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ORIGINAL ARTICLE

Novel strategies for genomic prediction of untested single-cross maize hybrids using unbalanced historical data

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Abstract

Key message **Weighted outperformed unweighted genomic prediction using an unbalanced dataset representative of a commercial breeding program. Moreover, the use of the two cycles preceding predictions as training set achieved optimal prediction ability.**

Abstract Predicting the performance of untested single-cross hybrids through genomic prediction (GP) is highly desirable to increase genetic gain. Here, we evaluate the predictive ability (PA) of novel genomic strategies to predict single-cross maize hybrids using an unbalanced historical dataset of a tropical breeding program. Field data comprised 949 single-cross hybrids evaluated from 2006 to 2013, representing eight breeding cycles. Hybrid genotypes were inferred based on their parents' genotypes (inbred lines) using single-nucleotide polymorphism markers obtained via genotyping-by-sequencing. GP analyses were fitted using genomic best linear unbiased prediction via a stage-wise approach, considering two distinct cross-validation schemes. Results highlight the importance of taking into account the uncertainty regarding the adjusted means at each step of a stage-wise analysis, due to the highly unbalanced data structure and the expected heterogeneity of variances across years and locations of a commercial breeding program. Further, an increase in the size of the training set was not always advantageous even in the same breeding program. The use of the two cycles preceding predictions achieved optimal PA of untested single-cross hybrids in a forward prediction scenario, which could be used to replace the first step of field screening. Finally, in addition to the practical and theoretical results applied to maize hybrid breeding programs, the stage-wise analysis performed in this study may be applied to any crop historical unbalanced data.

Introduction

Single-cross hybrids (Shull 1908) have been widely used to explore heterosis in selfing and outcrossing species. In order to explore the benefits of heterosis in maize (*Zea mays* L.), single-cross hybrids are obtained by crossing inbred lines from genetically distinct heterotic groups (e.g., Dent × Flint). Therefore, the challenge faced by breeders is to find a promising combination among many possible single-cross hybrids between pairs of inbred lines (Bernardo 1994; Schrag et al. 2010). Because it is unfeasible to obtain and to evaluate all possible pairwise inbred combinations, predicting the performance of untested single-cross hybrids prior to field trials is highly desirable.

Early prediction of single-cross hybrids based on inbred line per se performance (Smith 1986) or using genetic diversity between parents had very poor predictive accuracy for complex traits due to dominance effects and to dependence on the germplasm source (Charcosset et al. 1991; Garcia et al. 2004). Hybrid prediction based on best linear unbiased prediction (BLUP) has boosted PA and has become a benchmark in hybrid breeding. BLUP predictions make use of the covariance between untested and tested hybrids estimated either from pedigree or molecular markers (Bernardo 1994;

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Piepho 2009). Some advantages of the BLUP approach are as follows: (1) computational efficiency and flexibility to be extended to complex scenarios (Piepho 2009; Crossa et al. 2017), (2) connectivity with quantitative genetics theory (Gianola et al. 2009; Vitezica et al. 2013) and (3) straightforward genetic interpretation (de los Campos et al. 2013).

Genomic prediction (GP) was initially proposed as a marker-based strategy to predict yet-to-be-seen genetic responses for quantitative traits, based on regressing phenotypes on all marker information simultaneously (Meuwissen et al. 2001). Thus, increased genetic gain is expected by using GP, once it is possible to perform selection in early breeding stages, reducing the number of field-tested hybrids and breeding cycles. In addition, given the availability of high density markers, it is expected that each quantitative trait locus (QTL) is linked with at least one marker, such that under the assumption of Fisher's infinitesimal model this approach may capitalize most on the heritable fraction of genetic variance.

The benefits of applying GP models to predict grain yield for single-cross hybrids have been reported in simulated (Marulanda et al. 2016; dos Santos et al. 2016) and empirical data (Fritsche-Neto et al. 2010; Technow et al. 2014). Recently, the GP process has been extended to predict genotype-by-environment interaction (Burgueño et al. 2012; Dias et al. 2018), also for considering omics data (Westhues et al. 2017) and non-additive effects (Dias et al. 2018; Vieira et al. 2017; Viana et al. 2018). GP has also been boosted by novel optimization techniques to build representative training sets for predictions (Rincent et al. 2012; Fristche-Neto et al. 2018; Guo et al. 2019). Regardless of these valuable contributions, only a few studies have demonstrated the integration of the GP process into realistic scenarios observed in commercial maize breeding programs.

In commercial plant breeding, thousands of individuals are tested in many locations, breeding zones and years, in trials often laid out as incomplete block designs. Many plant breeders have been using several small lattice trials side-by-side (henceforth referred to as multiple lattice) to accommodate a large number of genotypes in early generations (Piepho et al. 2006). By using multiple lattices, the comparison between two adjusted means across lattices is based only on the performance of the common checks (Piepho et al. 2006). In the present study, breeders modified the design from a single lattice to a multiple lattice designs after three years of evaluation. This fact raised the question if the efficiency of comparisons between two adjusted means has increased or decreased.

Although a single-stage analysis is considered as the gold standard (Smith et al. 2001), due to the complexity of the data structure in plant breeding programs, GP has been routinely used in two stages. In the first stage, adjusted genotype means are obtained, and in the second stage adjusted means are regressed on marker covariates. Although theoretical and empirical studies have shown the advantages of using weights in prediction models (Welham et al. 2010; Piepho et al. 2012; Schulz-Streeck et al. 2013; Gezan et al. 2017), GP studies often assume independent and homoscedastic errors for the adjusted means. In this context, stage-wise analysis, which takes into account the heterogeneity of variances and covariances between adjusted means, and carries this information forward in all stages, should be used to obtain reliable predictions.

