

UC Davis

UC Davis Previously Published Works

Title

Average semivariance directly yields accurate estimates of the genomic variance in complex trait analyses.

Permalink

<https://escholarship.org/uc/item/30t4n7bs>

Journal

G3 (Bethesda, Md.), 12(6)

ISSN

2160-1836

Authors

Feldmann, Mitchell J

Piepho, Hans-Peter

Knapp, Steven J

Publication Date

2022-05-01

DOI


10.1093/g3journal/jkac080

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Average semivariance directly yields accurate estimates of the genomic variance in complex trait analyses

Mitchell J. Feldmann ^{1,*} Hans-Peter Piepho,² Steven J. Knapp ¹

¹Department of Plant Sciences, University of California, Davis, CA 95616, USA,

²Biostatistics Unit, Institute of Crop Science, University of Hohenheim, 70593 Stuttgart, Germany

*Corresponding author: Department of Plant Sciences, University of California, Davis, CA 95616, USA. Email: mjfeldmann@ucdavis.edu

Abstract

Many important traits in plants, animals, and microbes are polygenic and challenging to improve through traditional marker-assisted selection. Genomic prediction addresses this by incorporating all genetic data in a mixed model framework. The primary method for predicting breeding values is genomic best linear unbiased prediction, which uses the realized genomic relationship or kinship matrix (\mathbf{K}) to connect genotype to phenotype. Genomic relationship matrices share information among entries to estimate the observed entries' genetic values and predict unobserved entries' genetic values. One of the main parameters of such models is genomic variance (σ_g^2), or the variance of a trait associated with a genome-wide sample of DNA polymorphisms, and genomic heritability (h_g^2); however, the seminal papers introducing different forms of \mathbf{K} often do not discuss their effects on the model estimated variance components despite their importance in genetic research and breeding. Here, we discuss the effect of several standard methods for calculating the genomic relationship matrix on estimates of σ_g^2 and h_g^2 . With current approaches, we found that the genomic variance tends to be either overestimated or underestimated depending on the scaling and centering applied to the marker matrix (\mathbf{Z}), the value of the average diagonal element of \mathbf{K} , and the assortment of alleles and heterozygosity (H) in the observed population. Using the average semivariance, we propose a new matrix, \mathbf{K}_{ASV} , that directly yields accurate estimates of σ_g^2 and h_g^2 in the observed population and produces best linear unbiased predictors equivalent to routine methods in plants and animals.

Keywords: average semivariance; genomic heritability; genomic variance; genomic relatedness; linear mixed model; genomic best linear unbiased predictor

Introduction

Linear mixed model (LMM) analyses are routine in the prediction of breeding values in plants and animals (Henderson 1977; VanRaden 2008; Hayes et al. 2009; Albrecht et al. 2011; Endelman 2011; Crossa et al. 2014; Meuwissen et al. 2016; Pincot et al. 2020; Petrasch et al. 2021) and polygenic risk scores in humans (de los Campos et al. 2010; Makowsky et al. 2011; Lee et al. 2012; Dudbridge 2013; Maier et al. 2018; Wray et al. 2019; Truong et al. 2020), partitioning of sources of variance (Searle et al. 1992; Lynch and Walsh 1998; Visscher et al. 2008; Kang et al. 2010; Piepho 2019; Schmidt et al. 2019a, 2019b; Feldmann et al. 2021), and controlling for confounding effects in genome-wide association studies (GWAS) (Yu et al. 2006; Visscher et al. 2012; Korte and Farlow 2013; Visscher et al. 2017). Genomic prediction approaches are widely applied in the study of complex traits in natural and experimental populations and facilitate the estimation of genomic variance (σ_g^2), genomic heritability (h_g^2), and other quantitative, population, and evolutionary genetic parameters (Bulmer et al. 1980; Falconer and Mackay 1996; Lynch and Walsh 1998; Meuwissen et al. 2001; Bernardo 2002; Hill et al. 2008; Van Heerwaarden et al. 2008; Crossa et al. 2010; de los Campos et al. 2015; Huang and Mackay 2016; Lehermeier et al. 2017; Noble et al. 2019), and has been

widely adopted in plant breeding, human genetics, and biology (Habier et al. 2007; Goddard and Hayes 2007; Heffner et al. 2009; Bloom et al. 2013).

Genomic variance (σ_g^2)—the variance explained by genome-wide associations between the underlying quantitative trait locus and DNA markers genotyped in the training population—is often estimated in genetic experiments (Visscher et al. 2007; Gao et al. 2012; Lee et al. 2012, 2013; Lipka et al. 2014; Rutkoski et al. 2014; Kumar et al. 2015; Piaskowski et al. 2018; Rice and Lipka 2019; Krause et al. 2019; Pincot et al. 2020; Petrasch et al. 2021; Yadav et al. 2021) using genomic relationship matrices (GRMs, \mathbf{K}), which measure the relatedness among entries (Yang et al. 2010; Habier et al. 2013). The selection of \mathbf{K} is used directly in solutions to the mixed model equations and is central to estimating the correct variance components in LMM analyses (Henderson 1953; Searle et al. 1992; Lynch and Walsh 1998; Mrode 2014). The phenotypic variance–covariance (\mathbf{V}) is $\mathbf{V} = \mathbf{G} + \mathbf{R}$, where $\mathbf{R} = \mathbf{I}\sigma_e^2$ is the residual variance–covariance, and $\mathbf{G} = \mathbf{K}\sigma_g^2$ is the genomic variance–covariance (Henderson 1953; Searle et al. 1992; Lynch and Walsh 1998; Piepho 2019). The genomic variance σ_g^2 is a scalar and, thus, any change in \mathbf{K} will impact σ_g^2 estimates. Genomic variance is found in many ratios throughout modern quantitative genetic research, including genomic heritability, prediction accuracy,

Received: December 27, 2021. Accepted: March 17, 2022

© The Author(s) 2022. Published by Oxford University Press on behalf of Genetics Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

selection reliability, prediction error variance, and response to genomic selection (Goddard 2009; Hickey et al. 2009; Gorjanc et al. 2015). Of these ratios, genomic heritability has been the most frequently reported in public research (Speed et al. 2012, 2017; Speed and Balding 2015; de los Campos et al. 2015; Legarra 2016; Lehermeier et al. 2017; Yang et al. 2017).

Genomic heritability is

$$h_g^2 = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_e^2}, \quad (1)$$

where σ_g^2 is the genomic variance and σ_e^2 is the residual variance on an entry-mean basis. Genomic heritability is often estimated by substituting restricted maximum likelihood (REML) variance component estimates into (1). We studied how different forms of \mathbf{K} affect variance component estimates. We found that, even for large data sets, there are systematic differences in the genomic variance component estimates arising from different forms of \mathbf{K} (VanRaden 2008; Astle et al. 2009; Yang et al. 2010; Forni et al. 2011; Endelman and Jannink 2012) and that the resulting variance component estimates may not always be correct when directly substituted into (1), as is routine practice. Despite this, researchers often simultaneously use the same approaches for genomic prediction and variance component estimation and may consequently report incorrect genomic heritability estimates.

Here, using the average semivariance (ASV), introduced by Piepho (2019) and expanded by Feldmann et al. (2021), we derive a new form for \mathbf{K} , referred to as \mathbf{K}_{ASV} , which is the product $\bar{\mathbf{K}} = \bar{\mathbf{Z}} \bar{\mathbf{Z}}^T$ from the mean-centered marker matrix $\bar{\mathbf{Z}} = \mathbf{PZ}$, where $\mathbf{P} = \mathbf{I}_n - n^{-1} \mathbf{1}_n \mathbf{1}_n^T$ is the idempotent, mean-centering $n \times n$ -matrix. The ASV relationship matrix is

$$\mathbf{K}_{ASV} = \frac{\bar{\mathbf{K}}}{(n-1)^{-1} \text{tr}(\bar{\mathbf{K}})}. \quad (2)$$

This matrix is scaled to the residual variance-covariance matrix and directly yields accurate estimates of σ_g^2 and h_g^2 regardless of population constitution, population size, or true heritability. It is possible to scale other forms of the via a division by $(n-1)^{-1} \text{tr}(\mathbf{K})$ or to scale estimates of genomic variance from any form of \mathbf{K} by multiplying $(n-1)^{-1} \text{tr}(\mathbf{K})$ by $\hat{\sigma}_g^2$ to obtain ASV estimates of variance component. We explore the practical implications of \mathbf{K}_{ASV} for estimating σ_g^2 and h_g^2 in a wild population of *Arabidopsis thaliana* (Atwell et al. 2010), a wheat (*Triticum aestivum*) breeding population (Crossa et al. 2010), a laboratory mouse (*Mus musculus*) population (Valdar et al. 2006), an apple (*Malus × domestica*) breeding population (Kumar et al. 2015), and a pig (*Sus scrofa*) breeding population (Cleveland et al. 2012). The ASV approach that we propose can be used to estimate variance components in genetic evaluation studies in plants, animals, microbes, and humans.

The Average Semivariance

The ASV estimator of the total variance (Piepho 2019) is half the average total pairwise variance of a difference between entries and can be decomposed into independent sources of variance, e.g. genomic and residual. There are two alternative ASV derivations, both leading to the same definitions of the estimators. The first derivation originated in geostatistics and estimated the semivariance as half of the variance among all pairwise

differences among genotypic values (g), i.e. $2^{-1} \text{var}(g_i - g_j)$ (Webster and Oliver 2007; Piepho 2019). Piepho (2019) derived ASV from a study's observations, worked out the semivariance and took the average across all pairs of observations. In our context, there is an equivalent alternative derivation based on the sample variance of the genotypic values Estaghviroo et al. (2013). The sample variance among genotypic values is $(n-1)^{-1} \sum_{i=1}^n (g_i - \bar{g})^2$. That is to say that the expected values of the sample variance of genotypic values are the ASV, i.e. $E(s_g^2) = \theta_g^{ASV}$. ASV can be used to estimate and partition the total variance in LMM analyses into parts; such as the total variance, as in Piepho (2019), the variance explained by large effect markers and marker-marker interactions, as in Feldmann et al. (2021), and genomic variance, as shown below.

ASV definitions of genomic variance and heritability

In complex traits analyses, there is a crucial difference in the treatment of genotypes and effects in statistical models used for data analysis vs the quantitative genetics theory (Yang et al. 2010; Speed et al. 2012, 2017; de los Campos et al. 2015; Speed and Balding 2015; Legarra 2016). In quantitative genetics theory, between entry differences in genetic values and genomic variance are attributed to the a random sampling of marker genotypes (Bulmer et al. 1980; Lande and Thompson 1990; Falconer and Mackay 1996; Lynch and Walsh 1998) and, in an LMM framework, variation stems from a random sampling of the marker effects. Despite differences in derivation and assumptions regarding the source of randomness, the resulting variance-covariance structure between the two coincides under specific experimental, population, and marker sampling conditions (de los Campos et al. 2015; Legarra 2016). With this in mind, we derived an approach using the ASV that relies on the assumptions of LMM analyses, e.g. random marker effects, but yields correct estimates of genomic variance.

