

# 1 **Bivariate genomic prediction of phenotypes by selecting epistatic interactions** 2 **across years**

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8

## 9 **Key Message**

10 Bivariate models based on selected subsets of pairwise SNP interactions can increase the  
11 prediction accuracy by utilizing phenotypic data across years under the assumption of high  
12 genomic correlation across years.

## 13 **Abstract**

14 The importance of accurate genomic prediction of phenotypes in plant breeding is undeniable,  
15 as higher prediction accuracy can increase selection responses. In this study, we investigated the  
16 ability of three models to improve prediction accuracy by including phenotypic information from  
17 the last growing season. This was done by considering a single biological trait in two growing  
18 seasons (2017 and 2018) as separate traits in a multi-trait model. Thus, bivariate variants of the  
19 Genomic Best Linear Unbiased Prediction (GBLUP) as an additive model, Epistatic Random  
20 Regression BLUP (ERRBLUP) and selective Epistatic Random Regression BLUP (sERRBLUP) as  
21 epistasis models were compared with respect to their prediction accuracies for the second year.  
22 The results indicate that bivariate ERRBLUP is slightly superior to bivariate GBLUP in prediction  
23 accuracy, while bivariate sERRBLUP has the highest prediction accuracy in most cases. The  
24 average relative increase in prediction accuracy from bivariate GBLUP to maximum bivariate  
25 sERRBLUP across eight phenotypic traits and studied dataset from 471/402 doubled haploid lines  
26 in the European maize landrace Kemater Landmais Gelb/Petkuser Ferdinand Rot, were 7.61 and  
27 3.47 percent, respectively. We further investigated the genomic correlation, phenotypic  
28 correlation and trait heritability as the factors affecting the bivariate model's prediction  
29 accuracy, with genetic correlation between growing seasons being the most important one. For  
30 all three considered model architectures results were far worse when using a univariate version  
31 of the model, e.g. with an average reduction in prediction accuracy of 0.23/0.14 for  
32 Kemater/Petkuser when using univariate GBLUP.

## 33 **Keywords:**

34 Epistasis, Bivariate GBLUP, Prediction across years, Genomic correlation

## 35 Introduction

36 In plant breeding, genomic prediction has become a daily tool (Bernal-Vasquez *et al.* 2014; Stich  
37 and Ingheland 2018) which enables the optimization of phenotyping costs of breeding programs  
38 (Akdemir and Isidro-Sánchez 2019). The importance of genomic prediction of phenotypes is not  
39 restricted to plants. Livestock (Daetwyler *et al.* 2013) and human research (de los Campos *et al.*  
40 2013) also have been widely developed in this regard. In the context of plant and animal  
41 breeding, accurately predicting phenotypic traits is of special importance, since raising all animals  
42 and growing all crops to measure their performances requires a considerable amount of money  
43 under limited resources (Martini *et al.* 2016).

44 Several statistical models have been compared over the last decades in the term of prediction  
45 accuracy. In this context, genomic best linear unbiased prediction (GBLUP) (Meuwissen *et al.*  
46 2001; VanRaden 2007) as an additive linear mixed model has been widely used due to its high  
47 robustness, computing speed and superiority in predictive ability to alternative prediction  
48 models like Bayesian methods, especially in small reference populations (Da *et al.* 2014;  
49 Rönnegård and Shen 2016; Covarrubias-Pazarán *et al.* 2018; Wang *et al.* 2018). Furthermore,  
50 inclusion of genotype  $\times$  environment interaction into additive genomic prediction models can  
51 result in an increase in prediction accuracy (Hallauer *et al.* 2010; Bajgain *et al.* 2020). Such  
52 approaches allow borrowing information across environments which potentially leads to higher  
53 accuracy in phenotype prediction in multi environment models (Burgueño *et al.* 2012). In fact,  
54 multivariate mixed models have been originally proposed in the context of animal breeding  
55 (Henderson and Quaas 1976) with the purpose of modeling the genomic correlation among traits,  
56 longitudinal data, and modeling genotype by environment interactions across multiple years or  
57 environments (Mrode 2014; Lee and van der Werf 2016; Covarrubias-Pazarán *et al.* 2018). A  
58 multivariate GBLUP model was reported to have higher prediction accuracy than univariate  
59 GBLUP (Jia and Jannink 2012) when the genetic correlations were medium (0.6) or high (0.9)  
60 (Covarrubias-Pazarán *et al.* 2018). It was also shown that aggregating the phenotypic data over  
61 years to train the model and predict the performance of lines in the following years is a possible  
62 approach which can improve prediction accuracy (Auinger *et al.* 2016; Schrag *et al.* 2019a).

63 In addition, inclusion of epistasis, defined as the interaction between loci (Falconer and Mackay  
64 1996; Lynch and Walsh 1998), into the genomic prediction model results in more accurate  
65 phenotype prediction (Hu *et al.* 2011; Wang *et al.* 2012; Mackay 2014; Martini *et al.* 2016; Vojgani  
66 *et al.* 2019b) due to the considerable contribution of epistasis in genetic variation of quantitative  
67 traits (Mackay 2014). In this context, several statistical models have been proposed. Extended  
68 genomic best linear unbiased prediction (EG-BLUP, Jiang and Reif 2015) and categorical epistasis  
69 (CE, Martini *et al.* 2017) models are using a marker-based epistatic relationship matrix that is  
70 constructed in a highly efficient manner. It has been shown that the CE model is as good as or  
71 better than EG-BLUP and does not possess undesirable features of EG-BLUP such as coding-  
72 dependency (Martini *et al.* 2017).

73 Moreover, it was shown that the accuracy of the epistasis genomic prediction model can be  
74 increased in one environment by variable selection in another environment (Martini *et al.* 2016).  
75 In this approach, the full epistasis model was reduced to a model with a subset of the largest  
76 epistatic interaction effects, resulting in an increase in predictive ability (Martini *et al.* 2016),  
77 through borrowing information across environments. Vojgani *et al.* (2019b) showed that the  
78 prediction accuracy can be increased even further by selecting the interactions with the highest  
79 absolute effect sizes / variances in the epistasis model. Resulting higher computational needs  
80 were offset by the development of a highly efficient software package (Vojgani *et al.* 2019a) to  
81 perform computations in a bit-wise manner (Schlather 2020). Thus, enabling to conduct such  
82 predictions with data sets of practically relevant size across environments in the same year, both  
83 with respect to sample size and number of markers (Vojgani *et al.* 2019b).

84 The aim of this study is to assess the bivariate genomic prediction models which incorporate  
85 pairwise SNP interactions with the target of borrowing information across years to maximize the  
86 predictive ability. Since the accuracy of genomic prediction of phenotypes was shown to be  
87 increased by both borrowing information across environments and years (Covarrubias-Pazaran  
88 *et al.* 2018; Schrag *et al.* 2019b) and inclusion of epistasis into the prediction model (Martini *et al.*  
89 *et al.* 2016; Vojgani *et al.* 2020), we combine these two approaches to make the best use of the  
90 available information. We further aim to assess the optimum proportion of SNP interactions to  
91 be kept in the model in the variable selection step across years. The data used for this purpose  
92 were generated in multi-location trials of doubled haploid (DH) lines generated from two  
93 European maize landraces in 2017 and 2018.

## 94 **Materials and Methods**

### 95 **Data used for analysis**

96 A set of 948 doubled haploid lines of the European maize landraces Kemater Landmais Gelb (KE,  
97 Austria, 516 lines) and Petkuser Ferdinand Rot (PE, Germany, 432 lines) were genotyped with the  
98 600 k Affymetrix® Axiom® Maize Array (Unterseer *et al.* 2014).

99 After quality filtering and imputation, 910 DH lines remained (501 lines in KE and 409 lines in PE)  
100 and the panel of markers reduced to 501,124 markers (Hölker *et al.* 2019). Additionally, loci which  
101 were in high level of pairwise linkage disequilibrium (LD) were removed (Calus and Vandenplas  
102 2018) through linkage disequilibrium based SNP pruning with PLINK v1.07 (Purcell *et al.* 2007;  
103 Chang *et al.* 2015). LD pruning was done by the parameters of 50, 5 and 2 which considered as  
104 the SNPs window size, the number of SNPs at which the SNP window shifts and the variance  
105 inflation factor, respectively. This resulted in a data panel containing 25'437 SNPs for KE and  
106 30'212 SNPs for PE (Vojgani *et al.* 2020). Note that even a panel of 25'000 SNPs results in more  
107 than 1 billion SNP interactions to account for.

108 Out of 910 genotyped lines only 873 DH lines were phenotyped (471 lines in KE and 402 lines in  
109 PE). Einbeck (EIN, Germany), Roggenstein (ROG, Germany), Golada (GOL, Spain) and Tomeza

110 (TOM, Spain) were the four locations that these lines were phenotyped for a series of traits in  
111 both 2017 and 2018.

112 The means, standard deviations, maximum and minimum values of studied phenotypic traits in  
113 2017 and 2018 in each landrace are compared in Table 1 which were derived from the Best Linear  
114 Unbiased Estimations (BLUEs) of the genotype mean for each phenotypic trait by Hölker *et al.*  
115 (2019). The comparison of the respective detailed values for each trait in each environment and  
116 landrace in 2017 and 2018 are illustrated in the supplementary (Table S1).  $V_i$  in phenotypic traits  
117 represents the vegetative growth stage when  $i$  leaf collars are visible based on the leaf collar  
118 method of the corn growth (Abendroth *et al.* 2011). Early vigour at V3 stage (EV\_V3), female  
119 flowering (FF) and root lodging (RL) were not phenotyped in all four environments for both years.  
120 EV\_V3 was not phenotyped in EIN in 2018, FF was not phenotyped in GOL in 2017 and RL was not  
121 phenotyped in TOM and GOL in both 2017 and 2018.

