole-genome analysis provides the population mean, the average effects of SNP substitution, the SNP dominance deviations, and the SNP epistatic effects. The SNP additive, dominance, and epistatic variances are the sums of squares of the linear, quadratic, linear × linear, linear × quadratic, quadratic × linear, and quadratic × quadratic effects, respectively, as demonstrated below:

$$R(\beta_{x_{1}}) = 2p_{x_{1}}q_{x_{1}}d_{SNP}^{2} = \sigma_{d}^{2}(SNP)$$

$$R(\beta_{x_{1}}) = 4p_{x_{1}}q_{x_{1}}d_{SNP}^{2} = \sigma_{d}^{2}(SNP)$$

$$R(\beta_{x_{1}}) = 2p_{x_{1}}q_{x_{1}}d_{SNP}^{2} = \sigma_{d}^{2}(SNP)$$
\[
R(\beta_i, \beta_j, \beta_k, \beta_l, \beta_m, \beta_n) = 4pq^2p_3q_3k_{2}^{-1}(a_a)=\sigma_{\text{AQNPSNP}_i}\n\]
\[
R(\beta_i, \beta_j, \beta_k, \beta_l, \beta_m, \beta_n) = 2pq^2p_3q_3k_{2}^{-1}(a_a)=\sigma_{\text{AQNPSNP}_i}\n\]
\[
R(\beta_i, \beta_j, \beta_k, \beta_l, \beta_m, \beta_n) = 2pq^2p_3q_3k_{2}^{-1}(a_a)=\sigma_{\text{AQNPSNP}_i}\n\]
\[
R(\beta_i, \beta_j, \beta_k, \beta_l, \beta_m, \beta_n) = p_i^2p_j^2q_k^2q_l^2k_{2}^{-1}(a_a)=\sigma_{\text{AQNPSNP}_i}\n\]

where \(R_i\) is a difference between two nested \(R_i\) terms with the effect(s) common to both models after the vertical bar, \(\sigma_{\text{AQNPSNP}_i}\) is the SNP additive variance, \(\sigma_{\text{AQNPSNP}_i}\) is the SNP dominance variance, and \(\sigma_{\text{AQNPSNP}_i}\) are the epistatic variances for the SNPs.

**Extension for two QTLs in LD with a SNP**

Assume now one SNP [SNP 1; alleles C/c] in LD with two QTLs [QTL 1 and QTL 2; alleles B/b and E/e], a second SNP [SNP 2; alleles F/f] in LD with a third QTL [QTL 3; alleles H/h], and (for simplicity) that SNP 1 and QTLs 1 and 2 are in linkage equilibrium in relation to SNP 2 and QTL 3. Using the same procedure previously described, it can be demonstrated that:

\[\beta = M = \frac{\Delta^2}{pq}\]
\[\beta = \frac{\Delta^2}{pq} + \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq}\]
\[\beta = \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq}\]
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\[\beta = \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq} = \frac{\Delta^2}{pq}\]

**Relationship between SNP dominance value and QTL dominance value**

Assuming a SNP and a QTL in LD, the dominance values relative to the SNP are proportional to the dominance values relative to the QTL, as shown below for SNP 1 and QTL 1:

\[D_{1C} = (q, r)_{1}^{2} k_{2} \cdot d_{1a} = - (q, r)_{1}^{2} = k_{2} \cdot d_{1a}\]
\[D_{1C} = - (q, r)_{1}^{2} k_{2} \cdot d_{1a} = -(q, r)_{1}^{2} = k_{2} \cdot d_{1a}\]
\[D_{1C} = (q, r)_{1}^{2} k_{2} \cdot d_{1a} = -(q, r)_{1}^{2} = k_{2} \cdot d_{1a}\]
\[D_{1C} = (q, r)_{1}^{2} k_{2} \cdot d_{1a} = -(q, r)_{1}^{2} = k_{2} \cdot d_{1a}\]

where the SNP dominance values are \(D_{1C} = -2q_{1}d_{1a}\), \(D_{1C} = -2q_{1}d_{1a}\), and \(D_{1C} = -2q_{1}d_{1a}\), and \(D_{1C} = -2q_{1}d_{1a}\), and \(D_{1C} = -2q_{1}d_{1a}\).