The analyses shown throughout this paper assume the dependent variables are least squared means (LSMs) or other adjusted means for entries (\mathbf{y}). $\mathbf{R} = \mathbf{I}_n \sigma_e^2$ gives the residual variance of the LSMs. The ASV can efficiently deal with more general forms of variance-covariance matrices in generalized LMMs (Piepho 2019). The LMM for this analysis is

$$\mathbf{y} = \mathbf{1}_n \mu + \mathbf{I}_n \mathbf{g} + \boldsymbol{\epsilon} \quad (3)$$

where \mathbf{y} is the vector of phenotypic LSMs for n entries, n is the number of entries, $\mathbf{1}_n$ is an n -element vector of ones, μ is the population mean, \mathbf{I}_n is the identity matrix of size n , \mathbf{g} is an n -element vector of random effect values for entries with $\mathbf{g} \sim N(0, \mathbf{K} \sigma_g^2)$, and $\boldsymbol{\epsilon}$ is the residual for each entry with $\boldsymbol{\epsilon} \sim N(0, \mathbf{I}_n \sigma_e^2)$.

The ASV definition of variance from LMM (3) is

$$\theta_y^{ASV} = (n-1)^{-1} \text{tr}(\mathbf{V}\mathbf{P}) = \theta_g^{ASV} + \theta_e^{ASV}, \quad (4)$$

where θ_y^{ASV} is the phenotypic variance, $\mathbf{V} = \mathbf{K} \sigma_g^2 + \mathbf{I}_n \sigma_e^2$ is the variance-covariance among observations, θ_g^{ASV} is the genomic ASV, and θ_e^{ASV} is the ASV of the residuals. If we assume $\mathbf{G} = \mathbf{K} \sigma_g^2$, where \mathbf{G} is the variance-covariance of the best linear unbiased predictors (BLUPs) of the genotypic values \mathbf{g} , it can be inferred that the magnitude of σ_g^2 is directly inverse to $\text{tr}(\mathbf{K})$ because $\mathbf{V} = \mathbf{K} \sigma_g^2 + \mathbf{I}_n \sigma_e^2$.

The ASV definition of the genomic variance is

$$\theta_g^{ASV} = (n-1)^{-1} \text{tr}(\mathbf{Z}\mathbf{Z}^T\mathbf{P})\sigma_g^2 = (n-1)^{-1} \text{tr}(\bar{\mathbf{Z}}\bar{\mathbf{Z}}^T)\sigma_g^2 = (n-1)^{-1} \text{tr}(\bar{\mathbf{K}})\sigma_g^2 \quad (5)$$

where $\bar{\mathbf{Z}} = \mathbf{P}\mathbf{Z}$ is the mean-centered marker matrix, and $\bar{\mathbf{K}} = \bar{\mathbf{Z}}\bar{\mathbf{Z}}^T$ is the realized genomic relationship or kinship matrix described by VanRaden (2008), omitting the scaling constant $2\sum_j p_j(1-p_j)$, where p_j is the allele frequency of the j th SNP, which requires Hardy-Weinberg equilibrium (HWE) to hold (de los Campos et al. 2015), and $\text{tr}(\mathbf{Z}\mathbf{Z}^T\mathbf{P}) = \text{tr}(\bar{\mathbf{Z}}\bar{\mathbf{Z}}^T)$. The trace of $\bar{\mathbf{Z}}\bar{\mathbf{Z}}^T$ is a function of heterozygosity in the observed population (Vitezica et al. 2013, 2017; Legarra et al. 2018). When the observed population is in HWE, $n^{-1}\text{tr}(\bar{\mathbf{K}}) = 1$, and when the population is not in HWE due to inbreeding, the $n^{-1}\text{tr}(\bar{\mathbf{K}}) = 1+f$, where f is the inbreeding coefficient (Endelman and Jannink 2012; Legarra et al. 2018). In the general case, $\theta_g^{ASV} = \left((n-1)^{-1}\text{tr}(\mathbf{K}\mathbf{P})\right)\sigma_g^2$, where \mathbf{K} is any form of the GRM calculated from \mathbf{Z} , without centering, or $\bar{\mathbf{Z}}$, with centering, because $\text{tr}(\bar{\mathbf{K}}) = \text{tr}(\mathbf{K}\mathbf{P})$.

The ASV definition of the residual variance is

$$\theta_e^{ASV} = (n-1)^{-1}\sigma_e^2 \text{tr}(\mathbf{I}_n \mathbf{I}_n^T \mathbf{P}) = \sigma_e^2. \quad (6)$$

Notably, the genomic variance θ_g^{ASV} is on the same scale as the residual variance θ_e^{ASV} , and both are defined such that (4) is accurate. REML estimates of the residual variance are equivalent to ASV estimates when best linear unbiased estimators or LSMs are the response variable y .

Two equivalent methods yield accurate h_g^2 estimates

There are two equivalent ways to obtain accurate estimates of genomic variance and subsequently genomic heritability. The first method, our recommended approach, utilizes \mathbf{K}_{ASV} (2) in the LMM analysis and directly yields accurate estimates of the genomic variance components from the model by rescaling the GRM. The first method works because $\mathbf{V} = \mathbf{K}\sigma_g^2 + \mathbf{I}_n\sigma_e^2$ is a true statement regardless of \mathbf{K} , but different choices of \mathbf{K} change the scaling and interpretation of σ_g^2 . Thus, variance components estimated by ASV can then be substituted directly into (1) without any adjustment.

The second method is to adjust the genomic variance component estimates from any form of \mathbf{K} by multiplying them by a scaling factor $((n-1)^{-1}\text{tr}(\bar{\mathbf{K}}))$ defined by the population size (n) and the diagonals of the chosen GRM ($\text{tr}(\bar{\mathbf{K}})$). Through substitution of (5) and (6) into (1), the ASV estimator of genomic heritability h_g^{ASV} is

$$\hat{h}_g^{ASV} = \frac{\hat{\theta}_g^{ASV}}{\hat{\theta}_y^{ASV}} = \frac{\hat{\theta}_g^{ASV}}{\hat{\theta}_g^{ASV} + \hat{\theta}_e^{ASV}} = \frac{(n-1)^{-1}\text{tr}(\bar{\mathbf{K}})\hat{\sigma}_g^2}{(n-1)^{-1}\text{tr}(\bar{\mathbf{K}})\hat{\sigma}_g^2 + \hat{\sigma}_e^2}. \quad (7)$$

This formulation can be used directly with any form of \mathbf{K} or $\bar{\mathbf{K}}$ by substituting REML variance component estimates. Note that $(n-1)^{-1}\text{tr}(\bar{\mathbf{K}})$ is the same as the scaling coefficient used in (2). The second strategy is analogous to the post hoc adjustment approach Feldmann et al. (2021) proposed.

Materials and methods

Genomic relationship matrices

We calculated and applied seven relationship matrices for each population, simulated or case example, including \mathbf{K}_{ASV} . We used

`AGHmatrix::Gmatrix()` to calculate the Yang et al. (2010) (\mathbf{K}_Y) and VanRaden (2008) relationship (\mathbf{K}_{VR}) matrices (Rampazo Amadeu et al. 2016), `rBLUP::A.mat()` to calculate the Endelman and Jannink (2012) (\mathbf{K}_{EJ}) relationship matrix, and `statgenGWAS::kinship()` to estimate the Astle et al. (2009) (\mathbf{K}_{AB}) and IBS relationship (\mathbf{K}_{IBS}) matrices (van Rossum and Kruijer 2020).

The form proposed by VanRaden (2008) is

$$\mathbf{K}_{VR} = \frac{\bar{\mathbf{Z}}\bar{\mathbf{Z}}^T}{2\sum_{j=1}^m p_j(1-p_j)}, \quad (8)$$

where $\bar{\mathbf{Z}}$ is the marker matrix centered on column means ($2p_j$), and p_j is the minor allele frequency (MAF) for the j th SNP. This form assumes HWE and obtains p_j from a historical reference population, not the observed population. When p_j originates from the observed population, the centering by $2p_j$ is equivalent to column centering and \mathbf{K}_{VR} only differs from \mathbf{K}_{ASV} by a scaling factor.

The normalized relationship matrix, \mathbf{K}_{GN} , was explicitly introduced as the normalized relationship matrix by Forni et al. (2011) as

$$\mathbf{K}_{GN} = \frac{\bar{\mathbf{K}}}{n^{-1}\text{tr}(\bar{\mathbf{K}})}. \quad (9)$$

This form is the most numerically similar to \mathbf{K}_{ASV} and only differs by a single denominator degree of freedom.

The form of the relationship matrix proposed by Endelman and Jannink (2012) is

$$\mathbf{K}_{EJ} = \frac{\delta \mathbf{S}_{ii} \mathbf{I} + (1-\delta) \mathbf{S} + \langle \bar{\mathbf{Z}}_{\cdot j} \rangle \langle \bar{\mathbf{Z}}_{\cdot j}^T \rangle}{2\langle p_j(1-p_j) \rangle}, \quad (10)$$

where $\delta \approx (n/m)CV^{-2}$ is a shrinkage factor, CV^2 is the coefficient of variation of the eigenvalues of \mathbf{S} , $\mathbf{S} = m^{-1}\bar{\mathbf{Z}}\bar{\mathbf{Z}}^T - \langle \bar{\mathbf{Z}}_{\cdot k} \rangle \langle \bar{\mathbf{Z}}_{\cdot k}^T \rangle$, $\langle \mathbf{S}_{ii} \rangle$ is the mean of diagonal elements of \mathbf{S} . Notably, at high marker densities, when $\delta=0$, Endelman and Jannink (2012) is equivalent to VanRaden (2008).

The method proposed by Yang et al. (2010) also centers the columns of \mathbf{Z} by subtracting $2p_j$

$$\mathbf{K}_{Y_{ik}} = \begin{cases} m^{-1} \sum_{j=1}^m \frac{(z_{ji} - 2p_j)(z_{jk} - 2p_j)}{2p_j(1-p_j)}, & i \neq k \\ 1 + m^{-1} \sum_{j=1}^m \frac{z_{ji}^2 - (1+2p_j)z_{ji} + 2p_j^2}{2p_j(1-p_j)}, & i = k \end{cases}, \quad (11)$$

where z_{ij} is the j th SNP in the i th individuals, z_{jk} is the j th SNP in the k th individual when $j \neq k$, and m is the number of markers. The diagonals are treated differently than the off-diagonals in this form.