122 The number of phenotyped lines per year and environment for trait PH\_V4, as the main trait in  
123 this study, are summarized in Table 2. For EIN and ROG a higher number of phenotyped lines  
124 were generated in 2017. On the contrary, more lines were phenotypes in GOL and TOM in 2018.

## 125 **Statistical models for phenotype prediction**

126 We used the bivariate statistical framework as the basis of the genomic prediction models. In this  
127 regard, GBLUP, ERRBLUP and sERRBLUP as three different methods described in Vojgani *et al.*  
128 (2020) were used for genomic prediction of phenotypes which differ in dispersion matrices  
129 representing their covariance structure of the genetic effects. GBLUP as an additive model is  
130 based on a genomic relationship matrix calculated according to VanRaden (2008). ERRBLUP  
131 (Epistatic Random Regression BLUP) as a full epistasis model is based on all pairwise SNP  
132 interactions which generates a new marker matrix considered as a marker combination matrix.  
133 The marker combination matrix is a 0, 1 matrix indicating the absence (0) or presence (1) of each  
134 marker combination for each individual. sERRBLUP (selective Epistatic Random Regression BLUP)  
135 as a selective epistasis model is based on a selected subset of SNP interactions (Vojgani *et al.*  
136 2019b). Vojgani *et al.* (2020) proposed estimated effect variances in the training set as the  
137 selection criterion of pairwise SNP interactions due to its robustness in predictive ability  
138 specifically when only a small proportion of interactions are maintained in the model.

## 139 **Assessment of genomic prediction models**

140 GBLUP, ERRBLUP and sERRBLUP models have been assessed via 5-fold cross validation by  
141 randomly partitioning the original sample into 5 equal size subsamples in which one subsample  
142 was considered as the test set to validate the model, and the remaining 4 subsamples were  
143 considered as a joint training set (Erbe *et al.* 2010). The 5-fold cross validation technique was  
144 utilized with 5 replicates through which the Pearson correlation between the predicted genetic  
145 values and the observed phenotypes in the test set was considered as the predictive ability in  
146 each fold of each replicate, which then was averaged across 25 replicates. In this study, predictive  
147 ability was separately assessed for KE and PE for a series of phenotypic traits in four different

148 environments. Besides, we calculated the traits' prediction accuracies by dividing their predictive  
149 abilities by the square-root of the respective traits' heritabilities (Dekkers 2007) derived from all  
150 environments in both 2017 and 2018 jointly (Table S11 in the supplementary).

151 Univariate GBLUP within 2018 was assessed by training the model in the same year (2018) as the  
152 test set was sampled from. However, bivariate GBLUP, ERRBLUP and sERRBLUP were assessed by  
153 training the model with both the training set of the target environment in 2018 and the full  
154 dataset of the respective environment in 2017. The interaction selection step in bivariate  
155 sERRBLUP is done by first using the complete dataset of target environment in 2017 to estimate  
156 all pairwise SNP interaction effect variances. Then, an epistatic relationship matrix for all lines is  
157 constructed based on the subset of top ranked interaction effect variances, which is finally used  
158 to predict phenotypes of the target environment test set in 2018 (Vojgani *et al.* 2020).

### 159 **Variance component estimation**

160 Variance component estimation in univariate GBLUP was done by EMMREML (Akdemir and  
161 Godfrey 2015) based on the training set in each run of 5-fold cross validation with 5 replicates.  
162 In bivariate models this was done by ASReML-R (Butler *et al.* 2018) with the approach specified  
163 by Vojgani *et al.* (2020) for pre estimating the variance components from the full dataset to derive  
164 the initial values for the variance components in ASReML models in 100 iterations for each  
165 combination. If the variance estimation based on the full set did not converge after 100  
166 iterations, then the estimated variance components at the 100<sup>th</sup> iteration were extracted as  
167 initial values of the bivariate model in the cross validation step. Afterwards, the model used these  
168 values to re-estimate the variance components based on the training set in each run of 5-fold  
169 cross validation in 50 iterations. The estimated variance components in the converged models  
170 based on the full set deviated only slightly from the estimated variance components based on  
171 the training set (Fig. 1). However, the variance component estimations did not converge in all  
172 folds of 5-fold cross validation with 5 replicates. In such cases, the initial values were set as the  
173 fixed values for the model to predict the breeding values. This approach appears justifiable in the  
174 case of non-convergence of the bivariate model, since we have shown in Fig. 2 that the difference  
175 in mean predictive ability of all folds and only the converged folds is not critical. This difference  
176 can get higher as the number of non-converged folds increases. The number of not converged  
177 folds in all studied material is shown in the supplementary (Table S12).

### 178 **Genomic correlation estimation**

179 Genomic correlations were estimated from the genetic variances and covariance derived from  
180 the ASReML bivariate model based on the full dataset of each environment in both 2017 and  
181 2018.

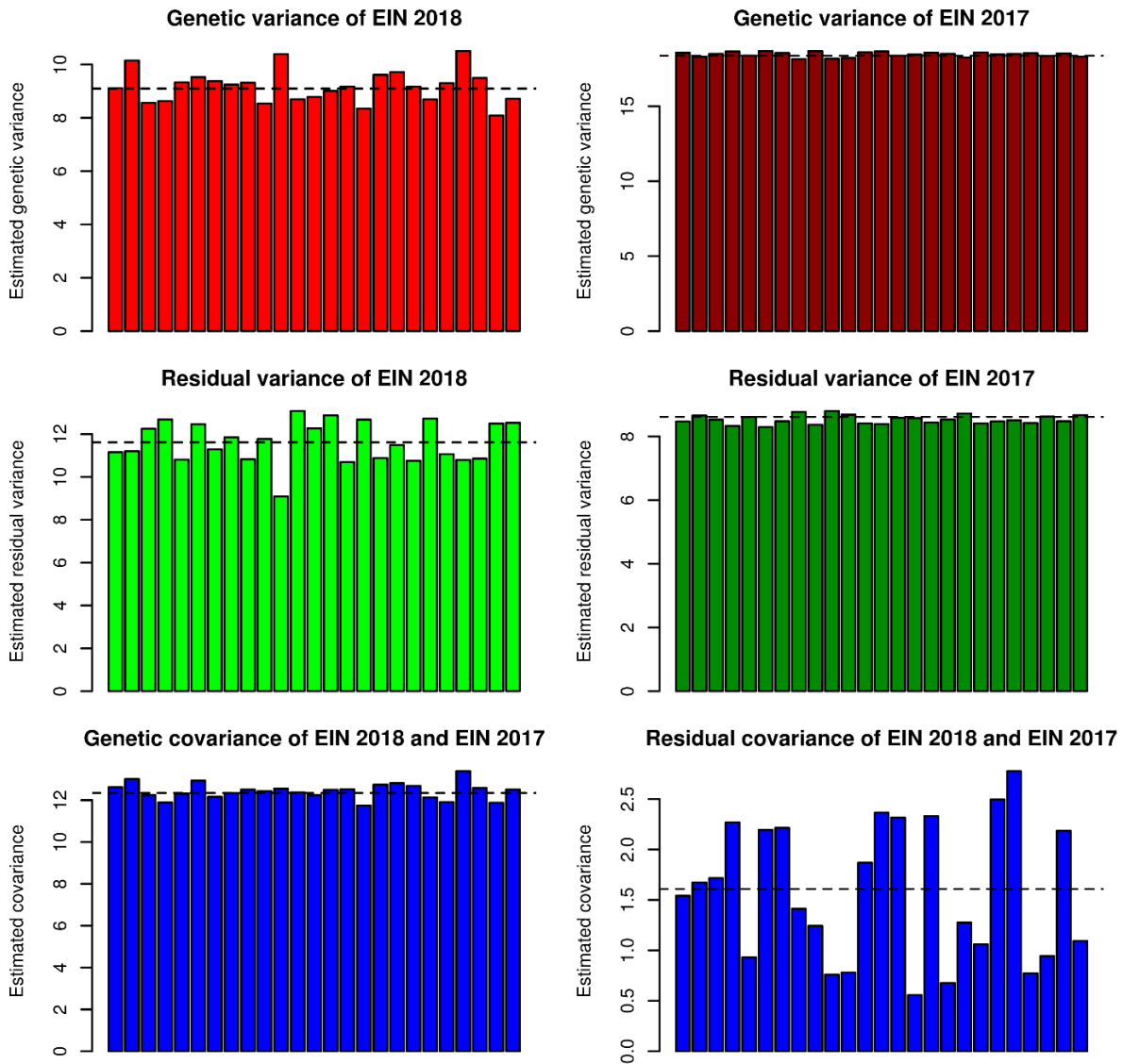
182 **Table 1:** Phenotypic trait description and the mean, minimum, maximum and standard deviation of the BLUEs for each phenotypic  
 183 trait in KE and PE landraces in the years 2017 and 2018.