**Accuracy of dominance value prediction**

Based on the previous results, a predictor of the QTL dominance value is the SNP dominance value, i.e., \(D_{\text{QTL}} = D_{\text{SNP}} = u_{i}d_{i}\) (equation 3), where \(u_{i} = -2q_{i}\) for SNP genotype CC, \(u_{i} = 2p_{i}q_{i}\) for Cc, or \(u_{i} = -2p_{i}\) for cc. However, the predictor that has been used in most of the whole-genome analysis of field and simulated data for predicting genotypic value is \(D_{\text{QTL}} = u_{i}d_{i}\), where \(u_{i} = 0\) for SNP genotype CC, \(u_{i} = 1\) for Cc, or \(u_{i} = 0\) for cc. These predictors have the same covariance with the dominance value for the QTL, given by:

\[\text{Cov}(D_{\text{SNP}}, D_{\text{QTL}}) = f_{i}(-2q_{i}d_{i}) + f_{i}(2p_{i}q_{i}d_{i}) + f_{i}(-2p_{i}d_{i}) - 0 = 4p_{i}q_{i}d_{i} = \sigma_{\text{SNP}}^{2}\]

Thus, the predictor of greater accuracy [lower variance] is \(D_{\text{QTL}}\). The predictors \(D_{\text{QTL}}\) and \(D_{\text{QTL}}\) have the same accuracy when the SNP allelic frequencies are equal [because (1/2pq)q = 1]. The accuracy (correlation between the dominance value for the QTL and the value predicted by the SNP) of predictor 1 is:

\[\rho_{\text{QTL}, D_{\text{SNP}}} = \frac{\sigma_{\text{SNP}}^{2}}{\sqrt{\sigma_{\text{SNP}}^{2}\sigma_{\text{QTL}}^{2}}}\]

where \(\sigma_{\text{SNP}}^{2}\) is the QTL 1 dominance variance.

**Dominance value predictor**

Generalizing, the dominance genetic value relative to k QTLs predicted by s SNPs is \(D_{k} = \sum_{i=1}^{s} u_{i}d_{i}\). The accuracy of predictor 1 is:

\[\rho_{\text{QTL}, D_{\text{SNP}}} = \frac{\sum_{i=1}^{s} \sigma_{\text{SNP}}^{2}}{\sqrt{\sum_{i=1}^{s} \sigma_{\text{SNP}}^{2}}}\]

where \(\sigma_{\text{SNP}}^{2} = 4p_{i}q_{i}d_{i}^{2}\) is the dominance variance for the SNP \(r_{i}\).
is the SNP dominance deviation \( |k'| \) is the number of QTLs in LD with the SNP \( r \),
\[
\sigma_D^2 = 4 \sum_{i=1}^{k} p_i^2 q_i^2 d_i^2 + 8 \sum_{i<j=1}^{k-1} \sum_{c=1}^{k} \left[ \Delta_{c}^{(i-j)} \right]^2 d_i d_j
\]
[Viana, 2004a] is the dominance variance, and
\[
\sigma_D^{2 \text{SNP}} = 4 \sum_{i=1}^{k} p_i^2 q_i^2 d_i^2 + 8 \sum_{i<j=1}^{k-1} \sum_{r=1}^{k-1} \sum_{t=r+1}^{k} \left[ \Delta_{r}^{(i-j)} \right]^2 d_{SNP,r} d_{SNP,t}
\]
[Viana, 2004a] is the variance of the dominance value predictor (dominance genomic value variance).

The best genotypic value predictor is \( \tilde{G} = M + A + D \) (assuming absence of epistasis), where \( M \) is the estimator of the population mean and \( A \) is the predictor of the breeding value.

**Prediction of epistatic values**

Based on the previous simplified additive-dominance with epistasis model (QTL 1 and SNP 1 in LD, QTL 2 and SNP 2 in LD, and QTL 1 and SNP 1 in linkage equilibrium relative to QTL 2 and SNP 2), we assessed the prediction accuracy of the additive \times additive epistatic value for a predictor based on Kempthorne [1954], given by:
\[
AA = AA_{\text{Sn}}, \alpha_a + \alpha_a \alpha_s + \alpha_a \alpha_t + \alpha_t \alpha_s
\]
where \( AA \) is the additive \times additive genetic value predictor of the individual with SNP genotype rsstu, \( r \) and \( s \) are the alleles for the first SNP, \( t \) and \( u \) are the alleles for the second SNP, and \( A_{\text{Sn}} \) is the additive \times additive value for the SNPs. The SNP additive \times additive effect is:
\[
\alpha_a = -\alpha_{rs} - \alpha_{st} - \alpha_{tu} + \alpha
\]
where \( \alpha_{rs} \) is the mean of the individuals with alleles \( r \) and \( s \), \( \alpha_{st} \) the mean of the individuals with allele \( r \), \( \alpha_{tu} \), the mean of the individuals with allele \( t \), and \( \alpha \) is the population mean.