The method proposed by Astle et al. (2009) is

$$\mathbf{K}_{AB} = (2m)^{-1} \sum_{j=1}^m \frac{(z_j - 2p_j)1)(z_j - 2p_j)1^T}{2p_j(1-p_j)}, \quad (12)$$

where z_j is the i -element vector of the j th SNP.

The classical identity-by-state definition is (Astle et al. 2009):

$$\mathbf{K}_{IBS} = (2m)^{-1} \sum_{j=1}^m (z_j - 1)(z_j - 1)^T + \frac{1}{2}. \quad (13)$$

Note that this is the only calculation that is not scaled or centered by any function of p_j .

For each model and each simulation, we estimated two variance components (σ_g^2 and σ_e^2) using `sommer::mmer()` and took the ratio of variance components in R v4.1.0 (R Core Team 2020). We estimated genomic heritability using the standard form by substituting REML estimates from (3) into (1).

LMM analysis in R

In the `sommer` R package (Covarrubias-Pazarán 2016), LMM (3) is expressed as

```
mmer(fixed = Y ~ 1,
     random = ~ vs(Entry, Gu = K),
     rcov = ~ units,
     data = data)
```

where `data` is an $n \times 2$ matrix with `Y` as a column of LSMs, `Entry` is a column of factor-coded entries, and `K` is one of the seven GRMs in this study given. A large number of statistical computing solutions can fit this model, including `regress` (Clifford and McCullagh 2006), `ASREML` (Butler 2021), `rrBLUP` (Endelman 2011), `GEMMA` (Zhou and Stephens 2012), `emmREML` (Akdemir and Okeke 2015), `brms` (Bürkner 2017), and `lme4GS` (Caamal-Pat et al. 2021).

Simulated data

We generated 36 experiment designs with different heterozygosity $H = 0.0, 0.25, 0.5,$ and 0.75 and different trait heritability $h_g^2 = 0.2, 0.5,$ and 0.8 and for population sizes of $n = 250, 500,$ and $1,000$. In all examples, 1,000 populations genotyped at $m = 5,000$ causal loci were used to generate the genetic traits. We simulated all $m = 5,000$ marker effects following a normal distribution $\mu = 0$ and $\sigma = 1$. When multiplied by the marker genotypes and summed, the score is an individual's true genetic value, g . Residuals were simulated with $\mu = 0$ and $\sigma_e^2 = (1 - h^2)/(h^2 s_g^2)$ to obtain a trait with the desired genomic heritability (Endelman 2011) and $s_g^2 = (n - 1)^{-1} \sum_{i=1}^n (g_i - \bar{g})^2$ is the sample variance among genotypic values (Estaghirou et al. 2013). In this study, the true value of $h_g^2 = 0.2, 0.5,$ or 0.8 . All plots were made with the `ggplot2` package (Wickham 2016) in R 4.1.0 (R Core Team 2020).

Empirical data

We analyzed four publicly available data sets using seven methods for calculating the realized relationship matrix and estimated h_g^2 . First, we analyzed six traits from Kumar et al. (2015), which evaluated a breeding population of $n = 247$ apple (*Malus × domestica*) hybrids genotyped at $m = 2,829$ SNPs with $H = 0.348$ (Kumar et al. 2015). The reported traits were fruit weight (WT), fruit firmness (FF), greasiness (GRE), crispiness (CRI), juiciness (JUI), and flavor intensity (FIN). The shrinkage factor δ from Endelman and Jannink (2012) was equal to 0.02. Second, we analyzed the wheat data set from Crossa et al. (2010), who evaluated $n = 599$ wheat (*Triticum aestivum*) fully inbred lines ($H = 0.0; \delta = 0.03$) for grain yield (GY) in four environments genotyped for $m = 1,278$ SNPs. We evaluated each environment (i.e. GY-E1, GY-E2, GY-E3, and GY-E4) with an independent model. Third, we analyzed data from Valdar et al. (2006) which evaluated a laboratory population of $n = 1,814$ stock mice (*M. musculus*) for body mass index (BMI), body length, and weight and genotyped for $m = 10,346$ SNPs ($H = 0.363; \delta = 0.01$). Fourth, we analyzed a population of $n = 1,057$ naturally occurring *Arabidopsis* (*A. thaliana*) ecotypes phenotyped for the mean (μ) and SD of flowering time under 10°C (FT10) and 16°C (FT16) and genotyped at $m = 193,697$ SNPs ($H = 0.0; \delta = 0.0$) from Atwell et al. (2010) and Alonso-Blanco et al. (2016). Fifth, we analyzed a commercial pig (*S. scrofa*) population

made available by PIC (a Genus company) with $n = 3,534$ entries genotyped at $m = 52,843$ SNPs ($H = 0.311; \delta = 0.0$) that were phenotyped for five traits: T1, T2, T3, T4, and T5 (Cleveland et al. 2012). For each population, we calculate the seven relationship matrices (8–9) and apply them in (3) for each trait to estimate \hat{h}_g^2 with (1).

We performed cross-validation to determine predictive ability $r(\hat{g}, y)$, or the correlation between BLUPs and LSM, which is a measure of success commonly reported in genome prediction studies that indicates how informative the phenotype is as a measure of the genomic value. We also estimated the prediction accuracy $r(\hat{g}, y)/\sqrt{\hat{h}_g^2}$, which is a measure of success that scales the predictive ability to the upper limit ($\sqrt{\hat{h}_g^2}$) (Crossa et al. 2014).

An ideal situation for genomic prediction is a low value of predictive ability and a high value of prediction accuracy. When the predictive ability is high, genomic selection is unlikely to outperform phenotypic selection. When the prediction accuracy is low, the model is bad at capturing the variation in genomic values. We first split each population into 80% train and 20% test and estimated genomic BLUPs and then calculated the accuracy as the correlation between the estimated LSM y and the BLUP \hat{g} for all entries in the test set. We performed this cross-validation scheme 100 times for each population and each trait.

Results

Analysis of simulated data confirms that ASV yields accurate estimates of genomic variance

The ASV relationship matrix yielded suitable estimates of genomic variance and genomic heritability in the observed populations, while the other methods varied with the level of heterozygosity. When heterozygosity $H < 0.5$, the genomic variance tends to be underestimated, and when $H > 0.5$, the genomic variance tends to be overestimated (Fig. 1) by methods excluding (2) and (9). This pattern was realized regardless of the population size, e.g. $n = 250, 500,$ and $1,000$. All methods tend to produce accurate estimates when $H = 0.5$, in which case the inbreeding coefficient $f = 0$ and HWE is not violated.

The precision (variance) improved by increasing the population size (n), but the accuracy (bias) did not improve. It has been demonstrated ad nauseam that increasing n increases precision or lowers the sampling variance of the estimates but does not eliminate bias (Laird and Ware 1982; Searle et al. 1992; Lynch and Walsh 1998; Legarra 2016). Notably, the entire parameter space of h_g^2 was observed when the population size is small (Fig. 1). Only \mathbf{K}_{ASV} and \mathbf{K}_{GN} yielded stable precision as H increased (Fig. 2). Other methods that we examined have variable precision and variable accuracy depending on the sample size, heterozygosity, and the true value of h_g^2 (Figs. 1 and 2). Interestingly, we observed an interaction between h_g^2 and H that impacted the precision of genomic heritability estimation did not affect \mathbf{K}_{GN} or \mathbf{K}_{ASV} . Precision improved as H increased for high heritability traits and precision worsened as H increased for low heritability traits. For traits where $h_g^2 = 0.5$, precision was constant.

Analysis of simulated and empirical data confirms that ASV does not impact BLUPs or prediction accuracy

Neither the predictive ability ($r(\hat{g}, y)$) nor the BLUPs from genomic best linear unbiased predictor are affected by ASV. In our simulated populations, the predictive ability was equal across all

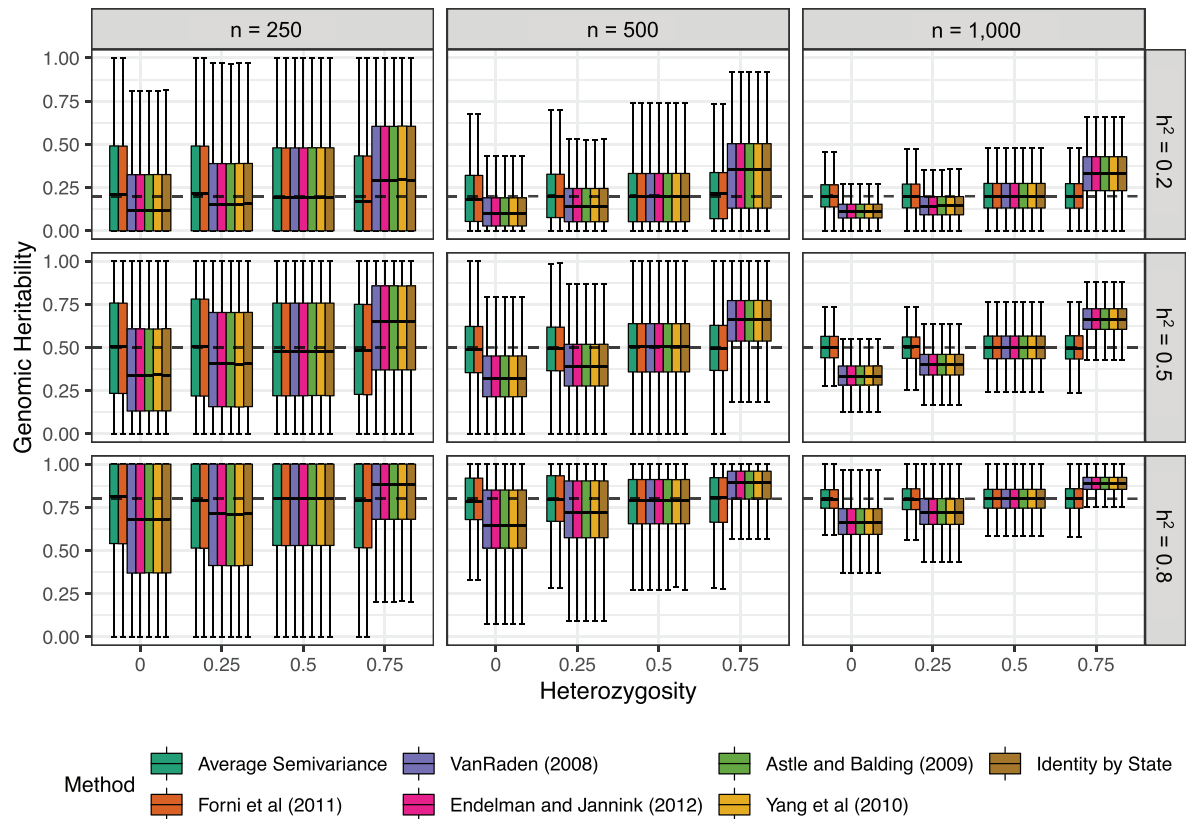


Fig. 1. Effect of heritability (h_g^2), population size (n), and heterozygosity (H) on the accuracy of genomic heritability estimates. Phenotypic observations were simulated for 1,000 samples with $n = 250, 500$, and $1,000$ (left to right) genotyped for $m = 5,000$ SNPs and the average heterozygosity $H = 0\%$, 25% , 50% , and 75% . The accuracy of genomic heritability estimates (\hat{h}_g^2) from LMMs fit using the seven relationship matrices is shown for true genomic heritability ($h_g^2 = 0.2$ (upper panel), 0.5 (middle panel), and 0.8 (lower panel)). The upper and lower halves of each box correspond to the first and third quartiles (the 25th and 75th percentiles). The notch corresponds to the median (the 50th percentile). The upper whisker extends from the box to the highest value that is within 1.5 IQR of the third quartile, where IQR is the interquartile range, or distance between the first and third quartiles. The lower whisker extends from the first quartile to the lowest value within 1.5 IQR of the quartile. The dashed line in each plot is the true value from simulations.