Trait	Definition	Landrace	Year	Mean	Minimum	Maximum	Standard deviation
EV_V3	Early vigour at V3 stage scored on scale from 1 (very poor early vigour) to 9 (very high early vigour)	KE	2017	4.94	0.78	9.00	1.35
			2018	5.06	0.32	8.67	1.33
		PE	2017	5.57	1.00	9.03	1.20
			2018	5.47	1.38	8.93	1.13
EV_V4	Early vigour at V4 stage scored on scale from 1 (very poor early vigour) to 9 (very high early vigour)	KE	2017	4.84	0.67	8.29	1.30
			2018	5.08	0.96	8.65	1.30
		PE	2017	5.45	0.93	8.49	1.15
			2018	5.25	1.63	9.07	1.19
EV_V6	Early vigour at V6 stage scored on scale from 1 (very poor early vigour) to 9 (very high early vigour)	KE	2017	5.13	0.54	8.75	1.31
			2018	5.54	1.07	9.60	1.35
		PE	2017	5.64	0.84	8.39	1.12
			2018	5.38	1.07	9.68	1.29
PH_V4	Mean plant height of three plants of the plot at V4 stage in cm	KE	2017	33.10	6.90	88.24	13.95
			2018	42.01	8.48	89.24	16.47
		PE	2017	38.01	11.89	95.30	14.96
			2018	46.19	16.14	93.20	17.78
PH_V6	Mean plant height of three plants of the plot at V6 stage in cm	KE	2017	62.03	8.34	127.54	19.95
			2018	92.27	21.90	173.66	21.04
		PE	2017	69.84	14.78	130.51	19.26
			2018	97.80	50.37	169.71	19.44

<b>PH_final</b>	Final plant height after flowering in cm	KE	2017	139.10	49.27	245.00	27.14
			2018	146.04	35.41	265.02	35.74
	PE	2017	124.09	30.21	211.14	24.54	
		2018	128.08	35.76	248.43	35.99	
<b>FF</b>	Days after sowing until female flowering (days until 50% of the plot showed silks)	KE	2017	79.72	62.45	102.02	6.27
			2018	76.99	62.22	100.14	6.09
	PE	2017	78.85	59.10	101.50	6.33	
		2018	76.70	60.14	93.96	6.52	
<b>RL</b>	Root lodging score from 1 to 9 (1 = no lodging and 9= severe lodging)	KE	2017	3.38	0.59	9.58	2.50
			2018	1.42	0.73	8.52	0.90
	PE	2017	2.14	0.03	9.22	1.74	
		2018	1.21	0.32	4.69	0.51	

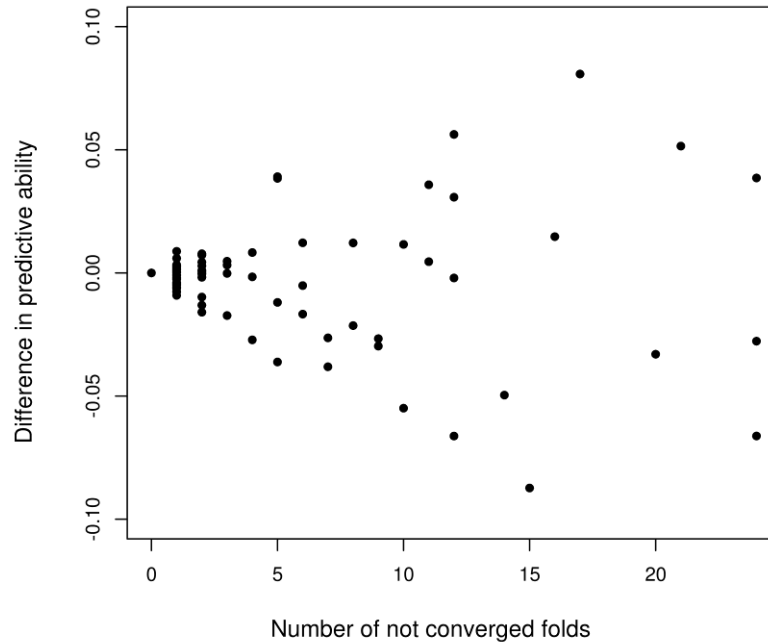
185 **Table 2:** Number of KE and PE lines phenotyped in each location for the years 2017 (blue numbers) and  
 186 2018 (red numbers) for trait PH\_V4.

	EIN (2017\2018)	ROG (2017\2018)	GOL (2017\2018)	TOM (2017\2018)
Phenotyped lines in KE	462\365	461\365	211\222	211\222
Phenotyped lines in PE	393\365	390\365	204\240	204\240



187  
 188 **Fig. 1:** Comparison of pre estimated genetic and residual variances and covariances of converged bivariate  
 189 sERRBLUP (top 10%) based on the full dataset (dashed horizontal lines) and estimated genetic and residual  
 190 variances and covariances of converged bivariate sERRBLUP (top 10%) based on training set in each run  
 191 of 5-fold cross validation with 5 replicates (colored bars) for predicting EIN in 2018 when the additional  
 192 environment is EIN in 2017 in KE for trait PH-V4.



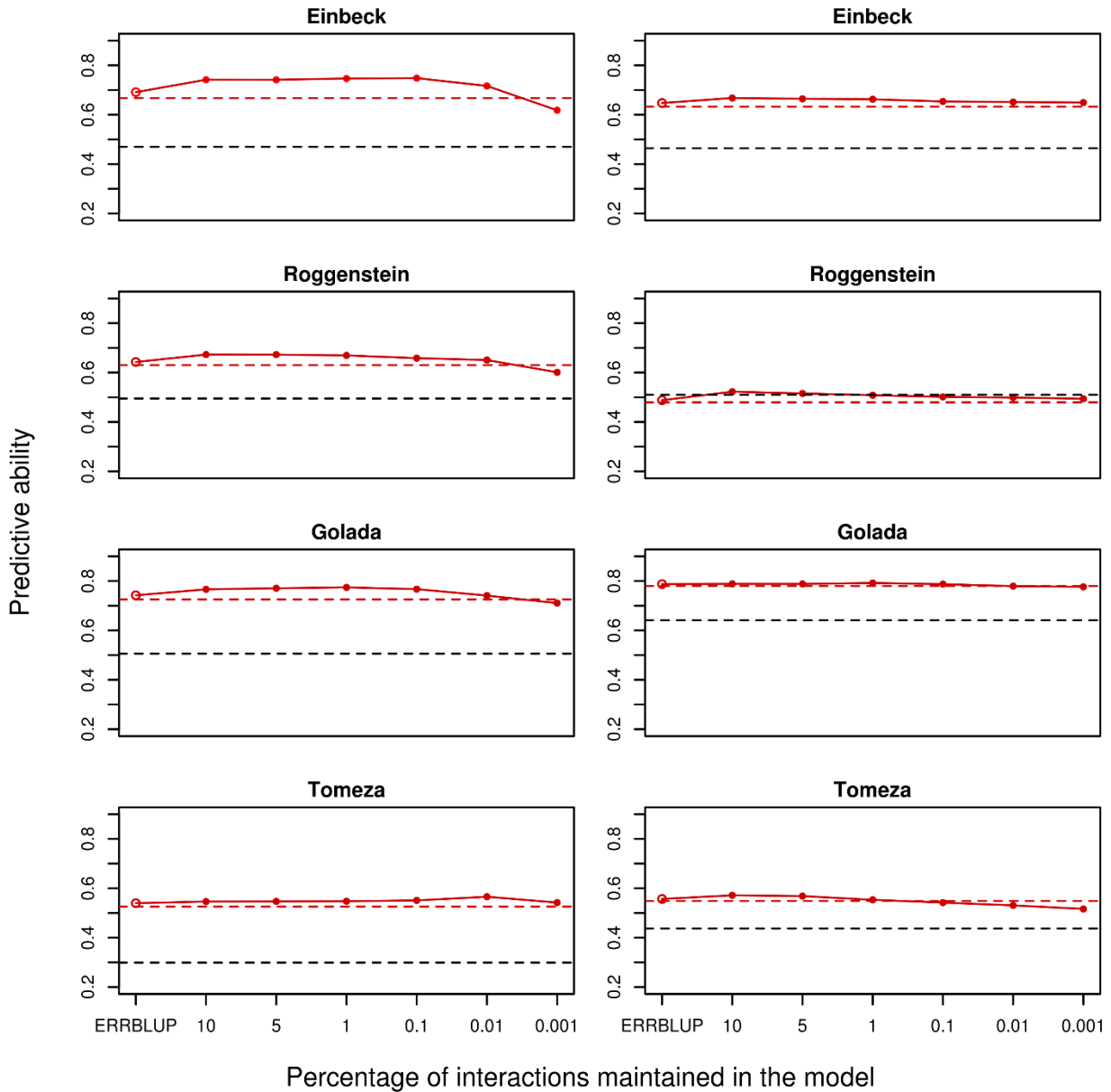


193

194 **Fig. 2:** The difference between the mean predictive ability of only the converged folds and the mean  
195 predictive ability of all folds in 5-fold cross validation with 5 replicates versus the number of the folds which  
196 did not converged across all traits in all combinations for both KE and PE in bivariate GBLUP, ERRBLUP,  
197 sERRBLUP.