Highly unbalanced historical data, with limited connectivity of hybrids evaluated across multiple years, is a key feature of many commercial breeding programs. In many cases, the only connection across years is the degree of genetic relatedness between hybrids. Proper modeling of the historical data is one of the greatest challenges faced by plant breeders. In addition, if genotype-by-year effects are not properly accounted for, GP can divert part of the molecular marker information to predict these effects rather than to estimate breeding values (Bernal-Vasquez et al. 2017). Benefits of GP using multiple breeding cycles of a historical dataset as training set have been reported in simulated (Cros et al. 2018) and empirical data (Auinger et al. 2016; Schrag et al. 2018). Therefore, in commercial breeding programs, it is expected that using many breeding cycles should be advantageous in GP. It is an open question, however, how many breeding cycles should be used as a training set for GP models.

In this context, our main goals were to (1) compare the statistical efficiency of a single lattice to multiple lattice designs; (2) compare the predictive ability of untested single-cross hybrids of weighted *vs* unweighted models using additive plus dominance effects in stage-wise analyses; (3) evaluate different scenarios of training set composition using historical unbalanced data to predict untested single-cross hybrids of subsequent breeding cycles; and (4) evaluate the predictive abilities when the model borrowed information across breeding zones or seasons.

Materials and methods

Plant material

We used hybrids from the ongoing Embrapa maize breeding program located in Brazil. Hybrids are derived from crosses of testers and inbred lines from opposite heterotic groups. In the initial trials of hybrid testing, F3 or F4 progenies from different families (mainly biparental within each genetic pool) were crossed with testers and evaluated in three different locations (data not available for this study).

In general, more than one tester was used for each heterotic group (Fig. 1). Then, successive cycles of inbreeding were performed only for the parents selected in the first step of hybrid testing.

In the second step of hybrid testing (henceforth intermediate trials; IT), approximately 120 selected hybrids (F4 progenies × testers) plus four checks were evaluated at an average of eight locations per year. Then, in the next step (henceforth elite trials; ET), 24 hybrids (F6 progenies × testers) from IT and 8 hybrids (F8 progenies × testers) selected in the previous year of ET plus four common checks were evaluated at an average of 25 locations per year.

Field data used in this study comprise 949 maize hybrids from IT and ET, evaluated from 2006 to 2013 representing eight breeding cycles of the same maize breeding program. Among the total number of hybrids, 659 hybrids have genomic information for both parents. A total of 545 inbred lines (234 Dent and 311 Flint) were used as parents, with an average of 1.21 cross per parent. The numbers of T2, T1 and T0 hybrids were 190, 460 and 9, respectively. T2 hybrids are defined as single-cross hybrids where both parents were evaluated in other hybrid combinations, while T1 and T0 hybrids have one or none of the parents in common with tested hybrids.

It is well known that PAs are different across T2, T1 and T0 hybrids (Technow et al. 2014). However, our main point was to explore the use of historical data in a commercial breeding program. Under such a realistic complex scenario, there is not enough balance of such groups of hybrids to make a fair comparison. In this context, we chose to build a training set composed by all the three types of hybrids, which might be a better practical representation of breeding programs.

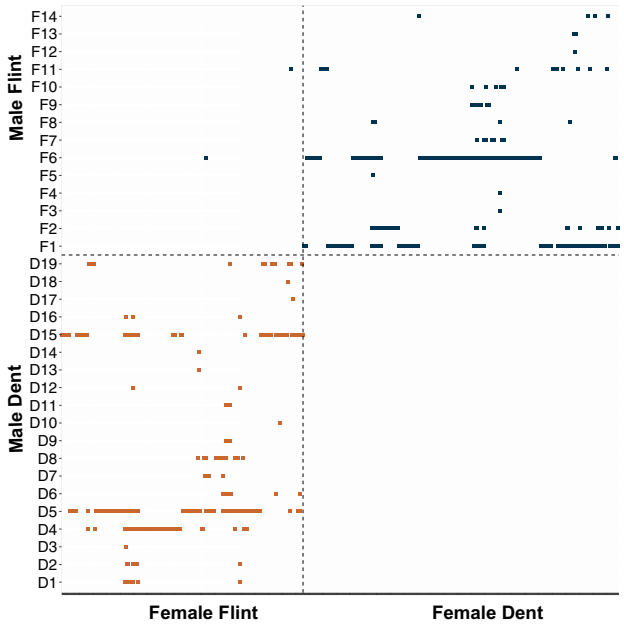

Fig. 1 Schematic representation of single-cross hybrids obtained by crossing flint (311) with dent (234) inbred lines. Each square represents a single-cross hybrid. F1 to F14 and D1 to D19 represent flint and dent lines used as male

Genotypic data

Young leaves of inbred lines were used for DNA extraction via the cetyl trimethyl ammonium bromide (CTAB) method (Saghai-Maroof et al. 1984). DNA samples were quantified using the Fluorometer Qubit 2.0, following the manufacturer's instructions (Life Technologies TM, USA). Samples were also evaluated on 1% agarose gel in Tris-acetate-EDTA buffer, stained with GelRed^{TM} (Biotium, USA) and recorded under UV light in the Imager Gel Doc L-PIX (Loccus Biotecnologia, Brazil).

Inbred lines were genotyped using genotyping-by-sequencing (GBS) based on the GBS standard protocol (Elshire et al. 2011). Libraries were created by digesting the DNA with the *Ape*KI restriction enzyme and adding unique bar-coded adapters to each DNA sample. Seven libraries of 96 samples and one library of 384 samples were multiplexed per Illumina flow cell for sequencing. Libraries of 96 and 384 samples were sequenced by HiSeq2500 (1 × 100 bp) and NextSeq500 (1 × 90 bp) equipments, respectively.

The GBS discovery pipeline was implemented using the software TASSEL v.5. (Glaubitz et al. 2014). First, raw data from Illumina was trimmed to remove reads that did not match a bar code and the cut site from *Ape*KI, leaving the good tags with at least 64pb. Second, sequenced tags were aligned to the B73 reference genome (AGPv3) using the Burrows-wheeler alignment tool (Li and Durbin 2009). Then, single-nucleotide polymorphisms (SNPs) were defined for every sample based on a binomial distribution from the aligned unique tags (Crossa et al. 2013) and saved in a variant call format (VCF file).