seven GRMs that we tested (Fig. 3), but the prediction accuracy ($\hat{h}_g^{-1} r(\hat{g}, y)$) varies with the choice of GRM and therefore the heterozygosity in the sampled populations. In 22 empirical trait \times population examples we evaluated, the differences in the prediction accuracy, when present, appeared to be negligible and do not lend themselves clearly to “better” or “worse” categories (Figs. 4 and 5). While the choice of \mathbf{K} does not impact BLUP, it does impact estimates of genomic variance $\hat{\sigma}_g^2$, genomic heritability \hat{h}_g^2 , prediction accuracy $\hat{h}_g^{-1} r(\hat{g}, y)$ (Fig. 5), average prediction error variance PEV, and selection reliability $1 - \sigma_g^{-2} \text{PEV}$, which all rely on $\hat{\sigma}_g^2$. Differences in Fig. 5 are more pronounced for the fully inbred populations, e.g. *Arabidopsis* and wheat, than the partially inbred populations, e.g. pig, mouse, and apple. ASV allows users to understand how well GS is performing relative to phenotypic selection and to predict how reliable genomic selection can be for certain traits in specific populations more accurately than other methods since it directly yields accurate estimates of σ_g^2 and h_g^2 (Figs. 3–5).

The relationship between \mathbf{K}_{ASV} and \mathbf{K}_{GN}

We found that the normalized \mathbf{K} , i.e. \mathbf{K}_{GN} (9), proposed by Forni et al. (2011) and further described by Legarra (2016), yields estimates of \mathbf{K} that only deviated from \mathbf{K}_{ASV} by a single degree of freedom in the denominator of the matrix scaling factor. Although these estimators were derived through different approaches and

with different concepts in mind, they are numerically similar, apart from a single degree of freedom difference in the divisor of the GRM: Forni et al. (2011) used the number of entries (n), whereas we used $df_g = n - 1$ for calculating the sample variance (Bulmer 1979). \mathbf{K}_{GN} , instead of being biased by a factor of $1/(1 + f)$, \mathbf{K}_{GN} is biased by a factor of $(n - 1)/n$. Our simulations confirm this deviation and the median genomic variance estimates using \mathbf{K}_{GN} were slightly larger than \mathbf{K}_{ASV} , which was equal to the true value in the simulations (Fig. 1). This work, Forni et al. (2011), and Legarra (2016) all arrive at numerically similar solutions through conceptually different derivations, which we feel is indicative of the value of these approaches for the plant, animal, and human genetic studies that rely on genomic relatedness, e.g. GWAS, genomic prediction, or inferring population structure and ancestry.

\mathbf{K}_{ASV} yields genomic variance estimates that naturally account for inbreeding

Inbreeding changes the patterns of among and within entry genomic variance and drives deviations from HWE (Bernardo 2002; Wricke and Weber 2010; Legarra 2016; Isik et al. 2017). A challenge of partial inbreeding is that researchers may not know or infer the reference population, making unadjusted genomic variance estimates hard to interpret (Legarra 2016). In genomic evaluations in plants and animals, the current population is often interpreted as the reference population, but this is an inaccurate

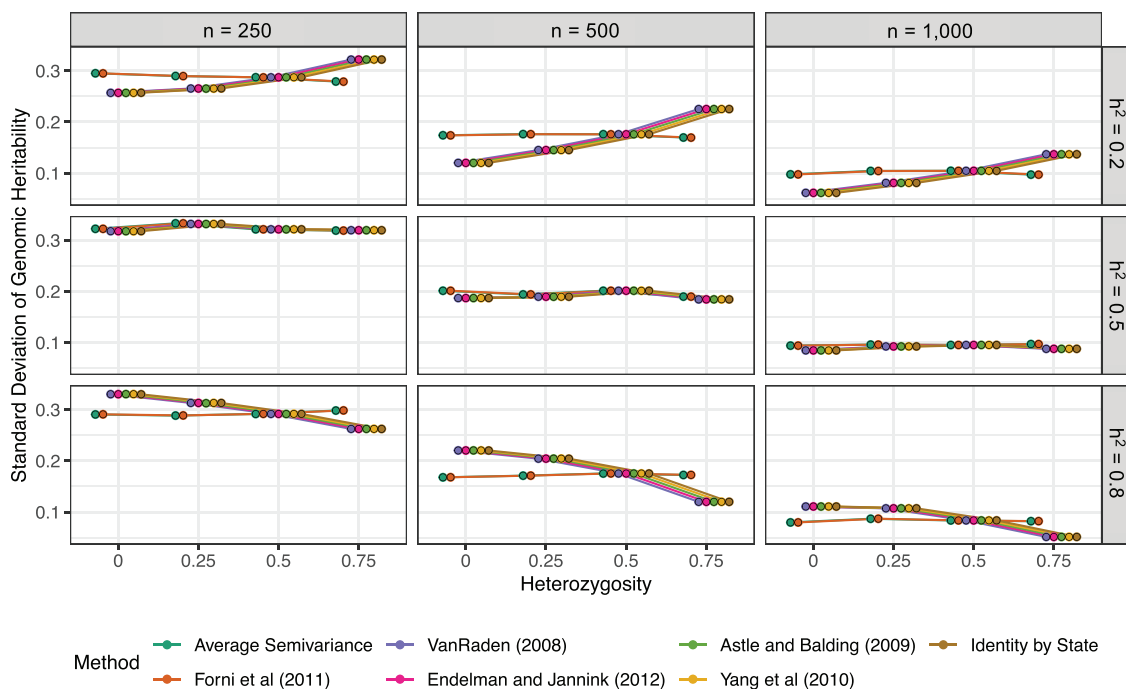


Fig. 2. Precision of genomic heritability estimates from simulations. The SDs from the simulation experiments are plotted against heterozygosity (H), population size (n), and true genomic heritability (h^2_g) for each of the seven GRMs evaluated in this study. Points and lines are jittered around each value of H to improve clarity as many of the lines are parallel and overlap one another.

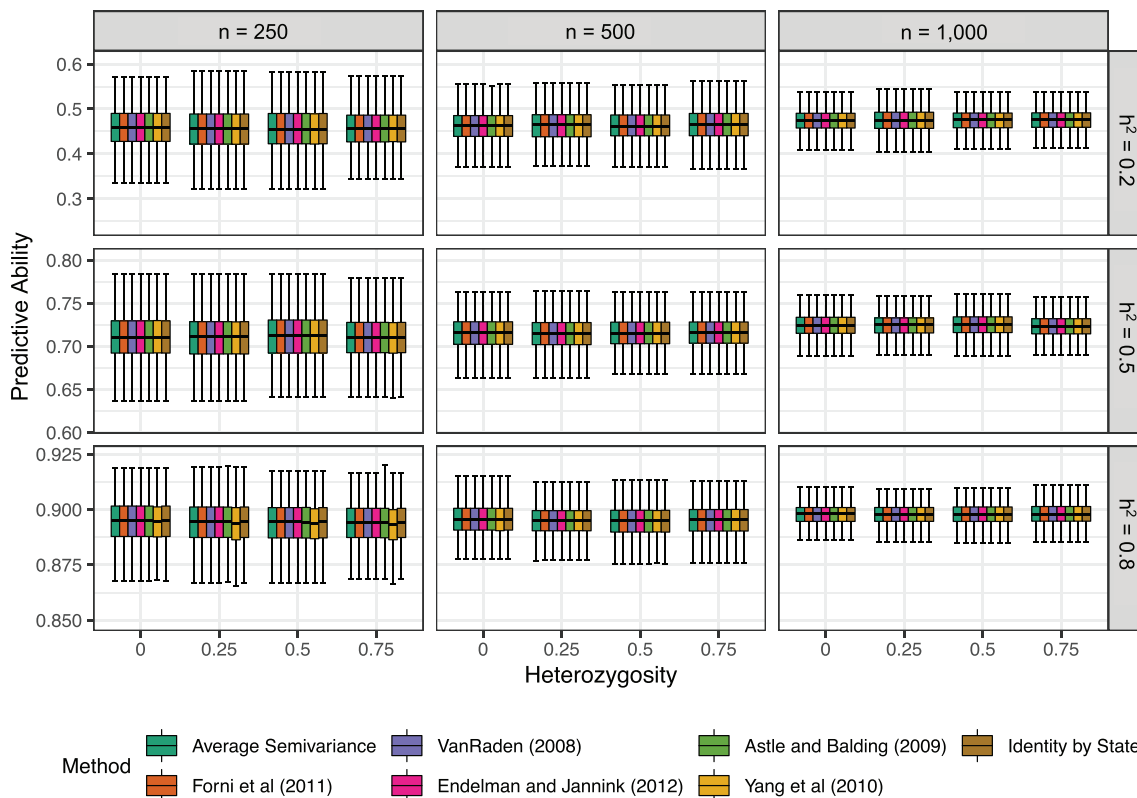


Fig. 3. Effect of heritability (h^2_g), population size (n), and heterozygosity (H) on the predictive ability $r(\hat{g}, y)$. Phenotypic observations were simulated for 1,000 samples with $n = 250, 500$, and 1000 (left to right) genotyped for $m = 5,000$ SNPs and the average heterozygosity $H = 0\%$, 25%, 50%, and 75%. $r(\hat{g}, g)$ estimates from LMMs fit using the seven relationship matrices is shown for true genomic heritability $h^2_g = 0.2$ (upper panel), 0.5 (middle panel), and 0.8 (lower panel). Each box's upper and lower halves correspond to the first and third quartiles (the 25th and 75th percentiles). The notch corresponds to the median (the 50th percentile). The upper whisker extends from the box to the highest value within 1.5 IQR of the third quartile, where IQR is the interquartile range or distance between the first and third quartiles. The lower whisker extends from the first quartile to the lowest value within 1.5 IQR of the quartile.