## 198 Results

199 Bivariate models outperform the univariate models (Vojgani *et al.* 2020) and this has been  
200 confirmed in our study through the comparison in predictive ability of bivariate GBLUP and  
201 univariate GBLUP for the trait PH-V4 in both landraces indicating the superiority of bivariate  
202 GBLUP to univariate GBLUP in most cases (see Fig. 3). Among the bivariate genomic prediction  
203 models, bivariate ERRBLUP increases the predictive ability only slightly compared to bivariate  
204 GBLUP in a range from +0.008 to +0.024 for the trait PH-V4 across all environments in both  
205 landraces. This predictive ability increases further in bivariate sERRBLUP and the highest gain in  
206 accuracy is generally obtained when the top 10 or 5 percent of pairwise SNP interactions kept in  
207 the model in most cases. A too strict selection like using only the top 0.001 percent interactions,  
208 results in a decrease in predictive ability (see Fig. 3). Robustness of the predictive ability  
209 depending on the share of selected markers was higher in PE. Similar patterns are observed  
210 across a series of other traits for bivariate models which are shown in the supplementary (Fig.  
211 S1-S7). Additionally, the predictive ability of univariate GBLUP by training the model on the  
212 average phenotypic values of both 2017 and 2018 was evaluated for a series of phenotypic traits,  
213 which yielded quite similar predictive ability as obtained with univariate GBLUP within year 2018  
214 or worse in some cases (Table S10a (KE) and S10b (PE) in supplementary).

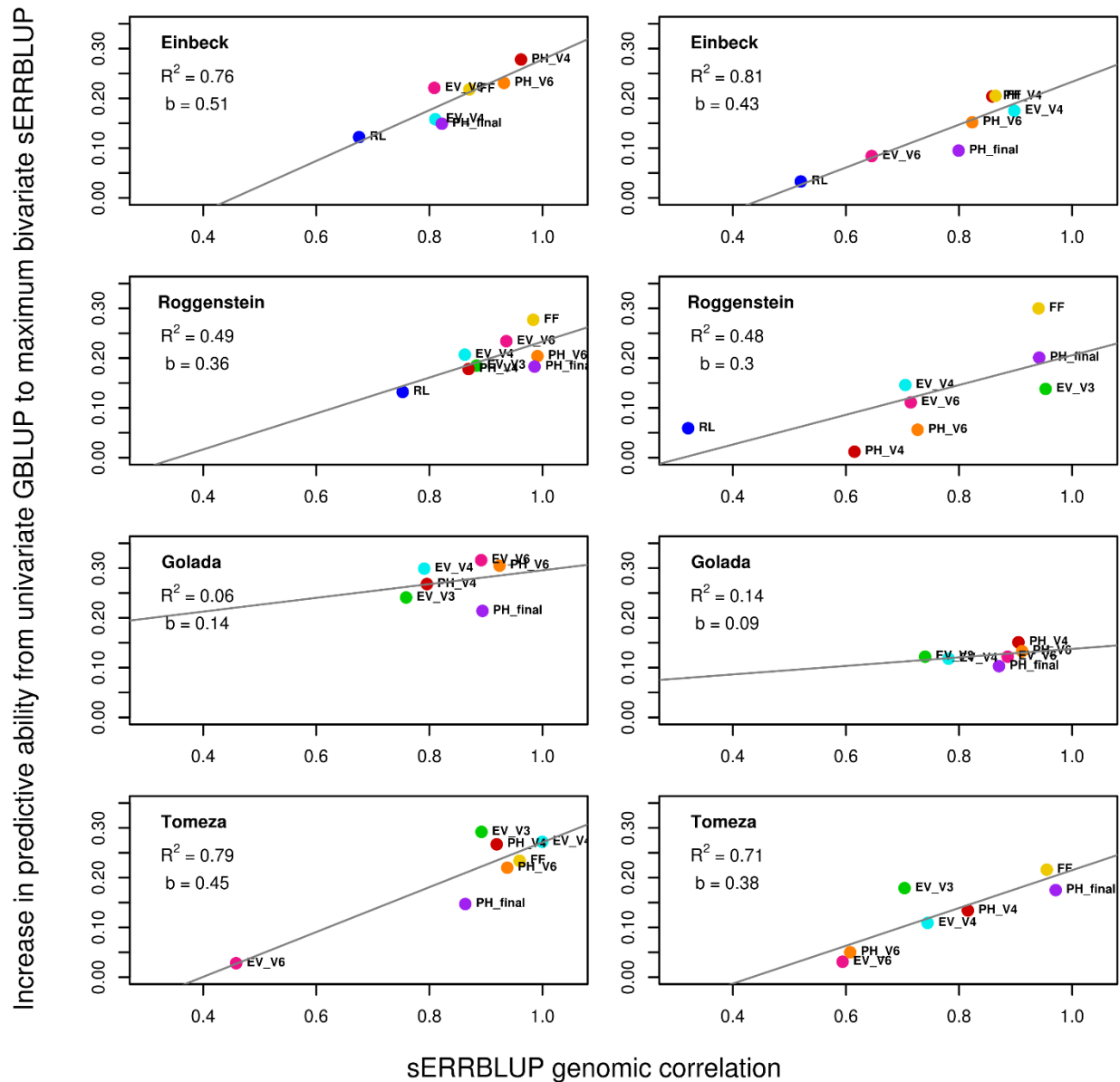


215

216 **Fig. 3:** Predictive ability for univariate GBLUP within 2018 (black dashed horizontal line), bivariate GBLUP  
 217 (red dashed horizontal line), bivariate ERRBLUP (red open circle) and bivariate sERRBLUP (red filled circles  
 218 and red solid line) for trait PH-V4 in KE (left) and in PE (right).

219 The absolute gain in predictive ability from univariate GBLUP to maximum bivariate sERRBLUP  
 220 was regressed on the respective sERRBLUP genomic correlation between the two respective  
 221 environment and across the series of studied traits (Fig. 4). Regression coefficients range  
 222 between 0.09 and 0.51 and thus show a clear association between the absolute gain in prediction  
 223 accuracy and the genomic correlation between environments. When combining all traits and

224 environments, this correlation is 0.64 (p-value = 0.00024) in KE and 0.73 (p-value = 1.072e-05) in  
 225 PE.



226

227 **Fig. 4:** Regression of the absolute increase in predictive ability from univariate GBLUP to maximum  
 228 bivariate sERRBLUP on the respective sERRBLUP genomic correlation between 2017 and 2018 in KE (left)  
 229 and in PE (right) for all studied traits. In each panel, the overall linear regression line (gray solid line) with  
 230 the regression coefficient ( $b$ ) and R-squared ( $R^2$ ) are shown.

231 The genomic correlations across years estimated with GBLUP and sERRBLUP for the trait PH\_V4  
 232 are illustrated in Table 3, indicating that the proportion of interactions in bivariate sERRBLUP  
 233 which maximized the predictive ability are not necessarily linked to the highest genomic

234 correlation. In contrast, the best sERRBLUP for trait PH\_V4 is linked to the lowest genomic  
 235 correlation in most cases. However, this is not the general pattern observed for series of other  
 236 traits and the best sERRBLUP for some traits and environments combinations are linked to the  
 237 highest genomic correlation (Table S3-S9 in supplementary).

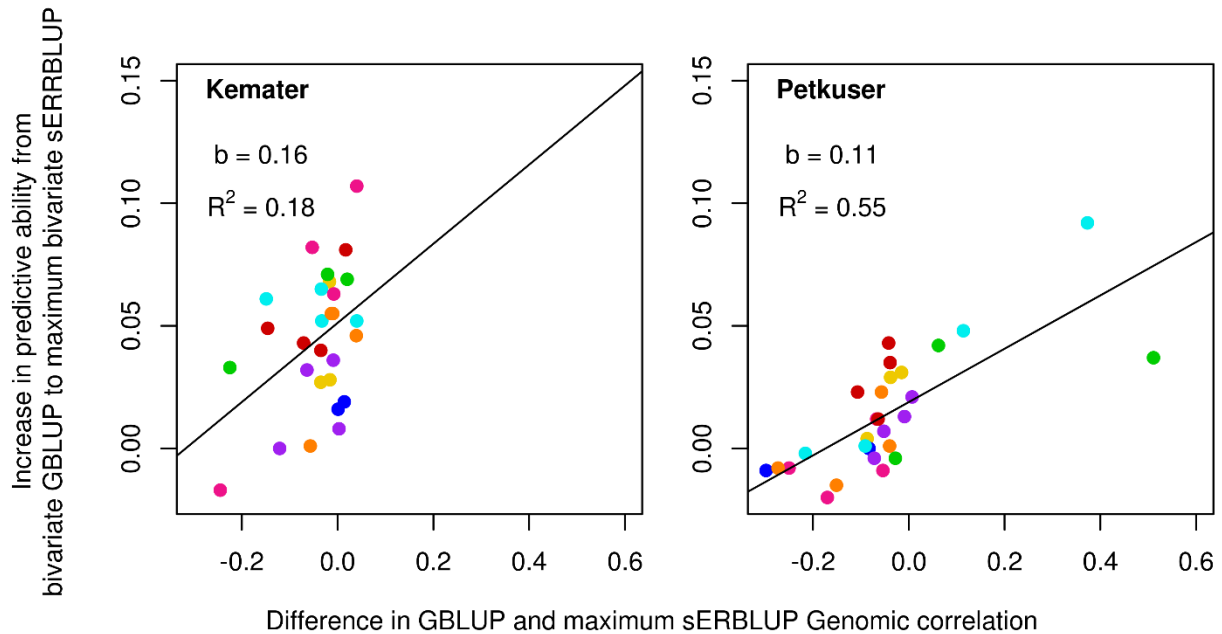
238 **Table 3:** Genomic correlation between 2017 and 2018 in each environment for trait PH\_V4 for KE (blue  
 239 numbers) and PE (red numbers). The blue and red bold numbers with stars indicate which proportion  
 240 of interactions in bivariate sERRBLUP maximized the predictive ability in each environment for KE and PE,  
 241 respectively.