Assuming distance SNP 1 - QTL 1 = 0.0002 cM, distance SNP 2 - QTL 2 = 0.0002 cM, \( p_r = 0.4662, p_s = 0.6241, p_t = 0.4914, p_u = 0.4460, a_s = 0.6672, a_t = 0.6435 \), degree of dominance = 1.0000, and duplicate recessive epistasis [complementary gene action], we have that \( \Delta_{rs} = 0.1154, \Delta_{st} = 0.1273, a_{\text{SNP}} = 0.3502, a_{\text{SNP}} = 0.3374, d_{\text{SNP}} = 0.1613, d_{\text{SNP}} = 0.1709, [\alpha_a]_{\text{SNP,SNP}} = 0.1238, [\alpha_a]_{\text{SNP,SNP}} = -0.0627, [\alpha_{rs}]_{\text{SNP,SNP}} = -0.0570, \) and \( [\delta_a]_{\text{SNP,SNP}} = 0.0289 \). The accuracy of the additive \times additive genetic value was 0.2232. This accuracy corresponds to the correlation between the SNP additive \times additive values [nine values, computed based on Kempthorne [1954]] and the QTL additive \times additive values [nine parametric values, computed from Kempthorne [1954]]. Thus, we correlated 81 values, weighted by the genotype probabilities.

The predictors of the additive \times dominance, dominance \times additive, and dominance \times dominance epistatic values can also be defined based on Kempthorne (1954). Thus,
\[
AD = AD_{\text{Sn}} = \alpha, \delta_a + \alpha, \delta_a
\]
\[
DD = DD_{\text{Sn}} = \delta_a, \delta_a
\]
where:
\[
\delta_a = \delta_{rs} + \delta_{st} - \delta_{tu} + \delta
\]
\[
\delta_{rs} = G_{rs} - (a_r + a_s) - (a_r + a_s) - \delta_{rs}
\]
\[
\delta_{st} = G_{st} - (a_s + a_t) - (a_s + a_t) - \delta_{st}
\]
\[
\alpha_a = G_{rs} - G_{st} + G_{tu} - G
\]
\[
\delta_{rs} = G_{rs} - G_{st} - G_{tu} + G
\]

Based on the estimated prediction accuracies of additive, dominance, and epistatic values on this simplified scenario, we can state that genomic prediction of epistatic values should be less accurate than genomic prediction of dominance and additive values. However, because the prediction accuracies of dominance and epistatic values are positive, inclusion of non-additive effects should increase the prediction accuracy of genotypic value in an inbred population (because the genetic values are not independent).

**Bias in the prediction of epistatic values**

The additive-dominance with epistasis model for genomic selection has a limitation for predicting epistatic values based on markers, owing to LD being between a QTL and two or more markers. That is, the linear \times linear, linear \times quadratic, quadratic \times linear, and quadratic \times quadratic effects and variances are not necessarily nil in the absence of epistasis. Assuming a QTL [alleles B/b] in LD with two SNPs [alleles C/c and E/e], distance SNP 1 - QTL 1 = 0.0002 cM, distance QTL 2 - SNP 2 = 0.0003 cM, complete interference, \( p_r = 0.4073, p_s = 0.4960, p_r = 0.4115, a_s = 4.5 \) and degree of dominance = -0.9958, we have that \( \Delta_{bc} = -0.0495, \Delta_{bc} = -0.0801, \Delta_{bc} = -0.0786, a_{\text{SNP}} = -0.9153, a_{\text{SNP}} = -1.4764, d_{\text{SNP}} = -0.1884, d_{\text{SNP}} = -0.4902 \), and \( [\alpha_{rs}]_{\text{SNP,SNP}} = 0.5155 \).