SNPs were obtained for all libraries simultaneously, and the parental lines of maize hybrids evaluated across the eight different breeding cycles were selected. The classification of inbred lines across heterotic groups is shown in Fig. S1. SNPs were discarded if: (1) the minor allele frequency was smaller than 5%; (2) more than 25% of missing genotypes were found; and/or (3) there were more than 5% of heterozygous genotypes. After filtering, missing data were imputed using Beagle 4.1 (Browning and Browning 2016). Nei's genetic diversity for the inbred lines within each of the eight breeding cycles (Fig. S2) was estimated using the R package snpReady (Granato et al. 2018). Linkage disequilibrium (LD) was estimated on a per-chromosome basis for

each breeding cycles, using r2 pairwise measures and the R package LDcorSV (Desrousseaux et al. 2017).

For each SNP, the *in silico* genotypes of the single-cross hybrids were inferred based on the genotype of their parents (inbred lines). After quality control, a total of 21.475 SNPs were obtained across the 10 maize chromosomes, with an average of 10.44 SNP per Mb (Fig. S3).

Experimental design

In IT, from 2006 to 2008, 100 hybrids were evaluated using a 10×10 square lattice design in each year with two replicates. From 2009 to 2013, a total of 124 hybrids were evaluated in each year side-by-side in two trials. In each trial, 60 hybrids plus four common checks were evaluated using an 8×8 square lattice design with two replicates. Hybrids of ET along with four checks were evaluated using an 6×6 square lattice design with two replicates.

Due to the elimination of low-performing hybrids and the inclusion of newly developed hybrids, the experiments are unbalanced over the years (Table 1 and Fig. S4). The connection across years is based on ET and common checks (Table S1).

A total of 21 locations were evaluated in IT, and those same 21 locations plus 40 different locations were evaluated in ET. These locations belong to five breeding zones representing a gradient between tropical and subtropical areas, on which the Embrapa's maize breeding program is focused (Fig. 2). The tropical region includes areas in almost all Brazilian states and is divided in tropical lowland (TB, areas with altitudes lower than 700 m) and tropical highland (TA, areas with altitudes higher than 700 m) zones. The transition region (TR) includes areas in the Northern and Northwest of Paraná state, Southern of Mato Grosso do Sul state and Southern of São Paulo state. The breeding zones MN and NE represent the north and the northeast geographic regions of Brazil, respectively.

For the breeding zones TA, TB and TR there are two main maize growing seasons: the first season, when sowing is done during the spring, which normally coincides with the beginning of the rainy season; and the second season, when sowing occurs during the summer, after soybeans harvesting, which is usually cultivated in the first season. Locations and number of locations were not constant over seasons, breeding zones and years (Table 2 and Fig. S5).

Grain yield was determined by weighing all the grains in each plot, adjusted to 13% of grain moisture and converted to tons per hectare (t/ha). All agronomic practices were performed as recommended for maize production for each location of Brazil.

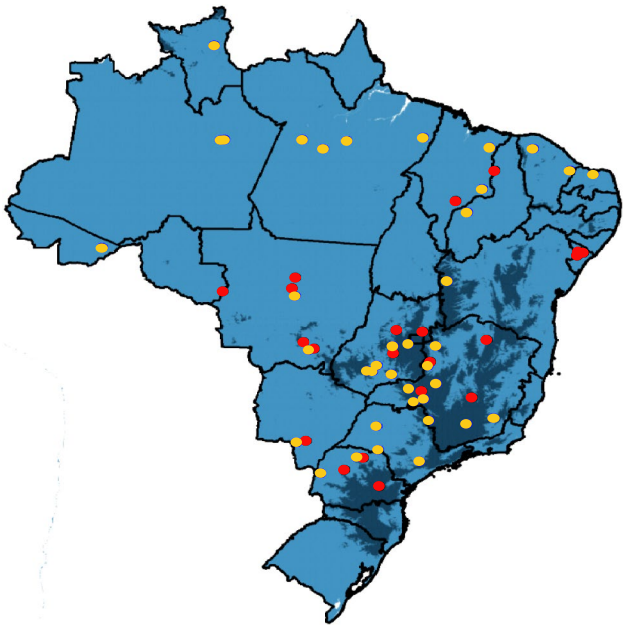

Fig. 2 Geographic map of locations for intermediate trials (red dots) and elite trials (yellow dots). The light-blue background represents the elevations up to 700 m and the dark-blue background corresponds to those above 700 m

Table 1 Number of common hybrids evaluated across years (off-diagonal) and number of hybrids tested in each year (diagonal). Above and below the diagonal results are from IT and IT+ET, respectively

Year	2006	2007	2008	2009	2010	2011	2012	2013
2006	136	7	3	0	1	1	1	1
2007	23	136	5	2	1	1	1	1
2008	13	30	136	4	2	2	2	1
2009	8	15	21	160	9	4	2	1
2010	3	4	7	35	160	8	5	2
2011	1	1	4	11	36	160	5	3
2012	1	1	3	8	14	35	160	4
2013	2	1	3	3	6	13	23	160

Phenotypic analysis

Due to the complexity of the data structure as outlined above, a stage-wise analysis was considered.

First-stage analysis

In the first stage, the following model was fitted within each location, season and year combination, from 2006 to 2008 for IT, and for ET. We used the notation described in Piepho et al. (2003):

$$\mathbf{y} = G + R : R.B + \epsilon \tag{1}$$

where $\mathbf{y}$ is the vector of phenotype, G represents the hybrids, R the replicates, B the incomplete blocks nested within replicates, and ϵ the error for each plot. The colon (:) is used to separate fixed from random effects. The dot operator (.) defines crossed effects.