242

Bivariate Models	EIN	ROG	GOL	TOM
GBLUP	0.945 / 0.898	0.940 / 0.658	0.942 / 0.969	0.954 / 0.923
sERRBLUP top 10%	0.955 / <b>0.859*</b>	<b>0.869*</b> / <b>0.615*</b>	0.835 / 0.895	0.929 / <b>0.816*</b>
sERRBLUP top 5%	0.958 / 0.868	0.850 / 0.631	0.797 / 0.888	0.912 / 0.826
sERRBLUP top 1%	<b>0.949*</b> / 0.895	0.848 / 0.820	<b>0.796*</b> / <b>0.905*</b>	0.918 / 0.863
sERRBLUP top 0.1%	0.962 / 0.966	0.917 / 0.922	0.884 / 0.948	0.929 / 0.959
sERRBLUP top 0.01%	0.963 / 0.980	0.951 / 0.985	0.911 / 0.983	<b>0.919*</b> / 0.987
sERRBLUP top 0.001%	0.997 / 0.976	0.963 / 0.970	0.908 / 0.973	0.933 / 0.968

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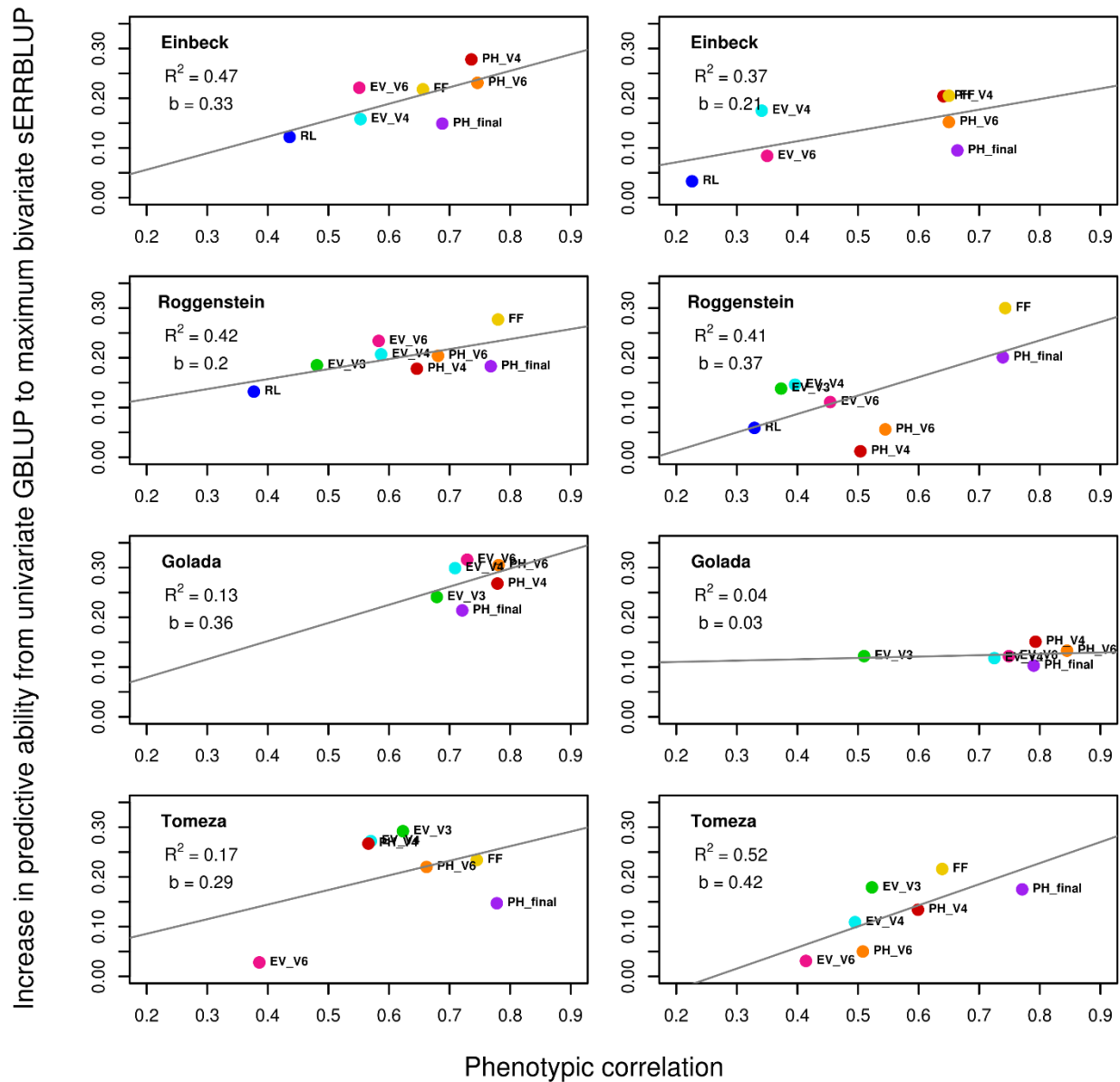
244 In this regard, the absolute increase in predictive ability from bivariate GBLUP to maximum  
 245 bivariate sERRBLUP was regressed on the difference between genetic correlations estimated with  
 246 GBLUP and maximum sERRBLUP, respectively, across all traits in both landraces. Fig. 5 shows a  
 247 significant correlation of 0.42 (p-value = 0.0255) in KE and 0.74 (p-value = 6.458e-06) in PE  
 248 between the absolute gain in the respective predictive ability and the difference in the  
 249 corresponding genetic correlations.



250

251 **Fig. 5:** Regression of the absolute increase in predictive ability from bivariate GBLUP to maximum bivariate  
252 sERRBLUP on the difference between the GBLUP genomic correlation and maximum sERRBLUP genomic  
253 correlation between 2017 and 2018 in KE (left) and in PE (right) for all studied traits. In each panel, the  
254 overall linear regression line with the regression coefficient ( $b$ ) and R-squared ( $R^2$ ) are shown. The colors  
255 green, light blue, pink, red, orange, purple, yellow and dark blue represent the phenotypic traits EV\_V3,  
256 EV\_V4, EV\_V6, PH\_V4, PH\_V6, PH\_final, FF and RL, respectively.

257 There might be some tendency that including phenotypes of the previous year into prediction  
258 becomes more efficient when the phenotypic correlation between years is high. In this context,  
259 the correlation between the absolute gain in predictive ability from univariate GBLUP to  
260 maximum bivariate sERRBLUP and the phenotypic correlation among the years (see Table S2)  
261 over all studied traits in all four environments and in both landraces was studied. Fig. 6  
262 demonstrates that the maximum correlation between the absolute gain in the respective  
263 predictive ability and the phenotypic correlation is obtained in EIN for KE (0.69) and in TOM for  
264 PE (0.72). Across all studied traits and environments, there is a significant correlation of 0.59 in  
265 KE (p-value= 0.001) and 0.47 in PE (p-value= 0.01).