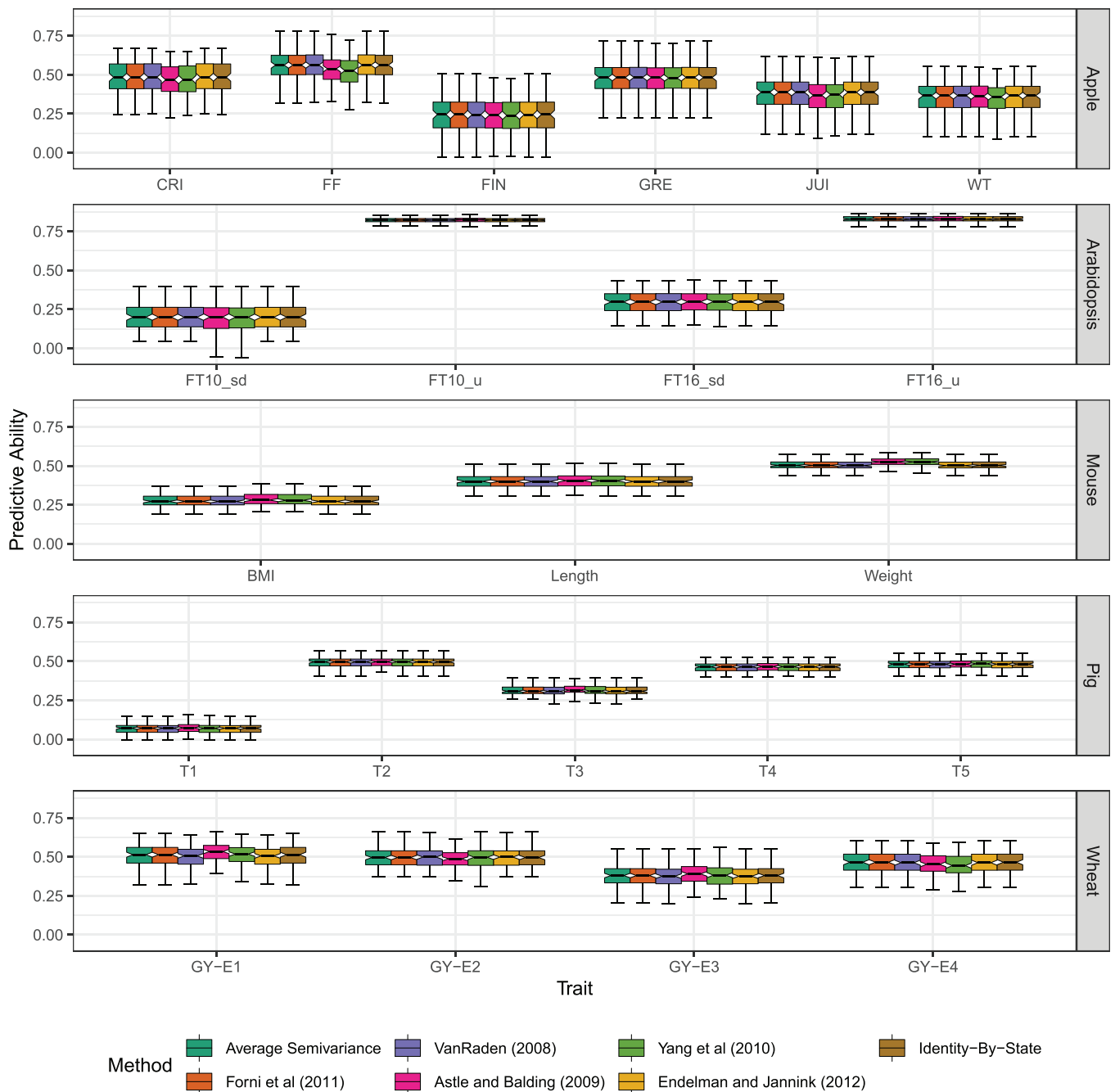


Fig. 4. Cross-validated predictive ability from five case studies and including 22 phenotypic traits using seven GRMs. Cross-validated predictive ability ($r(\hat{g}, y)$) results are presented from 100 realizations of 80 : 20 cross-validation using the seven relationship matrices for six traits in an apple population with $n = 247$ entries genotyped at $m = 2,829$ SNPs (Kumar et al. 2015) (first row), four traits in an *Arabidopsis* population with $n = 1,057$ entries genotyped at $m = 193,697$ SNPs (Atwell et al. 2010) (second row), three traits in an mouse population with $n = 1,814$ entries genotyped at $m = 10,346$ SNPs (Valdar et al. 2006) (third row), and five traits in a pig population with $n = 3,534$ entries genotyped at 52,843 SNPs (Cleveland et al. 2012) (fourth row), four traits in an wheat population with $n = 599$ entries genotyped at $m = 1,278$ SNPs (Crossa et al. 2010) (fifth row). For the *Arabidopsis* data set (second row), \mathbf{K}_Y systematically produced singular systems in *sommer::mmer()* and prediction accuracy was not estimated for either FT10 $_{\mu}$ or FT16 $_{\mu}$. Each box's upper and lower halves correspond to the first and third quartiles (the 25th and 75th percentiles). The notch corresponds to the median (the 50th percentile). The upper whisker extends from the box to the highest value within 1.5 IQR of the third quartile, where IQR is the interquartile range or distance between the first and third quartiles. The lower whisker extends from the first quartile to the lowest value within 1.5 IQR of the quartile.

interpretation unless the population is at HWE and $H = 0.5$ by design or happenstance. It may be that the only reference population that is concretely defined is the sample population. In connection to Legarra (2016), our work will allow researchers to directly obtain accurate estimates of the genomic variance in the sample population regardless of whether the assumptions of HWE are met.

When the study populations are entirely, or partially, inbred as in wheat, *Arabidopsis*, or inbred per se evaluations in hybrid crops, such as maize, tomato, rice, the covariance among marker effects increases. Lehermeier et al. (2017) proposed a novel method (termed method M2) to account for the covariance of marker effects, which increases the genomic variance estimates in recombinant inbred line populations. Our analyses of the same flowering time data with

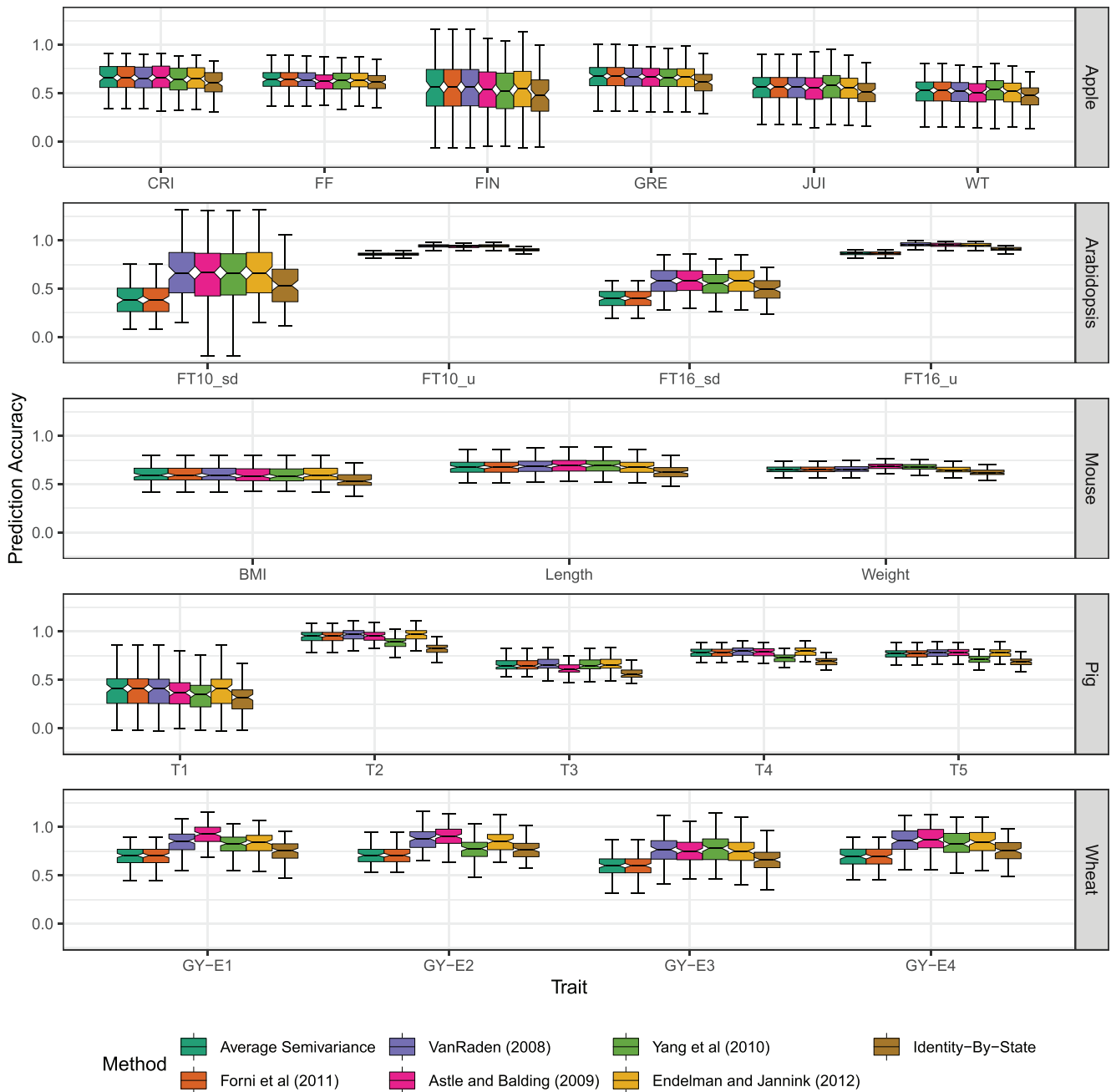


Fig. 5. Cross-validated prediction accuracy from five case studies and including 22 phenotypic traits using seven GRMs. Cross-validated prediction accuracy ($r(\hat{g}, y) / \sqrt{\hat{h}^2}$) results are presented from 100 realizations of 80 : 20 cross-validation using the seven relationship matrices for six traits in an apple population with $n = 247$ entries genotyped at $m = 2,829$ SNPs (Kumar et al. 2015) (first row), four traits in an *Arabidopsis* population with $n = 1,057$ entries genotyped at $m = 193,697$ SNPs (Atwell et al. 2010) (second row), three traits in an mouse population with $n = 1,814$ entries genotyped at $m = 10,346$ SNPs (Valdar et al. 2006) (third row), and five traits in a pig population with $n = 3,534$ entries genotyped at 52,843 SNPs (Cleveland et al. 2012) (fourth row), four traits in an wheat population with $n = 599$ entries genotyped at $m = 1,278$ SNPs (Crossa et al. 2010) (fifth row). For the *Arabidopsis* data set (second row), \mathbf{K}_Y systematically produced singular systems in *sommer::mmer()* and prediction accuracy was not estimated for either $FT10_u$ or $FT16_u$. Each box's upper and lower halves correspond to the first and third quartiles (the 25th and 75th percentiles). The notch corresponds to the median (the 50th percentile). The upper whisker extends from the box to the highest value within 1.5 IQR of the third quartile, where IQR is the interquartile range or distance between the first and third quartiles. The lower whisker extends from the first quartile to the lowest value within 1.5 IQR of the quartile.