**Simulation**

The data set was simulated using the REALbreed program [available on request], which is under development by the first author using the REALbasic software. A total of 5000 SNPs and 100 QTLs were distributed on 10 chromosomes with 500 SNPs and 10 QTLs per chromosome, covering 50 cM on average (density of one SNP each 0.1 cM on average). The QTLs were distributed in the regions covered by markers. Next, the software simulated a Hardy-Weinberg equilibrium population with LD. This population was a composite, generated by crossing two populations in linkage equilibrium followed by a generation of random crosses. The number of plants was 500 (effective population size of 1000).
Finally, based on user input, the software computed all genetic parameters and LD values between QTLs. The input information includes minimum and maximum genotypic values for homozygotes (allowing for computation of the parameter $a$ for each QTL), degree of dominance ($d/a$), direction of dominance, and the broad sense heritability. The REALbreeding program saves two main files, one with the marker genotypes and the other with the additive, dominance, and phenotypic values (the current version does not compute epistatic values). The true additive and dominance genetic values and variances are computed from the population gene frequencies (random values), LD values, average effects of gene substitution, and dominance deviations. The phenotypic values are computed from the true population mean, additive and dominance variances, and from error effects sampled from a normal distribution. The error variance is computed from the broad sense heritability. The LD in a composite is

$$
\Delta^{\text{LD}} = \left(1 - \frac{2\theta_d}{4}\right)(p_a - p_d)(p_a - p_d),
$$

where $\theta_d$ is the frequency of recombinant gametes and the indices 1 and 2 refer to the gene frequencies ($p$) in the parental populations.

We considered two popcorn traits, three SNP densities, two heritabilities, two sample sizes, and two populations showing LD, totaling 48 scenarios. For each scenario, 50 simulations were carried out. The minimum and maximum genotypic values of homozygotes for grain yield and expansion volume were 20 and 200 g per plant, and 5 and 50 mL g$^{-1}$. Positive unidirectional dominance [$0 < (d/a) \leq 1.2$] was assumed for grain yield and bidirectional dominance [$-1.2 \leq (d/a) \leq 1.2$] was assumed for expansion volume ($i = 1, 2, \ldots, 100$). The other SNP densities, one marker every cM and one marker every 10 cM on average, were obtained by random choices of 51 and 6 SNPs by chromosome, respectively, also using the REALbreeding software. The broad sense heritabilities were 0.3 and 0.7. Thus, the accuracies of the phenotypic values were 0.548 and 0.837. The sample size was 500 or 200 individuals genotyped and phenotyped. The second population with LD was obtained from the composite (generation 0) after five generations of random crosses (generation 5).

Regarding the SNPs, the averages of the absolute LD values (the difference between gametic frequencies observed and expected under linkage equilibrium) in the LD blocks in generation 0, were 0.0978, 0.1073, and 0.1413 for the densities 10, 1, and 0.1 cM, respectively. The values for generation 5 were 0.0581, 0.0565, and 0.1413 for the densities 10, 1, and 0.1 cM, respectively. The LD blocks were defined based on an LOD (logarithm [base 10] of odds) score of 3 (to declare LD for two linked SNPs), also using the REALbreeding software. The corresponding $r^2$ (the square of the correlation coefficient between the alleles of two loci) values were 0.1785, 0.2089, and 0.4079 for generation 0, and 0.0843, 0.0829, and 0.2420 for generation 5. All data used in this paper are accessible on request.

### Statistical analysis of the simulated data

The method used for genomic selection was RR-BLUP (ridge regression best linear unbiased prediction). For the analyses we used the $rrBLUP$ (Endelman, 2011). The accuracies of dominance and genotypic value prediction were obtained by the correlation between the true values computed by REALbreeding and the values predicted by RR-BLUP.

### Results

#### Theoretical results

We show that the predictor of dominance value is proportional to the square of the LD value and to the dominance deviation for each QTL that is in LD with each marker (see $\hat{D}^2$ and $d_{\text{error}}$). The dominance value predictor of greater accuracy [lower variance] is that weighted by the SNP frequencies [compare the variances of $\hat{D}^2$ and $\hat{D}^3$]. The linear × linear, linear × quadratic, quadratic × linear, and quadratic × quadratic SNP effects are proportional to the corresponding linear combinations of epistatic effects for QTLs and the LD values between SNPs and QTLs [see regression coefficients $\beta_3, \beta_4, \beta_5, \beta_6$]. Linkage disequilibrium between two SNPs with a common QTL results in a bias in the prediction of epistatic values. The SNP epistatic values are proportional to the corresponding epistatic genetic values.