For years 2009 to 2013, there were two 8×8 square lattice designs laid out side-by-side for IT, the following model was used:

$$\mathbf{y} = G + T + T.R : T.R.B + \epsilon \tag{2}$$

where T is the factor for trials, and the effects of blocks and replicates are nested within trials. Replicates were fitted as fixed and blocks as random effects to recover inter-block information (See Möhring et al. (2015) for details). Random effects were assumed to follow a normal distribution with mean zero and constant variance for models (1 and 2).

To ensure a Gaussian distribution for the residuals, outliers were detected and removed based on studentized residuals using Bonferroni–Holm test ($\alpha = 0.05$) as described in Bernal-Vasquez et al. (2016). Among 33,440 plots, 61 were considered outliers, in addition to 3 missing plots at the field trials, which represent 0.1913% of the total.

Table 2 Grain yield means (t/ha), number of locations and hybrids evaluated across the Brazilian breeding zones and seasons

Breeding zone	Season	Number of locations	Number of hybrids	Mean	Standard deviation
TB	First	18	950	7.00	2.42
	Second	8	785	5.22	1.59
TA	First	15	950	9.16	2.50
	Second	3	166	7.39	2.12
TR	First	5	950	9.19	2.14
	Second	8	950	6.06	2.07
MN	First	5	621	8.30	1.99
	Second	–	–	–	–
NE	First	6	462	7.71	2.12
	Second	–	–	–	–

Heritability

Heritability (H_P^2) as proposed by Piepho and Möhring (2007) was estimated in each location using the first-stage model:

$$H_P^2 = \frac{\sigma_g^2}{\sigma_g^2 + \bar{v_d}/2} \tag{3}$$

where σ_g^2 is the genetic variance of hybrids and $\bar{v_d}$ are the average pairwise variance of differences among two adjusted means.

Models (1) and (2) were fitted considering hybrids as random to estimate genetic variance. To estimate $\bar{v_d}$, the same model was fitted with genotypes as fixed. In this analysis, variance components of block and residuals were fixed at values obtained with the random hybrids model (Schmidt et al. 2019).

Second-stage analysis

In the second stage, models were fitted across locations, seasons, breeding zones and years using the adjusted means from the first stage ($\bar{\mathbf{y}}_1$) and associated weights:

$$\begin{aligned}\bar{\mathbf{y}}_1 = G : Y + S + M + S.M + S.M.L + Y.S + Y.M + Y.S.M.L \\ + Y.S.M + G.Y + G.S + G.M + G.S.M.L + G.S.M \\ + G.Y.S + G.Y.M + G.Y.S.M + G.Y.S.M.L + \epsilon_1\end{aligned} \tag{4}$$

where S represents the seasons, M the breeding zones, Y the years, L the locations within seasons and breeding zones. ϵ_1 is the residual, with $\epsilon_1 \sim MVN(0, \Sigma_1)$. Σ_1 is the variance matrix for ϵ_1 assumed to be known from the previous stage. As proposed by Smith et al. (2001), Σ is a diagonal matrix with diagonal elements equal to the reciprocals of the inverse of the variance-covariance of adjusted means in each location.

An unweighted model was fitted dropping the highest-order interaction as follows:

$$\begin{aligned}\bar{\mathbf{y}}_1 = G : Y + S + M + S.M + S.M.L + Y.S + Y.M + Y.S.M.L \\ + Y.S.M + G.Y + G.S + G.M + G.S.M.L + G.S.M \\ + G.Y.S + G.Y.M + G.Y.S.M + \epsilon\end{aligned} \tag{5}$$

where $\epsilon \sim MVN(0, I\sigma_\epsilon^2)$ comprised both the residual error and the highest-order interaction effect G.Y.S.M.L. The other terms were as previously described. Random effects were assumed to follow a normal distribution with mean zero and constant variance for models (4 and 5).

Variance components were estimated using the residual maximum likelihood method with the average information

algorithm (Gilmour et al. 1995). Asymptotic correlations between variance component estimates were estimated based on the model (4) considering all the effects as random.

Experimental design comparison

Trials with single and multiple lattice designs were compared via the average pairwise variance of difference of two adjusted means for each location as described in Piepho et al. (2006).

Plot data were simulated as done in Möhring et al. (2015) using the model (1) for a single lattice and model (2) for multiple lattice designs.

As block size, the block and error variances varied between years, a comparison of designs based only on the empirical data could be biased. Thus, four simulated scenarios to accommodate the IT were used (Table 3). For each of the four simulated designs, two different block variances were considered. First, the ratio of block-to-error variance was set to 0.13, which is the average value from the first-stage analysis. Second, the ratio was set to 5.

Datasets were simulated assuming a normal distribution for block and residual effects and with homogeneous variances. Replicate, trial and treatment effects were set to zero as done in Möhring et al. (2015). The average variance of a difference ($\bar{v}_d$) for each scenario was computed using the equation

$$\bar{v}_d = \frac{n}{n(n-1)}[n \times \text{trace}(V_m) - 1_n^T V_m 1_n] \quad (6)$$

where V_m is a variance-covariance matrix of adjusted means, and n is the number of columns of V_m.

For each scenario, 500 simulations were done and $\bar{v}_d$ was estimated as described above. Designs were generated using the R package "agricolae" (Mendiburu 2017) and analyzed using Asreml-R (Butler et al. 2009).

Genomic prediction models

Single-cross hybrids across multiple breeding cycles were used to train a GP model to predict the performance of untested hybrids in subsequent cycles. To this end, genomic best linear unbiased predictions (GBLUP) were obtained using additive and additive plus dominance effects based on the adjusted means of the second stage.

$$\bar{\mathbf{y}}_2 = 1\mu + Z_1 a + Z_2 d + \epsilon_2 \quad (7)$$

where $\bar{\mathbf{y}}_2$ is the vector of adjusted means from the second stage, μ is the intercept, a is the vector of random additive effects of genotypes, $a \sim N(0, \mathbf{A})$; d is the vector of random dominance effects of genotypes, $d \sim N(0, \mathbf{D})$; ϵ_2 is the vector of residuals, with $\epsilon_2 \sim MVN(0, \Sigma_2)$. Σ_2 is a diagonal matrix with diagonal elements equal to reciprocals of those of the inverse of variance-covariance matrix from the second stage. The matrix Σ_2 accounts for the information on main and interaction effects fitted in the models of the second stage. Z_1 and Z_2 represent incidence matrices for their respective effects. **A** and **D** are additive and dominance relationship matrices estimated as described in VanRaden (2008) and Vitezica et al. (2013), respectively. **A** and **D** were not positive definite, and their inverses were obtained by iterative bending methods as described in dos Santos et al. (2016). This GP model is equivalent to a single-stage model that accounts for all the genotype-by-environment interactions effects and considers the genomic relationship matrix only for the hybrid main effect.