ASV yielded equivalent results and patterns to Lehermeier et al. (2017), suggesting that \mathbf{K}_{ASV} may be providing an estimate of genomic variance that naturally accounts for linkage disequilibrium (LD) and the covariance of marker effects (Table 1). We believe that the similarity in results is because LD is associated with the off-diagonal elements of \mathbf{K} , which is taken into account using ASV.

Discussion

GRMs are routine in human, plant, animal, and microbial genetics in agriculture, medicine, and biology for both prediction of genetic values, e.g. breeding values and polygenic scores (Hayes et al. 2010; Jensen et al. 2012; Bloom et al. 2013; Gowda et al. 2014; Lipka et al. 2014, 2015; Goddard et al. 2016; Jivanji et al. 2019;

Table 1. Genomic heritability (\hat{h}_g^2) estimates for the 22 traits from five case studies, including six traits in an apple population with $n = 247$ entries genotyped at $m = 2,829$ SNPs (Kumar et al. 2015), four traits in an wheat population with $n = 599$ entries genotyped at $m = 1,278$ SNPs (Crossa et al. 2010), four traits in an *Arabidopsis* population with $n = 1,057$ entries genotyped at $m = 193,697$ SNPs (Atwell et al. 2010), and three traits in an mouse population with $n = 1,814$ entries genotyped at $m = 10,346$ SNPs (Valdar et al. 2006), and five traits in a pig population with $n = 3,534$ entries genotyped at 52,843 SNPs (Cleveland et al. 2012) using the seven GRMs compared in this article.

Case study	Trait	ASV	Forni et al. (2011)	VanRaden (2008)	Astle and Balding (2009)	Yang et al. (2010)	Endelman and Jannink (2012)	IBS
Apple	WT	0.48	0.48	0.49	0.51	0.44	0.50	0.59
	GRE	0.51	0.51	0.52	0.52	0.53	0.53	0.62
	FF	0.77	0.77	0.78	0.75	0.70	0.79	0.84
	CRI	0.54	0.54	0.55	0.50	0.54	0.56	0.64
	JUI	0.47	0.47	0.47	0.44	0.41	0.48	0.57
	FIN	0.19	0.19	0.19	0.20	0.21	0.20	0.26
<i>Arabidopsis</i>	FT10 _μ	0.92	0.92	0.76	0.77	–	0.76	0.83
	FT10 _{sd}	0.27	0.27	0.09	0.09	0.09	0.09	0.14
	FT16 _μ	0.92	0.92	0.75	0.76	–	0.76	0.83
	FT16 _{sd}	0.55	0.55	0.26	0.26	0.29	0.26	0.36
Mouse	BMI	0.21	0.21	0.21	0.23	0.23	0.21	0.26
	Length	0.35	0.35	0.34	0.34	0.34	0.35	0.41
	Weight	0.60	0.60	0.59	0.59	0.60	0.60	0.66
Pig	T1	0.03	0.03	0.03	0.04	0.04	0.03	0.05
	T2	0.27	0.27	0.26	0.27	0.31	0.26	0.36
	T3	0.23	0.23	0.22	0.27	0.23	0.22	0.31
	T4	0.35	0.35	0.34	0.35	0.41	0.34	0.45
	T5	0.39	0.39	0.38	0.38	0.46	0.38	0.49
Wheat	GY-E1	0.53	0.53	0.35	0.33	0.39	0.36	0.46
	GY-E2	0.49	0.49	0.32	0.29	0.41	0.34	0.42
	GY-E3	0.40	0.40	0.24	0.27	0.24	0.25	0.33
	GY-E4	0.45	0.45	0.29	0.27	0.29	0.30	0.38

Pincot et al. 2020; Petrasch et al. 2021; Fan et al. 2021), and for accounting for population structure and relatedness in marker-trait association analyses (Kang et al. 2010; Yang et al. 2010, 2011; Tian et al. 2011; Peiffer et al. 2014; Spindel et al. 2016; Alqudah et al. 2016; Pincot et al. 2018; Ferguson et al. 2021; Freebern et al. 2020). As advocated by Speed and Balding (2015) and Legarra (2016), the ragged diagonal elements of \mathbf{K}_{ASV} equal 1, on average, and the off-diagonal elements equal 0, on average. ASV directly yields accurate estimates of genomic heritability in the observed population and can be used to adjust deviations that arise from other commonly used methods for calculating genomic relationships regardless of the population constitution, such as inbred lines and F_1 hybrids, unstructured GWAS populations, and animal herds or flocks (Fig. 1).

The interpretation of genomic variance and heritability estimates was systematically affected by the available methods used to estimate \mathbf{K} . The bias that we show in this paper is independent of sampling error (large data sets mitigate sampling error) and exists even for enormous data sets. We derived a new relationship matrix, \mathbf{K}_{ASV} , using the ASV that yielded consistent variance component estimates. We also derived a correction factor $(n - 1)^{-1} \text{tr}(\mathbf{K})$ that allowed accurate estimates of genomic heritability in the observed population from LMM analyses using various software packages (Clifford and McCullagh 2006; Endelman 2011; Zhou and Stephens 2012; Pérez and de Los Campos 2014; Akdemir and Okeke 2015; Covarrubias-Pazarán 2016; Bürkner 2017; Runcie and Crawford 2019; Butler 2021; Caamal-Pat et al. 2021).

Adopting experiment designs that enable screening of a greater number of entries n yield more precise estimates of key variance components in research programs (Smith et al. 2006; Moehring et al. 2014; Borges et al. 2019; Mackay et al. 2019; Hoefler et al. 2020) and ASV can ensure that those estimates are accurate and comparable across populations. In many plant quantitative genetic

studies, the population sizes are $n \approx 500$, which may pose a general problem for variance component and ratio estimation as those variance components can have high sampling variability between replicated experiments (Fig. 1). For large populations, common in human and domesticated animal studies, it is possible to precise (low variance) but inaccurate (high bias) estimates of σ_g^2 and h_g^2 resulting from different relationship matrices, unless the assumptions of HWE happen to be perfectly met in the study population.

We did not explore differences that arise from population structure or rare alleles, which is a limitation to our simulation approach (Astle et al. 2009; Lee et al. 2012, 2013; Speed et al. 2012). We believe, but have not demonstrated, that our ASV approach could be applied to many of the existing methods that have been proposed to handle these real-world situations. For example, Lee et al. (2012) propose that \mathbf{K} be calculated among different sets of SNPs with similar MAFs and then the genomic variance for each MAF bin are jointly estimated and summed to account for unique variation attributable to common vs rare alleles. Speed et al. (2012) proposed a scaling factor for each SNP based on its own sample variance ($\text{var}(x_i)^s$), where s ranges from -2 to 2 and x_i is a vector of marker genotypes at the l th locus (Speed et al. 2012; Lee et al. 2013). This means that SNPs are either being centered and scaled ($s = -1$), which is equal to \mathbf{K}_{GN} , or that SNPs are being centered but not scaled ($s = 0$). While Speed et al. (2012) indicate that $s = -1$ yields more stable estimates of h_g^2 , it is not entirely clear how to optimally select a value of s for each locus.

Our simulations exposed systematic differences between (2) and other forms of \mathbf{K} . Our simulation and empirical experiments also suggested limited, if any, differences between genomic variance estimates from five other commonly cited GRMs (Fig. 1; Table 1). The lack of significant differences is perturbing. In every case, there are multiple reasons given for using one relationship

matrix over any other that do not seem to play any role in either bias (accuracy) or variance (precision) of the genomic variance component estimates. Both (2) and (9) have the necessary numeric properties advocated by [Speed and Balding \(2015\)](#) that enable the variance components from LMM (3) to be interpreted directly as the genomic variance in the sampled population. We recommend that the ASV approach be considered for adoption by genetic researchers working in humans, microbes, or (un)domesticated plants and animals.

Data availability

The input and output data from simulations and analyses have been deposited, along with the code for the simulations, in a public Zenodo repository (<https://doi.org/10.5281/zenodo.6211739>).

Acknowledgments

The authors thank Andrés Legarra for suggestions that significantly improved the manuscript.

MJF, HPP, and SJK: conceptualization, investigation, project administration, resources, supervision, and writing—review and editing; MJF: data curation, formal analysis, methodology, Software, validation, visualization, and writing—original draft preparation; HPP and SJK: funding acquisition.

Funding

This research was supported by grants to SJK from the United States Department of Agriculture (<http://dx.doi.org/10.13039/100000199>), National Institute of Food and Agriculture (NIFA) Specialty Crops Research Initiative (#2017-51181-26833), and California Strawberry Commission (<http://dx.doi.org/10.13039/100006760>), in addition to funding from the University of California, Davis (<http://dx.doi.org/10.13039/100007707>). HPP was supported by the German Research Foundation (DFG) grant PI 377/18-1. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

None declared.