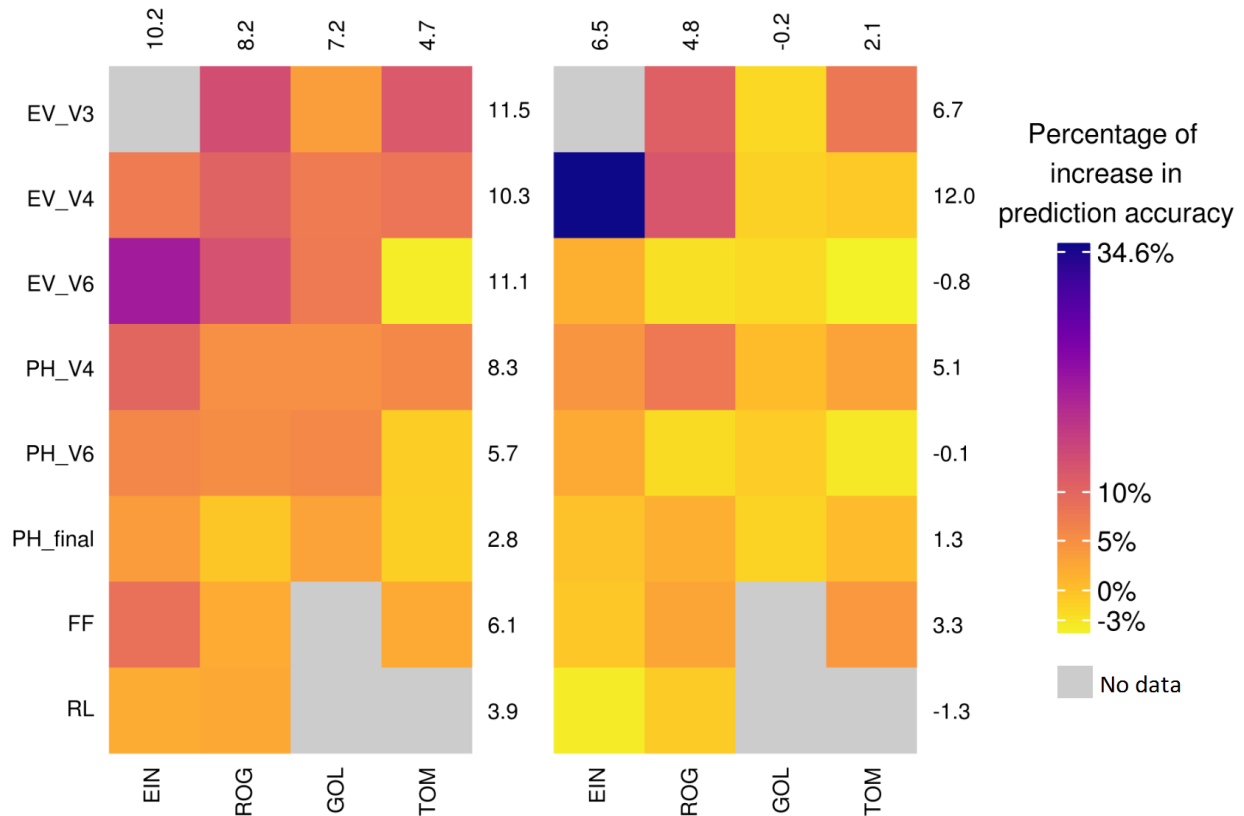


266

267 **Fig. 6:** Regression of the absolute increase in predictive ability from univariate GBLUP to maximum  
 268 bivariate sERRBLUP on the phenotypic correlation between 2017 and 2018 in KE (left) and in PE (right) for  
 269 all studied traits. In each panel, the overall linear regression line (gray solid line) with the regression  
 270 coefficient (**b**) and R-squared (**R<sup>2</sup>**) are shown.

271 Overall, the percentage of relative increase in prediction accuracy from the bivariate GBLUP to  
 272 the maximum bivariate sERRBLUP in both landraces reveals more increase in prediction accuracy  
 273 for KE than PE with the average increase of 7.61 percent in KE and 3.47 percent in PE over all  
 274 studied traits (see Fig. 7). Among all traits, the maximum increase in prediction accuracy for KE is  
 275 22.63 percent which was obtained in EV\_V6 in EIN, and for PE is 34.59 percent which was

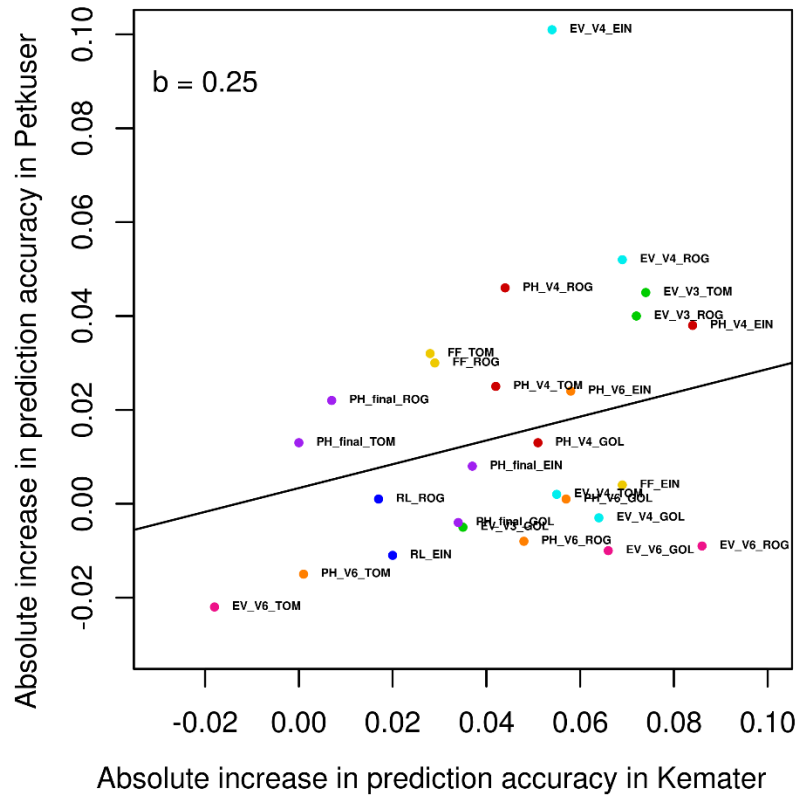
276 obtained in EV\_V4 in EIN. However, Fig. 7 shows some slight decreases in prediction accuracy  
 277 from bivariate GBLUP to maximum bivariate sERRBLUP for some combinations of traits and  
 278 environment in both landraces. This is more often observed in PE than KE, where the maximum  
 279 decrease was found in EV\_V6 in TOM for both PE (-3.198 percent) and KE (-2.795 percent).  
 280 Overall, the average relative increase from bivariate GBLUP to maximum bivariate sERRBLUP was  
 281 over 3 percent in most cases. The absolute increase in prediction accuracy is also illustrated in  
 282 the supplementary (Fig. S8) indicating the average increase of 0.046 in KE and 0.015 in PE over  
 283 all combinations of traits and environments.



284

285 **Fig. 7:** Percentage of change in prediction accuracy from bivariate GBLUP to the maximum prediction  
 286 accuracy of bivariate sERRBLUP in KE (left side plot) and in PE (right side plot). The average percentage of  
 287 change in prediction accuracy for each trait and environment is displayed in all rows and columns,  
 288 respectively.

289 Finally, a comparison between the absolute increase in prediction accuracy from bivariate GBLUP  
 290 to maximum bivariate sERRBLUP in PE versus KE shows a higher increase in KE compared to PE  
 291 with a regression coefficient 0.25 (see Fig. 8). This indicates some consistency of the observed  
 292 trends across landraces. This was also confirmed with paired t-test indicating that the mean  
 293 increase in prediction accuracy for KE is significantly higher than in PE (p-value= 3.921e-05).



294

295 **Fig. 8:** Absolute change in prediction accuracy from bivariate GBLUP to the maximum prediction accuracy  
296 of bivariate sERRBLUP in PE vs. KE. The black line represents the overall linear regression line.

## 297 Discussion

298 In this study, bivariate ERRBLUP as a full epistasis model incorporating all pairwise SNP  
299 interactions provides only a modest increase in predictive ability compared to bivariate GBLUP.  
300 This was expected, since ERRBLUP incorporates a high number of interactions by which a large  
301 number of unimportant variables are introduced into the model (Martini *et al.* 2016), thus  
302 introducing potential 'noise' which can prevent gains in predictive ability. In contrast, bivariate  
303 sERRBLUP substantially increases the predictive ability compared to bivariate GBLUP. In fact, the  
304 increase in predictive ability from bivariate GBLUP to bivariate sERRBLUP is only caused by  
305 inclusion of relevant pairwise SNP interactions. Note that all bivariate models substantially  
306 outperformed univariate GBLUP, as phenotypic data of the respective environment in the  
307 previous year was used.

308 It was shown that multivariate GBLUP is superior in predictive ability compared to univariate  
309 GBLUP under existence of medium (~0.6) or high (~0.9) genomic correlation, and that the low  
310 genomic correlation results in no increase in multivariate GBLUP compared to univariate GBLUP  
311 (Covarrubias-Pazaran *et al.* 2018). Calus *et al.* (2011) also found an increase of 3 to 14 percent in  
312 predictive ability of multi-trait SNP-based models in a simulation study when genetic correlations



313 ranged from 0.25 to 0.75. In our study, we also found a significant correlation between the  
314 absolute gain in prediction accuracy from univariate GBLUP to maximum bivariate sERRBLUP and  
315 the respective genomic correlation in both KE ( $r = 0.64$ ) and PE ( $r = 0.73$ ) across all traits and  
316 environments combinations.

317 Moreover, Martini *et al.* (2016) showed that the predictive ability in one environment can be  
318 increased by variable selection in the other environment under the assumption of positive  
319 phenotypic correlation between environments. It was shown in a wheat dataset (Pérez and de  
320 los Campos 2014), where environments 2 and 3 had the highest phenotypic correlation (0.661),  
321 that the predictive ability for phenotype prediction in environment 2 was maximized by variable  
322 selection in environment 3 and vice versa (Martini *et al.* 2016). Therefore, the increase in  
323 prediction accuracy is expected to be influenced by the phenotypic correlations between the  
324 environments or between the years in the same environment in bivariate models. In our study,  
325 although 2017 and 2018 were climatically quite different, since 2018 suffered from a major heat  
326 stress compared to 2017 (Table 1), we see a significant correlation between the absolute gain in  
327 predictive ability from univariate GBLUP to maximum predictive ability of bivariate sERRBLUP and  
328 the phenotypic correlation between years in each environment for both KE ( $r = 0.59$ ) and PE  
329 ( $r = 0.47$ ).