The model presented in Eq. (7) corresponds to the additive plus dominance (AD) model, which contains both additive and dominance effects. An alternative model including only additive effects (A) was also fitted by dropping the term d.

In order to investigate if models that borrowed information across breeding zones or seasons can increase PAs, a

Table 3 Simulated scenarios of experimental designs, considering different block sizes (k), number of trials (t), number of blocks (b), number of genotypes (v) and number of replicates (r), and their respective block variance (σ_b^2) and error variance (σ_e^2). For each scenario, simulations were repeated 500 times

Scenario	k	t	b	v[a]	r	Plots	σ_b^{2b}	σ_e^2
A	8	2	32	120 + 4C	2	256	0.13	1
	8	2	32	120 + 4C	2	256	5	1
B	8	1	32	128	2	256	0.13	1
	8	1	32	128	2	256	5	1
C	10	1	20	100	2	200	0.13	1
	10	1	20	100	2	200	5	1
D	10	1	26	130	2	260	0.13	1
	10	1	26	130	2	260	5	1
A	8	2	32	120 + 4C	2	256	–	1
B	8	1	32	128	2	256	–	1
C	10	1	20	100	2	200	–	1
D	10	1	26	130	2	260	–	1

[a]4C represents the four common checks across trials

[b]– represents that the effect of blocks was considered as fixed

compound symmetry model was fitted for additive effects of the same genotype in different zones. Adjusted means and weights for this GP model were obtained from the second stage analysis considering genotype nested within seasons or breeding zones.

Genomic estimated breeding values (GEBV) were predicted as $\text{GEBV} = \hat{\mu} + Z_1\hat{a}$ or $\text{GEBV} = \hat{\mu} + Z_1\hat{a} + Z_2\hat{d}$ based on the models described above.

Cross-validation

The PA of the A and AD models with and without considering the weights were assessed through cross-validation. Two different scenarios were evaluated. In the first scenario, forward and backward PA was estimated using each breeding cycle as separate training sets to predict subsequent (forward) or previous (backward) breeding cycles. In the second scenario, i.e., across breeding cycles, PAs were estimated using hybrids from multiple preceding cycles as training sets to predict hybrids in the subsequent breeding cycle, i.e., in the validation set. In order to investigate how many breeding cycles should be used as a training set, different combinations of cycles preceding predictions were used. PAs were estimated as the Pearson correlation between the adjusted means $\bar{\mathbf{y}}_2$ and the GEBV. In addition, the mean squared prediction error (MSPE, $\frac{1}{v}\sum_{i=1}^{v}(y_i - \hat{y}_i)^2$) was computed.

All analyses were performed using the mixed model package ASReml-R version 3.0 (Butler et al. 2009) in the R Statistical Computing Environment v.3.4 (R Core Team 2018).

Results

Estimates of genetic parameters and evaluation of experimental design

The values of heritabilities for grain yield from single environment analyses ranged from 0.21 to 0.83, with an average of 0.55 across eight breeding cycles (Fig. 3). Variance component estimates for each season and across seasons, expressed as a proportion of total variance all genotype-by-environment interactions, are presented in Table 4. In general, the major source of variation was the highest-order interaction. The values for the non-static variance components (i.e., those involving years) were always higher than those of the static components (those not involving years), which ranged from 47.29 to 50.89%. Similar results were found considering each season individually or both seasons simultaneously. Asymptotic correlations between variances component estimates are reported as supplementary information (Table S2 and S3).

The AIC and BIC values showed that the weighted model improved the goodness-of-fit measures compared with the unweighted model (Table 5). The same trend was observed for the AD model when compared to the additive model. Based on the best model, the additive and dominance variances were 0.1758 and 0.0251, respectively. This dominance variance represents 14% of the additive variance in the target population.

The average pairwise variance of a difference of two adjusted means varied considerably between single and multiple lattice designs (Fig. 4). In all the cases, based on empirical and simulated data, the average variance of a difference was smaller when using a single lattice design. As the number and size of blocks were different across years, we included scenarios of block sizes 8 and 10 (scenarios B and D) to allow a fair comparison. Scenario B has the same size and number as blocks of scenario A. Comparing scenarios A and B, results show a loss of information for phenotypic data obtained when multiple lattice designs are used.

Genomic prediction

Forward and backward prediction between breeding cycles showed that closer breeding cycles have more prediction power to predict subsequent cycles than more distant ones (Table 6). The first three cycles have little power to predict the C4. The reason for this is the introduction of new sources of variability to produce inbred lines into C4. This will be further considered in the discussion.