Literature cited

- Akdemir D, Okeke U. *Emmreml: Fitting Mixed Models with Known Covariance Structures*. CRAN. R Package Version 3.1; 2015.
- Albrecht T, Wimmer V, Auinger HJ, Erbe M, Knaak C, Ouzunova M, Simianer H, Schön CC. Genome-based prediction of testcross values in maize. *Theor Appl Genet*. 2011;123(2):339–350.
- Alonso-Blanco C, Andrade J, Becker C, Bemm F, Bergelson J, Borgwardt KM, Cao J, Chae E, Dezaan TM, Ding W, et al. 1,135 genomes reveal the global pattern of polymorphism in *Arabidopsis thaliana*. *Cell*. 2016;166(2):481–491.
- Alqudah AM, Koppolu R, Wolde GM, Graner A, Schnurbusch T. The genetic architecture of barley plant stature. *Front Genet*. 2016;7:117.
- Amadeu RR, Cellon C, Olmstead JW, Garcia AAF, Resende MFR, Muñoz PR. *Aghmatrix: R package to construct relationship matrices for autotetraploid and diploid species: a blueberry example*. *Plant Genome*. 2016;9(3):1–10.
- Astle W, Balding DJ. Population structure and cryptic relatedness in genetic association studies. *Stat Sci*. 2009;24:451–471.
- Atwell S, Huang YS, Vilhjálmsson BJ, Willems G, Horton M, Li Y, Meng D, Platt A, Tarone AM, Hu TT, et al. Genome-wide association study of 107 phenotypes in *Arabidopsis thaliana* inbred lines. *Nature*. 2010;465(7298):627–631.
- Bernardo R. *Breeding for Quantitative Traits in Plants*, Vol. 1. Woodbury (MN): Stemma Press; 2002.
- Bloom JS, Ehrenreich IM, Loo WT, Lite TLV, Kruglyak L. Finding the sources of missing heritability in a yeast cross. *Nature*. 2013;494(7436):234–237.
- Borges A, González-Reymundez A, Ernst O, Cadenazzi M, Terra J, Gutiérrez L. Can spatial modeling substitute for experimental design in agricultural experiments? *Crop Sci*. 2019;59(1):44–53.
- Bulmer MG. *Principles of Statistics*. North Chelmsford, Chelmsford, MA: Courier Corporation; 1979.
- Bulmer MG. *The Mathematical Theory of Quantitative Genetics*. Oxford: Clarendon Press; 1980.
- Bürkner PC. *brms: an R package for Bayesian multilevel models using Stan*. *J Stat Soft*. 2017;80(1):1–28.
- Butler D. 2021. *asreml: fits the Linear Mixed Model*. R package version 4.1.0.160.
- Caamal-Pat D, Pérez-Rodríguez P, Crossa J, Velasco-Cruz C, Pérez-Elizalde S, Vázquez-Peña M. *lme4gs: an r-package for genomic selection*. *Front Genet*. 2021;12(982):1–12.
- Cleveland MA, Hickey JM, Forni S. A common dataset for genomic analysis of livestock populations. *G3 (Bethesda)*. 2012;2(4):429–435.
- Clifford D, McCullagh P. The regress function. *News1 R Project*. 2006;6(2):6:6.
- Covarrubias-Pazarán G. Genome-assisted prediction of quantitative traits using the R package *sommer*. *PLoS One*. 2016;11(6):e0156744.
- Crossa J, de los Campos G, Pérez P, Gianola D, Burgueño J, Araus JL, Makumbi D, Singh RP, Dreisigacker S, Yan J, et al. Prediction of genetic values of quantitative traits in plant breeding using pedigree and molecular markers. *Genetics*. 2010;186(2):713–724.
- Crossa J, Perez P, Hickey J, Burgueno J, Ornella L, Cerón-Rojas J, Zhang X, Dreisigacker S, Babu R, Li Y, et al. Genomic prediction in CIMMYT maize and wheat breeding programs. *Heredity (Edinb)*. 2014;112(1):48–60.
- de los Campos G, Gianola D, Allison DB. Predicting genetic predisposition in humans: the promise of whole-genome markers. *Nat Rev Genet*. 2010;11(12):880–886.
- de los Campos G, Sorensen D, Gianola D. Genomic heritability: what is it? *PLoS Genet*. 2015;11(5):e1005048.
- Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet*. 2013;9(3):e1003348.
- Endelman JB. Ridge regression and other kernels for genomic selection with R package *rrblup*. *Plant Genome*. 2011;4(3):250–255.
- Endelman JB, Jannink JL. Shrinkage estimation of the realized relationship matrix. *G3 (Bethesda)*. 2012;2:1405–1413.
- Estaghirou SBO, Ogutu JO, Schulz-Streeck T, Knaak C, Ouzunova M, Gordillo A, Piepho HP. Evaluation of approaches for estimating the accuracy of genomic prediction in plant breeding. *BMC Genomics*. 2013;14:860.
- Falconer D, Mackay T. *Introduction to Quantitative Genetics*. Harlow, Essex (UK): longmans Green; 1996.
- Fan M, Hall ML, Roast M, Peters A, Delhey K. Variability, heritability and condition-dependence of the multidimensional male colour phenotype in a passerine bird. *Heredity*. 2021;127:300–311.
- Feldmann MJ, Piepho HP, Bridges WC, Knapp SJ. Average semivariance yields accurate estimates of the fraction of marker-

- associated genetic variance and heritability in complex trait analyses. *PLoS Genet.* 2021;17(8):e1009762.
- Ferguson JN, Fernandes SB, Monier B, Miller ND, Allen D, Dmitrieva A, Schmuker P, Lozano R, Valluru R, Buckler ES, et al. Machine learning-enabled phenotyping for GWAS and TWAS of WUE traits in 869 field-grown sorghum accessions. *Plant Physiol.* 2021; 187(3):1481–1500.
- Forni S, Aguilar I, Misztal I. Different genomic relationship matrices for single-step analysis using phenotypic, pedigree and genomic information. *Genet Sel Evol.* 2011;43:1–7.
- Freebern E, Santos DJ, Fang L, Jiang J, Gaddis KLP, Liu GE, VanRaden PM, Maltecca C, Cole JB, Ma L. Gwas and fine-mapping of livability and six disease traits in holstein cattle. *BMC Genomics.* 2020; 21(1):1–11.
- Gao H, Christensen OF, Madsen P, Nielsen US, Zhang Y, Lund MS, Su G. Comparison on genomic predictions using three GBLUP methods and two single-step blending methods in the nordic holstein population. *Gen Sel Evol.* 2012;44:1–8.
- Goddard M. Genomic selection: prediction of accuracy and maximisation of long term response. *Genetica.* 2009;136(2):245–257.
- Goddard M, Hayes B. Genomic selection. *J Anim Breed Genet.* 2007; 124(6):323–330.
- Goddard M, Kemper K, MacLeod I, Chamberlain A, Hayes B. Genetics of complex traits: prediction of phenotype, identification of causal polymorphisms and genetic architecture. *Proc Roy Soc B: Biol Sci.* 2016;283:20160569.
- Gorjanc G, Bijma P, Hickey JM. Reliability of pedigree-based and genomic evaluations in selected populations. *Genet Sel Evol.* 2015; 47:1–15.
- Gowda M, Zhao Y, Würschum T, Longin CFH, Miedaner T, Ebmeyer E, Schachschneider R, Kazman E, Schacht J, Martinant J-P, et al. Relatedness severely impacts accuracy of marker-assisted selection for disease resistance in hybrid wheat. *Heredity (Edinb).* 2014;112(5):552–561.
- Habier D, Fernando RL, Dekkers JC. The impact of genetic relationship information on genome-assisted breeding values. *Genetics.* 2007;177(4):2389–2397.
- Habier D, Fernando RL, Garrick DJ. Genomic BLUP decoded: a look into the black box of genomic prediction. *Genetics.* 2013;194(3): 597–607.
- Hayes BJ, Pryce J, Chamberlain AJ, Bowman PJ, Goddard ME. Genetic architecture of complex traits and accuracy of genomic prediction: coat colour, milk-fat percentage, and type in holstein cattle as contrasting model traits. *PLoS Genet.* 2010;6(9):e1001139.
- Hayes BJ, Visscher PM, Goddard ME. Increased accuracy of artificial selection by using the realized relationship matrix. *Genet Res (Camb).* 2009;91(1):47–60.
- Heffner EL, Sorrells ME, Jannink JL. Genomic selection for crop improvement. *Crop Sci.* 2009;49(1):1–12.
- Henderson C. Best linear unbiased prediction of breeding values not in the model for records. *J. Dairy Sci.* 1977;60(5):783–787.
- Henderson CR. Estimation of variance and covariance components. *Biometrics.* 1953;9(2):226–252.
- Hickey JM, Veerkamp RF, Calus MP, Mulder HA, Thompson R. Estimation of prediction error variances via Monte Carlo sampling methods using different formulations of the prediction error variance. *Genet Sel Evol.* 2009;41:1–9.
- Hill WG, Goddard ME, Visscher PM. Data and theory point to mainly additive genetic variance for complex traits. *PLoS Genet.* 2008; 4(2):e1000008.
- Hoeftler R, González-Barrios P, Bhatta M, Nunes JA, Berro I, Nalin RS, Borges A, Covarrubias E, Diaz-Garcia L, Quincke M, et al. Do spatial designs outperform classic experimental designs? *JABES.* 2020;25(4):523–552.
- Huang W, Mackay TFC. The genetic architecture of quantitative traits cannot be inferred from variance component analysis. *PLoS Genet.* 2016;12(11):e1006421.
- Isik F, Holland J, Maltecca C. *Genetic Data Analysis for Plant and Animal Breeding.* Berlin (Germany): Springer; 2017.
- Jensen J, Su G, Madsen P. Partitioning additive genetic variance into genomic and remaining polygenic components for complex traits in dairy cattle. *BMC Genet.* 2012;13:44.
- Jivanji S, Worth G, Lopdell TJ, Yeates A, Couldrey C, Reynolds E, Tiplady K, McNaughton L, Johnson TJ, Davis SR, et al. Genome-wide association analysis reveals qtl and candidate mutations involved in white spotting in cattle. *Genet Sel Evol.* 2019;51(1):62.
- Kang HM, Sul JH, Service SK, Zaitlen NA, Kong S, Freimer NB, Sabatti C, Eskin E. Variance component model to account for sample structure in genome-wide association studies. *Nat Genet.* 2010; 42(4):348–354.
- Korte A, Farlow A. The advantages and limitations of trait analysis with GWAS: a review. *Plant Methods.* 2013;9:29.
- Krause MR, González-Pérez L, Crossa J, Pérez-Rodríguez P, Montesinos-López O, Singh RP, Dreisigacker S, Poland J, Rutkoski J, Sorrells M, et al. Hyperspectral reflectance-derived relationship matrices for genomic prediction of grain yield in wheat. *G3 (Bethesda).* 2019;9(4):1231–1247.
- Kumar S, Molloy C, Muñoz P, Daetwyler H, Chagné D, Volz R. Genome-enabled estimates of additive and nonadditive genetic variances and prediction of apple phenotypes across environments. *G3 (Bethesda).* 2015;5:2711–2718.
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38(4):963–974.
- Lande R, Thompson R. Efficiency of marker-assisted selection in the improvement of quantitative traits. *Genetics.* 1990;124(3): 743–756.
- Lee SH, DeCandia TR, Ripke S, Yang J, Sullivan PF, Goddard ME, Keller MC, Visscher PM, Wray NR; Molecular Genetics of Schizophrenia Collaboration (MGS). Estimating the proportion of variation in susceptibility to schizophrenia captured by common snps. *Nat Genet.* 2012;44(3):247–250.
- Lee SH, Yang J, Chen GB, Ripke S, Stahl EA, Hultman CM, Sklar P, Visscher PM, Sullivan PF, Goddard ME, et al. Estimation of SNP heritability from dense genotype data. *Am J Hum Genet.* 2013; 93(6):1151–1155.
- Legarra A. Comparing estimates of genetic variance across different relationship models. *Theor Popul Biol.* 2016;107:26–30.
- Legarra A, Lourenco DA, Vitezica ZG. Bases for Genomic Prediction; 2018. [accessed 2021 May 24] <http://genoweb.toulouse.inra.fr/~alegarra/GSIP.pdf>.
- Lehermeier C, De los Campos G, Wimmer V, Schön CC. Genomic variance estimates: with or without disequilibrium covariances? *J Anim Breed Genet.* 2017;134(3):232–241.
- Lipka AE, Kandianis CB, Hudson ME, Yu J, Drnevich J, Bradbury PJ, Gore MA. From association to prediction: statistical methods for the dissection and selection of complex traits in plants. *Curr Opin Plant Biol.* 2015;24:110–118.
- Lipka AE, Lu F, Cherney JH, Buckler ES, Casler MD, Costich DE. Accelerating the switchgrass (*Panicum virgatum* L.) breeding cycle using genomic selection approaches. *PLoS One.* 2014;9(11): e112227.
- Lynch M, Walsh B. *Genetics and Analysis of Quantitative Traits, Vol. 1.* Sunderland (MA): Sinauer; 1998.
- Mackay I, Piepho HP, Garcia AAF. Statistical methods for plant breeding. In: Balding D, Moltke I, Marioni J, editors. *Handbook of*