330 In addition to the genomic and phenotypic correlations between the years, the trait heritability  
331 is another factor which is expected to be influential for such an increase in bivariate sERRBLUP  
332 predictive ability as well. Therefore, the traits with lower heritability are expected to obtain less  
333 gain in sERRBLUP predictive ability than the traits with higher heritability. In our study, the  
334 correlation between the absolute gain in prediction accuracy from univariate GBLUP to maximum  
335 bivariate sERRBLUP and a trait's heritability over all studied material was considerable in both KE  
336 ( $r = 0.35$ ) and PE ( $r = 0.45$ ) (Fig. S9 in the supplementary). Based on the obtained results, the  
337 traits with low heritability (e.g. 0.59 for RL in PE) showed only a small increase in prediction  
338 accuracy. However, not all traits with higher heritabilities did necessarily show a higher gain in  
339 predictive ability for all traits. Overall, this association between the absolute gain in predictive  
340 ability and the trait heritabilities were close to significant in KE (p-value=0.07) and highly  
341 significant in PE (p-value=0.02). It should be noted that the trait heritabilities were calculated on  
342 an entry-mean basis within each KE and PE landraces (Hallauer *et al.* 2010) over all eight  
343 environments in both years 2017 and 2018 jointly. The trait heritabilities obtained only from 2017  
344 are significantly higher than the trait heritabilities obtained only from 2018 in both KE and PE  
345 based on a paired t-test (Table S11 in the supplementary). This also results in an increase in  
346 predictive ability from univariate GBLUP to maximum bivariate sERRBLUP in KE and PE, since  
347 multi-trait models have the potential of increasing the predictive ability when traits with low  
348 heritability are joined with traits with higher heritability, given they are genomically correlated  
349 (Thompson and Meyer 1986).

350 It should be noted that the increase in predictive ability from univariate GBLUP to maximum  
351 bivariate sERRBLUP is caused by both borrowing information across years and capitalizing on  
352 epistasis, while the increase in predictive ability from bivariate GBLUP to maximum bivariate  
353 sERRBLUP is caused by accounting for epistasis alone. Overall, the traits behave differently  
354 among different environments and landraces due to their genomic correlations, phenotypic  
355 correlations and heritabilities. To shed light on this, the maximum increase in prediction accuracy  
356 from bivariate GBLUP to bivariate sERRBLUP in KE was observed for the trait EV\_V6 (0.112) in EIN  
357 where the corresponding sERRBLUP genomic correlation (0.809) is higher than the GBLUP  
358 genomic correlation (0.768). This trait has a high heritability (0.90) and high phenotypic  
359 correlation (0.551) as well. In contrast, the respective prediction accuracy decreases (-0.018) for  
360 EV\_V6 in TOM for KE indicating the lower sERRBLUP genomic correlation (0.458) than GBLUP  
361 genomic correlation (0.703) and the particularly low phenotypic correlation (0.383). It should be  
362 noted that the phenotypic correlation does not play a major role for the increase in prediction  
363 accuracy from bivariate GBLUP to bivariate sERRBLUP, since both models are bivariate and  
364 benefit from the same phenotypic correlations. Therefore, EV\_V6 obtaining the maximum and  
365 minimum increase in the respective prediction accuracy for KE indicates the significant role of  
366 genomic correlation among the possible causes. In general, bivariate sERRBLUP improves the  
367 prediction accuracy compared to bivariate GBLUP more in KE than PE which is potentially due to  
368 significantly higher sERRBLUP genomic correlation and heritability in KE compared to PE, based  
369 on paired t-test.

370 In our study, 5-fold cross validation with 5 replicates was utilized to evaluate our bivariate  
371 genomic prediction models. Different split of cross validation such as 10-fold cross validation did  
372 not make a considerable difference in our bivariate models' predictive abilities (Fig. S10 in the  
373 supplementary). The maximum increase in bivariate models' predictive abilities when utilizing  
374 10-fold cross validation with 10 replicates compared to utilizing 5-fold cross validation with 5  
375 replicates was 0.018 in KE and 0.006 in PE for trait PH\_V4. Overall, our cross validation scenario  
376 is not expected to bias the predictive abilities obtained from our bivariate models for reasons as  
377 outlined by Runcie and Cheng (2019), who observed a bias when the test set of the target trait is  
378 predicted from the full dataset of the second trait in multi-trait model. In our study, utilizing the  
379 full dataset of the target trait in one environment from 2017 to predict the same biological trait  
380 in the respective environment in 2018 should not lead to such a bias in predictive ability, since  
381 the individuals do not share the same source of non-genetic variation and they have been grown  
382 in two different years which have been climatically very different from each other.

383 Overall, our results indicate that incorporating a suitable subset of epistatic interactions besides  
384 utilizing information across years can substantially increase the predictive ability. The amount of  
385 this increase is affected by the genomic and phenotypic correlations between the years and the  
386 heritability of the phenotypic trait. Therefore, this approach is potentially beneficial for genomic  
387 prediction of phenotypes under the assumption of sufficient genomic and phenotypic correlation  
388 between years for highly heritable traits. This may allow to reduce the number of lines which

389 have to be phenotyped over several years and thus reduce phenotyping costs which and thus be  
390 of high interest in practical plant breeding.

391

392 **Declaration**

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397 031B0195)

398 **Conflict of interest**

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

400 **Ethics approval**

401 The authors declare that this study complies with the current laws of the countries in which the  
402 experiments were performed.

403 **Consent to participate**

404 Not applicable

405 **Consent for publication**

406 Not applicable

407 **Availability of data and materials**

408 All data and material are available through material transfer agreements upon request.

409 **Code availability**

410 Not applicable

411 **Authors' contributions**

412 EV derived the results, analyzed the data, wrote the manuscript; TP proposed epistasis  
413 relationship matrices; ACH, MM and CCS prepared the material; ACH proposed cross validation  
414 strategy in bivariate model; HS proposed the original research question, guided the structure of  
415 the research. TP ACM MM CCS HS read, revised and approved the manuscript.

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427 of maize to improve quantitative traits”; Funding ID: 031B0195).

## 428 **References**

- 429 Abendroth LJ, Elmore RW, Boyer MJ, and Marlay SK (2011) Corn Growth and Development. *PMR*  
430 *1009*. Iowa State University of Science and Technology, Cooperative Extension Service, Ames,  
431 Iowa.
- 432 Akdemir D and Godfrey OU (2015) EMMREML: Fitting Mixed Models with Known Covariance  
433 Structures. Available at: <https://cran.r-project.org/package=EMMREML>
- 434 Akdemir D and Isidro-Sánchez J (2019) Design of training populations for selective phenotyping  
435 in genomic prediction. *Scientific Reports* 9(1446).  
436 <https://doi.org/https://doi.org/10.1038/s41598-018-38081-6>
- 437 Auinger H-J, Schönleben M, Lehermeier C, Schmidt M, Korzun V, Geiger HH, Piepho H-P, Gordillo  
438 A, Wilde P, Bauer E, and Schön C-C (2016) Model training across multiple breeding cycles  
439 significantly improves genomic prediction accuracy in rye (*Secale cereale* L.). *Theoretical and*  
440 *Applied Genetics* 129(11): 2043–2053. <https://doi.org/10.1007/s00122-016-2756-5>
- 441 Bajgain P, Zhang X, and Anderson JA (2020) Dominance and G×E interaction effects improve  
442 genomic prediction and genetic gain in intermediate wheatgrass (*Thinopyrum intermedium*). *The*  
443 *Plant Genome*. John Wiley & Sons, Ltd 13(1): e20012.  
444 <https://doi.org/https://doi.org/10.1002/tpg2.20012>
- 445 Bernal-Vasquez A-M, Möhring J, Schmidt M, Schönleben M, Schön C-C, and Piepho H-P (2014)  
446 The importance of phenotypic data analysis for genomic prediction - a case study comparing  
447 different spatial models in rye. *BMC Genomics* 15(1): 646. [https://doi.org/10.1186/1471-2164-](https://doi.org/10.1186/1471-2164-15-646)  
448 15-646
- 449 Burgueño J, Campos G de los, Weigel K, and Crossa J (2012) Genomic Prediction of Breeding  
450 Values when Modeling Genotype × Environment Interaction using Pedigree and Dense Molecular  
451 Markers. *Crop Science* 52(2): 707–719. <https://doi.org/10.2135/cropsci2011.06.0299>
- 452 Butler DG, Cullis BR, Gilmour AR, Gogel BJ, and Thompson R (2018) ASReml-R Reference Manual  
453 Version 4. VSN International Ltd., Hemel Hempstead
- 454 Calus MPL and Vandenplas J (2018) SNPrune: an efficient algorithm to prune large SNP array and  
455 sequence datasets based on high linkage disequilibrium. *Genetics Selection Evolution* 50(1): 34.  
456 <https://doi.org/10.1186/s12711-018-0404-z>
- 457 Calus MPL and Veerkamp RF (2011) Accuracy of multi-trait genomic selection using different  
458 methods. *Genetics Selection Evolution* 43(1): 26. <https://doi.org/10.1186/1297-9686-43-26>
- 459 Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, and Lee JJ (2015) Second-generation PLINK:  
460 rising to the challenge of larger and richer datasets. *Gigascience* 4(7).  
461 <https://doi.org/10.1186/s13742-015-0047-8>
- 462 Covarrubias-Pazarán G, Schlautman B, Diaz-García L, Grygleski E, Polashock J, Johnson-Cicalese J,  
463 Vorsa N, Iorizzo M, and Zalapa J (2018) Multivariate GBLUP Improves Accuracy of Genomic