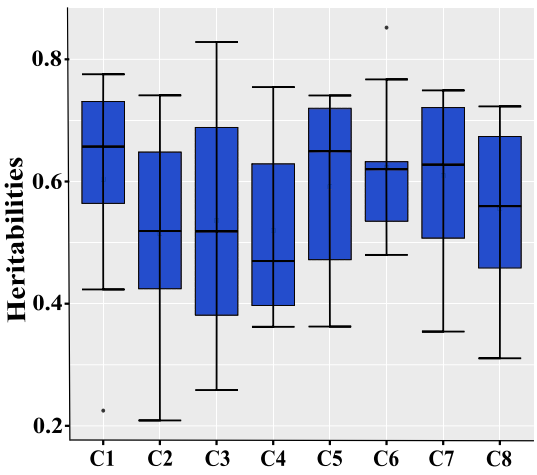

Fig. 3 Estimated heritabilities for grain yield from single environment analysis based on model (3) for the intermediate trials of the eight breeding cycles (C)

Table 4 Estimates of the variance components via individual analyses per season (first or second) and joint analysis for both seasons. The multi-season model considered the effect of location nested within season and breeding zone. Values are expressed as the correspoding proportion of the genotype-by-environment interaction variance

Variance	Effect	Season		
		First	Second	Both
Static	G	22.76	19.87	16.80
	G.M	2.14	0.00	0.00
	G.L	7.01	7.71	8.35
	G.S	–	–	4.00
	G.S.M	–	–	1.58
Non-Static	G.Y	16.06	21.53	17.36
	G.Y.S	–	–	0.28
	G.Y.M	4.37	0.00	3.29
	G.Y.S.M	–	–	1.05
	G.Y.M.L	47.64	50.89	47.29

Table 5 Estimates of the genetic parameters and the goodness-of-fit measures obtained via model (7)

	Stage-wise analysis			
	Weighted		Unweighted	
	A	AD	A	AD
σ^2_A	0.2918	0.1758	0.3566	0.2334
σ^2_D	–	0.0251	–	0.0436
Log L	97.9397	109.8383	77.127	91.5494
AIC	−193.8795	−215.6765	−150.2540	−177.0990
BIC	−189.3903	−206.6981	−141.2756	−163.6314

A: additive model; AD: additive plus dominance model;

σ^2_A and σ^2_D: additive and dominance genetic variance components, respectively

In order to check the impact of genotype-by-season and genotype-by-breeding zone interaction, a compound symmetry variance-covariance model was fitted for these effects (Table 7). Results showed that the interaction terms were of lower magnitude. The genetic correlation across first and second season was 0.91. For breeding zones TA and TB, the genetic correlation was 0.89. These values of genetic correlation show that it is possible to borrow information across seasons or breeding zones in order to increase PA. A compound symmetry was used only to compare the PAs across TA and TB breeding zones, which are the main focus for breeding recommendations in Brazil.

PA varied across the different training sets of the cross-validation procedure (Table 8 and Table S4). The use of the two cycles preceding predictions provided the highest PA, which decreased in the majority of cases when other past cycles were added.

In the majority of cases, the use of weights increased PA. In addition, the use of weights showed lower MSPE than the unweighted model. Further, the use of the AD-GP model was always advantageous compared to the A-GP model. On average, PA considering the two cycles preceding predictions increased up to 15% when dominance was included.

Discussion

In this study, we applied a stage-wise analysis for GP of single-cross hybrids using unbalanced historical data from an active maize breeding program. The data set covered different crop seasons, locations, years and tropical breeding zones. Our results suggest that increasing the training set even from a single breeding program is not always advantageous in a multiple background population. Forward prediction using multiple breeding cycles achieved optimal PA using the two cycles preceding predictions. In addition, the PA of the weighted models outperformed the unweighted models.

The maize growing areas of Brazil can be subdivided into target breeding zones widely explored by breeders for hybrids recommendation. Information from these breeding zones and seasons are important to decide if breeders should perform selection for global or specific adaptation. The main source of genotype-by-environment interaction was due to the non-static effects. Our finding suggests that non-static effects are the major source of genotype-by-environment interaction replicates the findings of Cullis et al. (2000) using a crop variety data at Australia and of Kleinknecht et al. (2013) using simulated data based on maize trials. Further, according to a study performed by Windhausen et al. (2012), maize hybrids were broadly adapted for different agroecological conditions across Africa, rendering selection for local adaptation not necessary. In our study, the hybrid by breeding zone interaction effect was not significant. One possible explanation is that Embrapa's maize breeding program has been selected for global adaptation over more than 10 years. However, the decision of breeders for global or specific adaptation depends on other factors beyond grain yield, such as market needs, disease resistance, among others. Novel studies are necessary to better explore the breeding zones in Brazil.

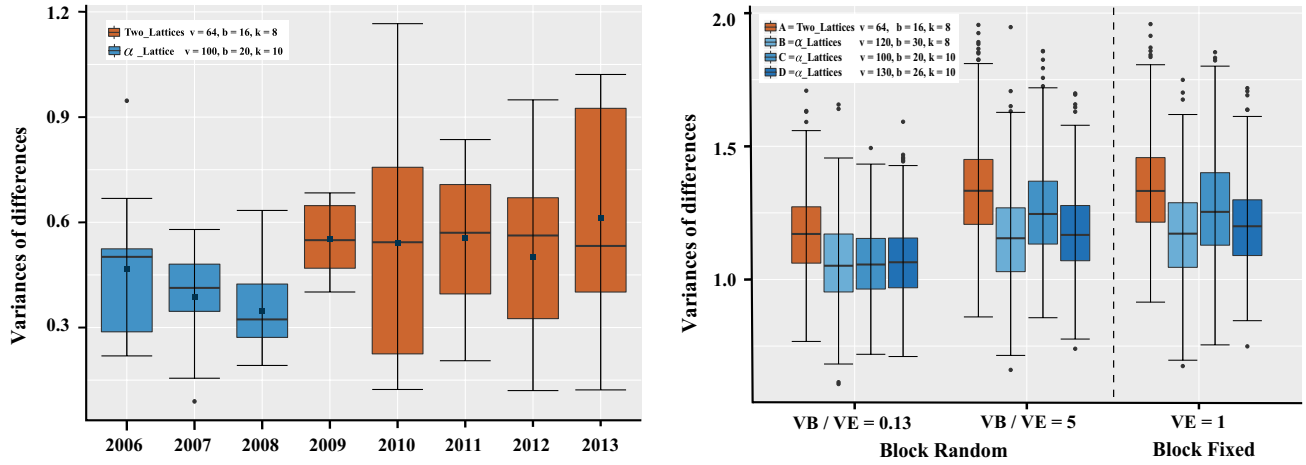

Fig. 4 Variances of differences (v_d) among entries real data (left) and simulated (right) scenarios. v represents the number of genotypes, b is the number of blocks, k is the block size, VB is the block variance and VE is the error variance. A, B, C, D and the ratio VB/VE correspond to the scenarios previously described in Table 3. Orange and blue colors represent single and multiple lattice designs, respectively. Simulation were done 500 times for each scenario