- Statistical Genomics: Two Volume Set; 2019. p. 501–520. New York, NY.
- Maier RM, Zhu Z, Lee SH, Trzaskowski M, Ruderfer DM, Stahl EA, Ripke S, Wray NR, Yang J, Visscher PM, et al. Improving genetic prediction by leveraging genetic correlations among human diseases and traits. *Nat Comm*. 2018;9:1–17.
- Makowsky R, Pajewski NM, Klimentidis YC, Vazquez AI, Duarte CW, Allison DB, de Los Campos G. Beyond missing heritability: prediction of complex traits. *PLoS Genet*. 2011;7(4):e1002051.
- Meuwissen T, Hayes B, Goddard M. Prediction of total genetic value using genome-wide dense marker maps. *Genetics*. 2001;157(4):1819–1829.
- Meuwissen T, Hayes B, Goddard M. Genomic selection: a paradigm shift in animal breeding. *Anim Front*. 2016;6(1):6–14.
- Moehring J, Williams ER, Piepho HP. Efficiency of augmented p-rep designs in multi-environmental trials. *Theor Appl Genet*. 2014;127(5):1049–1060.
- Mrode RA. *Linear Models for the Prediction of Animal Breeding Values*. Boston: CABI; 2014.
- Noble DW, Radersma R, Uller T. Plastic responses to novel environments are biased towards phenotype dimensions with high additive genetic variation. *Proc Natl Acad Sci U S A*. 2019;116(27):13452–13461.
- Peiffer JA, Romay MC, Gore MA, Flint-Garcia SA, Zhang Z, Millard MJ, Gardner CA, McMullen MD, Holland JB, Bradbury PJ, et al. The genetic architecture of maize height. *Genetics*. 2014;196(4):1337–1356.
- Pérez P, de Los Campos G. Genome-wide regression and prediction with the *bglr* statistical package. *Genetics*. 2014;198(2):483–495.
- Petrasch S, Mesquida-Pesci SD, Pincot DDA, Feldmann MJ, López CM, Famula R, Hardigan MA, Cole GS, Knapp SJ, Blanco-Ulate B. Genomic prediction of strawberry resistance to postharvest fruit decay caused by the fungal pathogen *Botrytis cinerea*. *G3 (Bethesda)*. 2021;12(1):jkab378.
- Piaskowski J, Hardner C, Cai L, Zhao Y, Iezzoni A, Peace C. Genomic heritability estimates in sweet cherry reveal non-additive genetic variance is relevant for industry-prioritized traits. *BMC Genet*. 2018;19(1):23.
- Piepho HP. A coefficient of determination (R^2) for generalized linear mixed models. *Biom J*. 2019;61(4):860–872.
- Pincot DD, Hardigan MA, Cole GS, Famula RA, Henry PM, Gordon TR, Knapp SJ. Accuracy of genomic selection and long-term genetic gain for resistance to verticillium wilt in strawberry. *Plant Genome*. 2020;13(3):e20054.
- Pincot DD, Poorten TJ, Hardigan MA, Harshman JM, Acharya CB, Cole GS, Gordon TR, Stueven M, Edger PP, Knapp SJ. Genome-wide association mapping uncovers *fw1*, a dominant gene conferring resistance to fusarium wilt in strawberry. *G3 (Bethesda)*. 2018;8(5):1817–1828.
- R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna (Austria): R Foundation for Statistical Computing; 2020.
- Rice B, Lipka AE. Evaluation of *rr-blup* genomic selection models that incorporate peak genome-wide association study signals in maize and sorghum. *Plant Genome*. 2019;12(1):180052.
- Runcie DE, Crawford L. Fast and flexible linear mixed models for genome-wide genetics. *PLoS Genet*. 2019;15(2):e1007978.
- Rutkoski JE, Poland JA, Singh RP, Huerta-Espino J, Bhavani S, Barbier H, Rouse MN, Jannink JL, Sorrells ME. Genomic selection for quantitative adult plant stem rust resistance in wheat. *Plant Genome*. 2014;7(3):1–10.
- Schmidt P, Hartung J, Bennewitz J, Piepho HP. Heritability in plant breeding on a genotype-difference basis. *Genetics*. 2019a;212(4):991–1008.
- Schmidt P, Hartung J, Rath J, Piepho HP. Estimating broad-sense heritability with unbalanced data from agricultural cultivar trials. *Crop Sci*. 2019b;59(2):525–536.
- Searle SR, Casella G, McCulloch CE. *Variance Components*. New York: John Wiley & Sons; 1992.
- Smith A, Lim P, Cullis BR. The design and analysis of multi-phase plant breeding experiments. *J Agric Sci*. 2006;144(5):393–409.
- Speed D, Balding DJ. Relatedness in the post-genomic era: is it still useful? *Nat Rev Genet*. 2015;16(1):33–44.
- Speed D, Cai N, Johnson MR, Nejentsev S, Balding DJ, Consortium U; UCLEB Consortium. Reevaluation of snp heritability in complex human traits. *Nat Genet*. 2017;49(7):986–992.
- Speed D, Hemani G, Johnson MR, Balding DJ. Improved heritability estimation from genome-wide snps. *Am J Hum Genet*. 2012;91(6):1011–1021.
- Spindel J, Begum H, Akdemir D, Collard B, Redoña E, Jannink J, McCouch S. Genome-wide prediction models that incorporate *de novo* gwas are a powerful new tool for tropical rice improvement. *Heredity (Edinb)*. 2016;116(4):395–408.
- Tian F, Bradbury PJ, Brown PJ, Hung H, Sun Q, Flint-Garcia S, Rocheford TR, McMullen MD, Holland JB, Buckler ES. Genome-wide association study of leaf architecture in the maize nested association mapping population. *Nat Genet*. 2011;43(2):159–162.
- Truong B, Zhou X, Shin J, Li J, van der Werf JH, Le TD, Lee SH. Efficient polygenic risk scores for biobank scale data by exploiting phenotypes from inferred relatives. *Nat Comm*. 2020;11:1–11.
- Valdar W, Solberg LC, Gauguier D, Burnett S, Klenerman P, Cookson WO, Taylor MS, Rawlins JNP, Mott R, Flint J. Genome-wide genetic association of complex traits in heterogeneous stock mice. *Nat Genet*. 2006;38(8):879–887.
- Van Heerwaarden B, Willi Y, Kristensen TN, Hoffmann AA. Population bottlenecks increase additive genetic variance but do not break a selection limit in rain forest *Drosophila*. *Genetics*. 2008;179(4):2135–2146.
- van Rossum BJ, Kruijer W. *statgenGWAS: Genome Wide Association Studies*. CRAN. R Package Version 1.0.5; 2020.
- VanRaden PM. Efficient methods to compute genomic predictions. *J Dairy Sci*. 2008;91(11):4414–4423.
- Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90(1):7–24.
- Visscher PM, Hill WG, Wray NR. Heritability in the genomics era—concepts and misconceptions. *Nat Rev Genet*. 2008;9(4):255–266.
- Visscher PM, Macgregor S, Benjamin B, Zhu G, Gordon S, Medland S, Hill WG, Hottenga J-J, Willemsen G, Boomsma DI, et al. Genome partitioning of genetic variation for height from 11,214 sibling pairs. *Am J Hum Genet*. 2007;81(5):1104–1110.
- Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 years of GWAS discovery: biology, function, and translation. *Am J Hum Genet*. 2017;101(1):5–22.
- Vitezica ZG, Legarra A, Toro MA, Varona L. Orthogonal estimates of variances for additive, dominance, and epistatic effects in populations. *Genetics*. 2017;206(3):1297–1307.
- Vitezica ZG, Varona L, Legarra A. On the additive and dominant variance and covariance of individuals within the genomic selection scope. *Genetics*. 2013;195(4):1223–1230.
- Webster R, Oliver MA. *Geostatistics for Environmental Scientists*. New York (NY): John Wiley & Sons; 2007.
- Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York (NY): Springer-Verlag; 2016.
- Wray NR, Kemper KE, Hayes BJ, Goddard ME, Visscher PM. Complex trait prediction from genome data: contrasting EBV in livestock to PRS in humans: genomic prediction. *Genetics*. 2019;211(4):1131–1141.

- Wricke G, Weber E. *Quantitative Genetics and Selection in Plant Breeding*. New York (NY): Walter de Gruyter; 2010.
- Yadav S, Wei X, Joyce P, Atkin F, Deomano E, Sun Y, Nguyen LT, Ross EM, Cavallaro T, Ks A, et al. Improved genomic prediction of clonal performance in sugarcane by exploiting non-additive genetic effects. *Theor Appl Genet*. 2021;134:1–18.
- Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, et al. Common SNPs explain a large proportion of the heritability for human height. *Nat Genet*. 2010;42(7):565–569.
- Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, de Andrade M, Feenstra B, Feingold E, Hayes MG, et al. Genome partitioning of genetic variation for complex traits using common snps. *Nat Genet*. 2011;43(6):519–525.
- Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of snp-based heritability. *Nat Genet*. 2017;49(9):1304–1310.
- Yu J, Pressoir G, Briggs WH, Bi IV, Yamasaki M, Doebley JF, McMullen MD, Gaut BS, Nielsen DM, Holland JB, et al. A unified mixed-model method for association mapping that accounts for multiple levels of relatedness. *Nat Genet*. 2006;38(2):203–208.
- Zhou X, Stephens M. Genome-wide efficient mixed-model analysis for association studies. *Nat Genet*. 2012;44(7):821–824.

Communicating editor: A. Lipka