- 464 Selection for Yield and Fruit Weight in Biparental Populations of *Vaccinium macrocarpon* Ait.  
465 *Frontiers in Plant Science* 9(1310). [https://doi.org/https://doi.org/10.3389/fpls.2018.01310](https://doi.org/10.3389/fpls.2018.01310)
- 466 Da Y, Wang C, Wang S, and Hu G (2014) Mixed Model Methods for Genomic Prediction and  
467 Variance Component Estimation of Additive and Dominance Effects Using SNP Markers. *PLOS*  
468 *ONE* 9(1). <https://doi.org/10.1371/journal.pone.0087666>
- 469 Daetwyler HD, Calus MPL, Pong-Wong R, Campos G de los, and Hickey JM (2013) Genomic  
470 Prediction in Animals and Plants: Simulation of Data, Validation, Reporting, and Benchmarking.  
471 *Genetics* 193: 347–365. <https://doi.org/10.1534/genetics.112.147983>
- 472 Dekkers JCM (2007) Prediction of response to marker-assisted and genomic selection using  
473 selection index theory. *Journal of Animal Breeding and Genetics*. John Wiley & Sons, Ltd 124(6):  
474 331–341. <https://doi.org/10.1111/j.1439-0388.2007.00701.x>
- 475 Erbe M, Pimentel E, Sharifi AR, and Simianer H (2010) Assessment of cross-validation strategies  
476 for genomic prediction in cattle. *Proceedings of the World Congress on Genetics Applied to*  
477 *Livestock Production Methods an*: 553
- 478 Falconer DS and Mackay TFC (1996) *Introduction to Quantitative Genetics*. Longman. Essex Engl.
- 479 Hallauer AR, Carena MJ, and Miranda Filho JB (2010) *Quantitative genetics in maize breeding*.  
480 Springer. Berlin
- 481 Henderson CR and Quaas RL (1976) Multiple Trait Evaluation Using Relatives' Records. *Journal of*  
482 *Animal Science* 43(6): 1188–1197. <https://doi.org/10.2527/jas1976.4361188x>
- 483 Hölker AC, Mayer M, Presterl T, Bolduan T, Bauer E, Ordas B, Brauner PC, Ouzunova M,  
484 Melchinger AE, and Schön C-C (2019) European maize landraces made accessible for plant  
485 breeding and genome-based studies. *Theoretical and Applied Genetics* 132(12): 3333–3345.  
486 <https://doi.org/10.1007/s00122-019-03428-8>
- 487 Hu Z, Li Y, Song X, Han Y, Cai X, Xu S, and Li W (2011) Genomic value prediction for quantitative  
488 traits under the epistatic model. *BMC Genet* 12(15).  
489 <https://doi.org/https://doi.org/10.1186/1471-2156-12-15>
- 490 Jia Y and Jannink J-L (2012) Multiple-Trait Genomic Selection Methods Increase Genetic Value  
491 Prediction Accuracy. *Genetics* 192(4): 1513 LP – 1522.  
492 <https://doi.org/10.1534/genetics.112.144246>
- 493 Jiang Y and Reif JC (2015) Modeling Epistasis in Genomic Selection. *Genetics* 201(2): 759–768.  
494 <https://doi.org/10.1534/genetics.115.177907>
- 495 Lee SH and van der Werf JHJ (2016) MTG2: an efficient algorithm for multivariate linear mixed  
496 model analysis based on genomic information. *Bioinformatics* 32(9): 1420–1422.  
497 <https://doi.org/10.1093/bioinformatics/btw012>
- 498 de los Campos G, Vazquez AI, Fernando R, Klimentidis YC, and Sorensen D (2013) Prediction of  
499 Complex Human Traits Using the Genomic Best Linear Unbiased Predictor. *PLoS Genetics* 9(7).

- 500 <https://doi.org/https://doi.org/10.1371/journal.pgen.1003608>
- 501 Lynch M and Walsh B (1998) *Genetics and Analysis of Quantitative Traits*. Sinauer Associates
- 502 Mackay TFC (2014) Epistasis and Quantitative Traits: Using Model Organisms to Study Gene-Gene  
503 Interactions. *Nat Rev Genet.* 15(1): 22–33. <https://doi.org/10.1038/nrg3627>
- 504 Martini JWR, Wimmer V, Erbe M, and Simianer H (2016) Epistasis and covariance: how gene  
505 interaction translates into genomic relationship. *Theoretical and Applied Genetics* 129(5): 963–  
506 976. <https://doi.org/10.1007/s00122-016-2675-5>
- 507 Martini JWR, Gao N, Cardoso DF, Wimmer V, Erbe M, Cantet RJC, and Henner S (2017) Genomic  
508 prediction with epistasis models: on the marker-coding-dependent performance of the extended  
509 GBLUP and properties of the categorical epistasis model (CE). *BMC Bioinformatics* 18(3).  
510 <https://doi.org/https://doi.org/10.1186/s12859-016-1439-1>
- 511 Meuwissen THE, Hayes BJ, and Goddard ME (2001) Prediction of total genetic value using  
512 genome-wide dense marker maps. *Genetics* 157(4): 1819–1829
- 513 Mrode RA (2014) *Linear Models for the Prediction of Animal Breeding Values*. CABI.  
514 <https://doi.org/10.1079/9781780643915.0000>
- 515 Pérez P and de los Campos G (2014) Genome-wide regression and prediction with the BGLR  
516 statistical package. *Genetics*. 2014/07/09. Genetics Society of America 198(2): 483–495.  
517 <https://doi.org/10.1534/genetics.114.164442>
- 518 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, Bakker  
519 PIW de, Daly MJ, and Sham PC (2007) PLINK: A Tool Set for Whole-Genome Association and  
520 Population-Based Linkage Analyses. *American Journal of Human Genetics* 81(3): 559–575.  
521 <https://doi.org/10.1086/519795>
- 522 Rönnegård L and Shen X (2016) Genomic prediction and estimation of marker interaction effects.  
523 *bioRxiv* 38935. <https://doi.org/https://doi.org/10.1101/038935>
- 524 Runcie D and Cheng H (2019) Pitfalls and Remedies for Cross Validation with Multi-trait Genomic  
525 Prediction Methods. *G3: Genes/Genomes/Genetics* 9(11): 3727 LP – 3741.  
526 <https://doi.org/10.1534/g3.119.400598>
- 527 Schlather M (2020) Efficient Calculation of the Genomic Relationship Matrix. *bioRxiv*.  
528 <https://doi.org/https://doi.org/10.1101/2020.01.12.903146>
- 529 Schrag TA, Schipprack W, and Melchinger AE (2019a) Across-years prediction of hybrid  
530 performance in maize using genomics. *Theoretical and Applied Genetics*. Springer Verlag 132(4):  
531 933–946. <https://doi.org/10.1007/s00122-018-3249-5>
- 532 Schrag TA, Schipprack W, and Melchinger AE (2019b) Across-years prediction of hybrid  
533 performance in maize using genomics. *Theoretical and Applied Genetics* 132: 933–946
- 534 Stich B and Ingheland D Van (2018) Prospects and Potential Uses of Genomic Prediction of Key



- 535 Performance Traits in Tetraploid Potato. *Frontiers in Plant Science* 9(159).  
536 <https://doi.org/10.3389/fpls.2018.00159>
- 537 Thompson R and Meyer K (1986) A review of theoretical aspects in the estimation of breeding  
538 values for multi-trait selection. *Livestock Production Science* 15(4): 299–313.  
539 [https://doi.org/https://doi.org/10.1016/0301-6226\(86\)90071-0](https://doi.org/https://doi.org/10.1016/0301-6226(86)90071-0)
- 540 Unterseer S, Author EB, Haberer G, Seidel M, Knaak C, Ouzunova M, Meitinger T, Strom TM, Fries  
541 R, Pausch H, Bertani C, Davassi A, Mayer KF, and Schön C-C (2014) A powerful tool for genome  
542 analysis in maize: 584 development and evaluation of the high density 600 k SNP genotyping  
543 array. *BMC Genomics* 15(823). <https://doi.org/10.1186/1471-2164-15-823>
- 544 VanRaden P (2007) Efficient estimation of breeding values from dense genomic data. *Journal of*  
545 *Dairy Science* 90: 374–375
- 546 VanRaden P (2008) Efficient methods to compute genomic predictions. *Journal of Dairy Science*  
547 91(11): 4414–4423. <https://doi.org/10.3168/jds.2007-0980>
- 548 Vojgani E, Pook T, Martini JWR, Hoelker AC, Mayer M, Schoen C-C, and Simianer H (2020)  
549 Accounting for epistasis improves genomic prediction of phenotypes with univariate and  
550 bivariate models across environments. *bioRxiv* 2020.10.08.331074.  
551 <https://doi.org/10.1101/2020.10.08.331074>
- 552 Vojgani E, Pook T, and Simianer H (2019a) EpiGP: Epistatic relationship matrix based genomic  
553 prediction of phenotypes. Available at: <https://github.com/evojgani/EpiGP>
- 554 Vojgani E, Pook T, and Simianer H (2019b) Phenotype Prediction under Epistasis. in KC, W. (ed.)  
555 *Epistasis: Methods and Protocols*. Springer
- 556 Wang D, El-Basyoni IS, Baenziger PS, Crossa J, Eskridge KM, and Dweikat I (2012) Prediction of  
557 genetic values of quantitative traits with epistatic effects in plant breeding populations. *Heredity*  
558 109(5): 313–319. <https://doi.org/10.1038/hdy.2012.44>
- 559 Wang J, Zhou Z, Zhang Zhe, Li H, Liu D, Zhang Q, Bradbury PJ, Buckler ES, and Zhang Zhiwu (2018)  
560 Expanding the BLUP alphabet for genomic prediction adaptable to the genetic architectures of  
561 complex traits. *Heredity* 121(6): 648–662. <https://doi.org/10.1038/s41437-018-0075-0>
- 562