Table 6 Forward (above diagonal) and backward (below diagonal) predictive ability obtained via additive genomic prediction model (7). Diagonal represents the breeding cycle used as training set

	C1	C2	C3	C4	C5	C6	C7	C8
C8	0.38	0.29	0.41	− 0.22	0.35	0.43	0.39	–
C7	0.15	0.16	0.17	0.13	0.03	0.23	–	0.10
C6	0.32	0.21	0.17	0.35	0.29	–	0.20	0.15
C5	0.23	0.04	0.03	0.36	–	0.44	0.03	0.13
C4	0.07	0.00	− 0.16	–	0.37	0.43	0.21	− 0.11
C3	0.55	0.45	–	− 0.33	0.22	0.49	0.59	0.62
C2	0.57	–	0.35	− 0.05	0.20	0.57	0.39	0.37
C1	–	0.33	0.33	0.12	0.35	0.47	0.26	0.37

Table 7 Estimates of the variance components using a compound symmetry model and additive genomic relationship matrix for breeding zone (M) and season (S)

Breeding zone		Season	
Effect	Component	Effect	Component
G	0.4281	G	0.3815
G.M	0.0478	G.S	0.0368

From the historical dataset of Embrapa's maize breeding program, we observed that locations were not constant over the years (Fig. S5). The impact of this choice on the variance of a difference (v_d) among adjusted means can be studied by considering a balanced scenario of the same J locations in each of K years, in which case the variance of a difference can be expressed as $v_d = 2 \times (\sigma^2_{GL}/J + \sigma^2_{GY}/K + \sigma^2_{GLY}/JK)$. By contrast, when a different set of J locations is used each year, we have $v_d = 2 \times (\sigma^2_{GL}/JK + \sigma^2_{GY}/K + \sigma^2_{GLY}/JK)$. Thus, v_d will be smaller if locations are modified over the years, and more precise comparison between adjusted means can be obtained. It should be stressed that σ^2_{GL} and σ^2_{GLY} will be confounded in this scenario, meaning that one of the two effects needs to be dropped from the model.

Accurate phenotypic data are required to calibrate GP models and for the successful use of any breeding tool. We showed in this study through empirical and simulated data that the use of a single lattice is statistically more efficient than multiple lattice designs (Fig. 4). The main reason of using multiple lattices is the smaller number of plots per replication. However, according to Piepho et al. (2006), it is necessary to use a high number of checks for multiple lattices in order to reach the same accuracy of single lattice designs. Moreover, as the number of checks becomes smaller across multiple lattices, an efficiency reduction is expected. Furthermore, to estimate the genotype-by-trial interaction, there is a strong assumption of variance homogeneity between checks and entries, but this variance is estimated based only on the check's performance (Piepho et al. 2006). In summary, we would like to reinforce the importance of

Table 8 Predictive ability (PA) and mean squared prediction error (MSPE) of additive (A) and additive plus dominance (AD) models, using weighted and unweighted approaches across breeding cycles (C)

Number of cycles preceding prediction	Size of training set	Training set	Validation set	Stage-wise analysis							
				Weighted				Unweighted			
				A		AD		A		AD	
				PA	MSPE	PA	MSPE	PA	MSPE	PA	MSPE
1	113	C7	C8	0.185	0.317	0.315	0.305	0.128	0.387	0.317	0.351
1	92	C6	C7	0.240	0.810	0.366	0.834	0.174	0.884	0.181	0.973
1	105	C5	C6	0.405	0.489	0.483	0.436	0.437	0.513	0.512	0.449
1	91	C4	C5	0.468	0.558	0.468	0.558	0.492	0.674	0.492	0.674
1	33	C3	C4	− 0.192	0.556	0.065	0.434	− 0.262	0.587	− 0.235	0.408
2	205	C6:C7	C8	0.262	0.305	0.348	0.300	0.227	0.371	0.350	0.350
2	197	C5:C6	C7	0.312	0.477	0.411	0.463	0.347	0.483	0.447	0.454
2	196	C4:C5	C6	0.461	0.371	0.461	0.371	0.445	0.394	0.445	0.394
2	124	C3:C4	C5	0.539	0.536	0.539	0.536	0.526	0.673	0.526	0.673
2	98	C2:C3	C4	− 0.072	0.441	− 0.143	0.409	− 0.068	0.499	− 0.142	0.484
3	310	C5:C7	C8	0.240	0.310	0.266	0.305	0.229	0.372	0.240	0.370
3	288	C4:C6	C7	0.312	0.435	0.312	0.435	0.307	0.459	0.360	0.436
3	229	C3:C5	C6	0.466	0.372	0.466	0.372	0.449	0.404	0.449	0.404
3	189	C2:C4	C5	0.537	0.361	0.537	0.361	0.542	0.463	0.542	0.463
3	164	C1:C3	C4	-0.429	0.542	-0.378	0.457	− 0.444	0.602	− 0.418	0.567

using a single design, such as alpha-lattice or resolvable row-column designs, in place of multiple lattice designs.

In agreement with theoretical expectation, the inclusion of weights increased goodness-of-fit measures and PAs, and reduced MSPE for untested single-cross hybrids (Tables 5 and 8). Similar conclusion was already reported in simulated and empirical studies (Welham et al. 2010; Piepho et al. 2012; Schulz-Streeck et al. 2013; Damesa et al. 2017). Likewise, the use of unbalanced historical data and expected heterogeneity of variances in commercial breeding programs highlight the importance of taking into account the uncertainty regarding adjusted means. A single-stage analysis is preferable when feasible, but in a historical multi-year unbalanced data could be either unfeasible or too time consuming, making a stage-wise approach a more attractive option. In a stage-wise analysis, genotypes should be taken as fixed in all stages except the last. If this is done, BLUP of genotypic effects will be identical in single-stage and stage-wise analysis if the same variance component values are used in both strategies and the full variance-covariance matrix of adjusted means is carried forward to the next stage (Piepho et al. 2012). It should be stressed that the use of genotypes as random in multiple stages needs to be avoided due to the associated problem of double shrinkage (Smith et al. 2001; Garrick et al. 2009).