#### Simulation results

Regardless of generation, sample size, SNP density, and heritability, the prediction accuracy of the dominance genetic value was, with one exception, higher for grain yield, indicating that the prediction is less accurate when dominance is bidirectional (Table 1). The ratio between the accuracies of grain yield and expansion volume ranged from 1.0 to 3.1, with the ratio being inversely proportional to heritability. Regardless of the other factors, the accuracy of dominance value prediction was proportional to the SNP density. On average, the increase from 1 SNP every 10 cM to 1 SNP every cM and from 1 SNP every cM to 1 SNP every 0.1 cM determined increments in the accuracy of 114 and 46 %, respectively. The increments were higher for grain yield under high heritability. The decrease in sample size from 500 to 200 caused a decrease in dominance value prediction accuracy, regardless of the other factors, although the decreases were of reduced magnitude. The average decreases ranged from 1 to 12 % and were also inversely proportional to the heritability. The decrease in LD with five generations of random mating also caused a decrease, generally of low magnitude, in dominance value prediction accuracy that is inversely proportional to the SNP density and heritability. The average decreases ranged from 0 to 51 %. For the two traits and regardless of the other factors, increasing heritability led to an increase in dominance value prediction accuracy, ranging from 16 to 100 %.
The degree of dominance did not affect genotypic value prediction accuracy and the approach to maximum accuracy is asymptotic with the increase in SNP density (Table 2). The ratio between the accuracies of the traits ranged from 1.0 to 1.1 and, in general, an increase of relevant magnitude occurred only in genotypic value prediction accuracy when increasing the density from 1 SNP every 10 cM to 1 SNP every cM (49 % on average). The average increase in accuracy when increasing the density from 1 SNP every cM to 1 SNP every 0.1 cM was 9 % (maximum of 16 %). Reducing the sample size from 500 to 200 did not affect the magnitude of the accuracy of genotypic value prediction, with a maximum decrease in magnitude of 4 %. Also the decrease in LD after 5 generations of random mating also did not considerably decrease genotypic value prediction accuracy, regardless of the other factors. The decreases ranged from 0 to 26 %. Also, regardless of generation, sample size, SNP density, and trait, the accuracy of genotypic value prediction was proportional to heritability. The increases ranged from 11 to 44 %.

Assuming absence of epistasis, the accuracy of breeding value prediction by fitting the additive, additive-dominance and additive-dominance with additive × additive epistasis models were equivalent, regardless of heritability and SNP density (Table 3). The same was found for the accuracy of dominance value prediction by fitting the additive-dominance and additive-dominance with additive × additive epistasis models.

**Discussion**

The prediction of breeding values based on markers is relevant to both animal and plant population improvement. The selection of couples in animal breeding [Toro and Varona, 2010], of clones in forestry breeding [Denis and Bouvet, 2013], and of hybrids in annual crop breeding [Zhao et al., 2013] are examples.
of the relevance of predicting genotypic value based on markers in animal and plant breeding. Zeng et al. (2013) concluded that genomic selection based on the dominance model maximized the cumulative response to selection of purebred animals for crossbred performance. Comparing genomic selection and pedigree-based BLUP by assuming dominance gene action, Denis and Bouvet (2013) observed that genomic selection provided higher gain per unit time for a clone population, mainly in the first selection cycle. Massman et al. (2013) also compared genomic selection and pedigree-based BLUP for prediction of maize single-cross performance for grain yield and other traits. They observed high accuracy in the genome-wide predictions, but the accuracy was inferior to those obtained with pedigree-based BLUP.

Although our simulation study revealed lower accuracy of dominance value prediction with bidirectional dominance, relative to unidirectional dominance, genotypic value prediction follows the same rules governing the breeding value prediction. Under high SNP density [at least 1 SNP every cM], the accuracy of additive and genotypic value predictions are equivalent, regardless of the degree of dominance. As already established for genomic selection based on breeding value prediction, in relation to phenotypic selection, the efficiency of genomic selection based on genotypic value prediction is inversely proportional to heritability. Assuming high SNP density and low heritability, genomic selection is at least as efficient as phenotypic selection. Maximum efficiency can reach 27 %. With regard to traits with high heritability, the efficiency of genomic selection is also high, reaching at least 90 % of phenotypic selection efficiency.

Our results showed as expected because the population analyzed was not inbred (i.e., additive, dominant and epistatic genetic values are independent), that the accuracy of breeding value prediction is equivalent when fitting the additive, additive-dominance, and additive-dominance with epistasis models. It is noteworthy that in our study, in the absence of epistasis and under high SNP density, fitting additive × additive epistatic effects in relation to SNPs led to an increase in the accuracy of genotypic value prediction. Concerning the fitting of the additive-dominance with the epistasis model, several results evidenced an increase in breeding value prediction accuracy with the inclusion of the dominance [Wellmann and Bennewitz, 2012; Technow et al., 2012] and epistatic [Dudley and Johnson, 2009; Long et al., 2010; Wittenburg et al., 2011; Hu et al., 2011; Wang et al., 2012; Su et al., 2012] effects. Carlberg and Haley (2004) emphasized the importance of fitting epistatic effects in complex trait studies. In some genome-wide analyses the proportion of the phenotypic variance explained by epistatic effects ranged from 6 to 83 % [Xu, 2007; Wang et al., 2010, 2012]. Interestingly, Xu and Jia (2007) found that whether two markers interact does not depend on whether the loci have individual main effects.

A criticism of the RR-BLUP method is one variance for the additive, dominance and epistatic effects for the SNPs. However the accuracy of additive and genotypic value prediction with the use of the RR-BLUP method based on the likelihood approach is in full agreement with the accuracy obtained with penalized regression and Bayesian methods. Thus, our results showed that RR-BLUP is a suitable method for genomic selection because it provides at least the same accuracy level of phenotypic selection for traits of low heritability, or at least a slightly lower accuracy level than that of phenotypic selection for traits of high heritability. Using simulated and empirical datasets, Sun et al. (2012) compared the non-parametric methods RKHS (reproducing kernel Hilbert spaces) and pRKHS (which combine supervised principal component analysis and RKHS regression), with RR-BLUP, BayesA and BayesB. Assuming no, low and high epistasis, the non-parametric methods were superior to the other methods in terms of accuracy of additive and genotypic values prediction. Zhao et al. (2013) used RR-BLUP, BayesA, BayesB, BayesC and BayesCt to analyze wheat and simulated data assuming the additive with dominance model. The cross validation approach showed slight superiority of RR-BLUP and BayesB regarding the accuracy of predicting the hybrid performance. Interestingly, ignoring dominance effects resulted in equal or even higher prediction accuracies.

Table 3 – Accuracy of additive (A), dominance (D), and genotypic (G) values by fitting the additive-dominance (AD) model and the additive-dominance with additive × additive epistasis (ADE) model, assuming no epistasis, generation 0, two accuracy levels of the phenotypic value, two SNP (single nucleotide polymorphisms) densities, and 500 individuals.

<table>
<thead>
<tr>
<th>Model</th>
<th>Value</th>
<th>SNP density (cM)</th>
<th>Accuracy of the phenotypic value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Expansion volume</td>
<td>Grain yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>A</td>
<td>10</td>
<td>0.598 ± 0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>0.693 ± 0.03</td>
</tr>
<tr>
<td>ADE</td>
<td>A</td>
<td>10</td>
<td>0.599 ± 0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>0.696 ± 0.03</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>0.089 ± 0.06</td>
<td>0.207 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.175 ± 0.08</td>
<td>0.548 ± 0.07</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>0.446 ± 0.04</td>
<td>0.421 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.676 ± 0.03</td>
<td>0.666 ± 0.04</td>
</tr>
</tbody>
</table>

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As final comments, it is important to highlight the contribution of the theory presented and the relevance of the assessment of genomic prediction of dominance and genotypic values in breeding populations of open-pollinated crops. Since the advent of genomic selection (Meuwissen et al., 2001) some theoretical aspects have been presented (Goddard, 2009; Gianola et al., 2009; Vitezica et al., 2013). However, the theory presented in this paper gives proofs of genomic selection efficacy that have not been fully presented in the previously mentioned relevant papers. Furthermore, based on a simplified scenario including digenic epistasis and in simulated data, we can state that although prediction accuracy of additive value has greater magnitude than the prediction accuracy of dominance and epistatic values, breeders should expect that genome-wide prediction of genotypic value would be as successful as genomic prediction of breeding value, conditional on the choice of adequate SNP density, sample size, and genomic model. Finally, we demonstrated that genomic selection can be successfully applied in recurrent breeding programs for open-pollinated crops, without training population and validation process.

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