An increase in the size of the training set was not always advantageous even in the same breeding program. The use of the two cycles preceding predictions achieved optimal PA of untested single-cross hybrids in a forward prediction scenario (Table 8). It is well known that GP exploits cosegregation, LD between markers and QTL and the genetic relationship between training and validation set (Habier et al. 2007, 2013; Schopp et al. 2017). In the same breeding program, where there is a genetic relationship across cycles, it is expected that including past cycles would increase PA. In contrast, each cycle has generations of independent intermating, leading to a reduction in the LD extension and consequently in the size of parental haplotype blocks, which can decrease PA. Based on our investigations, the LD pattern per chromosome varied across cycles (Fig. S6 to S15). Therefore, we believe that using the two cycles preceding predictions resulted in a more similar LD pattern between training and validation set, preventing the breakage of important parental haplotype blocks containing grain yield adaptive loci physically linked to SNP markers.

The inclusion of genetic diversity, as done for C4, is a common activity in plant breeding programs and can lead to genetic substructures in the selection cycle (Albrecht et al. 2014). Using the first three cycles to predict the C4, the PA was zero (Table 6 and Table S4). Here, it is important to state how the introgression of genetic diversity in C4 was performed. From C4, breeders started using elite genotypes/individuals from different sources to introduce genetic variability and favorable alleles. Those introduced individuals were crossed, and sometimes backcrossed with well-known lines in each genetic pool to generate new inbreed lines to be

included as part of the new breeding cycle. Looking forward, strategies of optimal cross selection to balance selection and exploitation of genetic diversity should be used to increase long-term genetic gains through GP (Gorjanc et al. 2018).

The use of historical unbalanced data from IT and ET enables estimating genotype-by-year interaction (Table S2). This result is consistent with what has been found in previously reported results using multiple breeding cycles in rye (Bernal-Vasquez et al. 2017). There are two main factors that limit the GP of future cycles. First, genotype-by-year interaction is unpredictable, and the use of multiple breeding cycles is necessary to obtain more precise adjusted means. Second, in practical routines of maize breeding, 90% of the lines are untested and about 81% of the hybrids are T0 hybrids, when neither of the parents was already evaluated in other hybrids combinations (Westhues et al. 2017). This scenario leads to lower PA when compared to T1 and T2 hybrids (one or both parents were tested in other hybrid combinations, respectively) (Technow et al. 2014). Strategies to increase PA of T0 hybrids deserve the attention of future studies.

The exploration of heterosis using inter-pool crosses is a benchmark in commercial maize breeding. In hybrid prediction, the use of dominance effects has been recently used in empirical and in silico studies and was reported to increase PA, as happened in our study (dos Santos et al. 2016; Dias et al. 2018; Viana et al. 2018). Moreover, the best training set composition for hybrid prediction was investigated by Fristche-Neto et al. (2018). The results showed that using top-crosses is the worst scenario of a training set to predict untested single-cross hybrids compared to a North Carolina Design II and a full diallel. One of the reasons is that the dominance effect can not be estimated in test-crosses when only one tester is considered (Albrecht et al. 2014). Furthermore, given a high number of inbreds in each genetic group, the use of Design II or full diallel could be unfeasible to be exploited in practical situations. Normally in breeding programs, more than one tester is used for each heterotic group. Then, groups of lines are crossed with different testers depending on the target breeding region or the germplasm maturity cycle. Loosely speaking this structure is close to North Carolina Design I, in which it is possible to estimate additive and dominance effects based on orthogonal contrasts. However, these breeding schemes deserve further study.

There are three limitations of this study that deserve to be mentioned. First, part of the test-cross hybrids was phenotyped in early selfing generation and the genotypic data assumed that hybrids are from completely homozygous lines. We here follow Bernardo (1991), who suggested that there is a high expected correlation between the early and late selfing generation of test-crosses. Second, the number of hybrids and testers are not constant across breeding cycles, which could have an impact on the cycle effect. On the other hand, we argue that this scenario represents the dynamic of a commercial breeding program where different sets of hybrids and testers are included and discarded every year. Third, this study did not use all the data employed in the selection steps since the dataset from the first step of test-crossing was not available. The use of data from all steps is recommended to avoid selection bias (Piepho and Möhring 2006).

Finally, in addition to the practical and theoretical results applied to the maize hybrid breeding program, the stage-wise analysis performed in this study may be applied for any crop when historical unbalanced data are available. Likewise, this approach has the potential to reduce costs and accelerate the release of new hybrids. By means of prediction of hybrids, using unbalanced historical data of previous breeding cycles could replace the first step of field screening. Moreover, the available breeding germplasm can be better explored through the prediction of *in silico* genotypes, testing in the field only the genotypes with high GEBVs.

Conclusion

In this study, we showed that the use of a single lattice is statistically more efficient than multiple lattices per location. In agreement with Piepho et al. (2006), this finding suggests an advantage of a single lattice over multiple lattice designs. We also showed the superiority of weighted genomic prediction models compared to the unweighted formulation. The highly unbalanced data structure and expected heterogeneity of variance in commercial breeding programs highlight the importance of taking into account the uncertainty regarding adjusted means at each step of a stage-wise analysis. Moreover, the training set design considering variable training set sizes indicates the importance of evaluating different sample sizes representative of the plant breeding germplasm across different breeding cycles. Finally, our findings suggest that the evaluation of the two cycles preceding predictions achieved optimal prediction ability of untested single-cross hybrids in maize of Embrapa's maize breeding program.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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