Robust Genomic Modelling Using Expert Knowledge about Additive, Dominance and Epistasis Variation

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Abstract

A major challenge with modelling non-additive genetic variation is that it is hard to separate non-additive variation from additive and environmental variation. In this paper, we describe how to alleviate this issue, and improve genomic modelling of additive and non-additive variation, by leveraging the ample expert knowledge available about the relative magnitude of the sources of phenotypic variation. The method is Bayesian and uses the recently introduced penalized complexity and hierarchical decomposition prior frameworks, where priors can be specified and visualized in an intuitive way, and be used to induce parsimonious modelling. We evaluate the potential impact for plant breeding through a simulated case study of a wheat breeding program. We compare different models and different priors with varying amounts of expert knowledge. The results show that the proposed priors and expert knowledge improved the robustness of the genomic modelling and the selection of the genetically best individuals in the breeding program. We observed this improvement in both variety selection on genetic values and parent selection on additive values, but the variety selection benefited the most. An improvement was not observed in the overall accuracy of estimating genetic values for all individuals and variance components. Finally, we discuss the importance of expert-knowledge priors for genomic modelling and breeding, and point to future research areas of easy-to-use and parsimonious priors in genomic modelling.

Introduction

In this paper, we describe the use of expert knowledge to improve genomic modelling of additive and non-additive variation, and evaluate its potential impact for plant breeding with a simulated case study. Plant breeding programs are improving productivity of a range of crops and with this addressing the global and rising hunger problem that impacts 820 million people across the world (FAO *et al.*, 2019). One of the most important food sources in the world is wheat (Shewry and Hey, 2015), however, recent improvements in wheat yield are smaller than the projected requirements (Ray *et al.*, 2013) and might become more variable or even decrease due to climate change (Asseng *et al.*, 2015). This trend is in stark contrast to the United Nation's Sustainable Development Goals that aim to end hunger and malnutrition by 2030 (General Assemby of the United Nations, 2015). Breeding has contributed significantly to the improvement of wheat yields in the past (e.g., Mackay *et al.*, 2011; Rife *et al.*, 2019), and the recent adoption of genomic selection could enable further significant improvements (Gaynor *et al.*, 2017; Belamkar *et al.*, 2018; Sweeney *et al.*, 2019).

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Breeding programs generate and evaluate new genotypes with the aim to improve key characteristics such as plant height, disease resistance and yield. Nowadays, a key component in breeding is genomic modelling, where we aim to reduce environmental noise in phenotypic observations and associate the remaining variation with variation in individual genomes. We use these associations to estimate genetic values for phenotyped or even non-phenotyped individuals and with this identify the genetically best individuals (Meuwissen *et al.*, 2001). Improving this process involves improving the methods for disentangling genetic variation from environmental variation.

Genetic variation can be decomposed into additive and non-additive components (Fisher, 1918; Falconer and Mackay, 1996; Lynch *et al.*, 1998; Mäki-Tanila and Hill, 2014). Additive variation is defined as variation of additive values, which are sums of allele substitution effects over the unobserved genotypes of causal loci. Statistically, the allele substitution effects are coefficients of multiple linear regression of phenotypic values on causal genotypes coded in an additive manner. Non-additive variation is defined as the remaining genetic variation not captured by the additive values. It is commonly partitioned into dominance and epistasis values. Dominance values capture deviations from additive values at individual loci. Epistasis values capture deviations from additive and/or dominance values at combinations of loci. Statistically, dominance and epistasis values capture deviations due to allele interactions at individual loci and combinations of loci, respectively. Modelling interactions between two loci at a time gives additive-by-additive, additive-by-dominance and dominance-by-dominance epistasis. Modelling interactions between a larger number of loci increases the number of interactions.

Estimates of genetic values and their additive and non-additive components have different applications in breeding (Acquaah, 2009). Breeders use estimates of additive values to identify parents of the next generation, because additive values indicate the expected change in mean genetic value in the next generation under the assumption that allele frequencies will not change. Breeders use estimates of genetic values to identify individuals for commercial production, because genetic values indicate the expected phenotypic value. Estimates of genetic values are particularly valuable in plant breeding where individual genotypes can be effectively cloned. While genomic modelling currently focuses on additive values (Meuwissen *et al.*, 2001; Varona *et al.*, 2018), the literature on modelling non-additive variation is growing (Oakey *et al.*, 2006; Wittenburg *et al.*, 2011; Muñoz *et al.*, 2014; Bouvet *et al.*, 2016; Martini *et al.*, 2017; Vitezica *et al.*, 2017; Varona *et al.*, 2018; de Almeida Filho *et al.*, 2019; Santantonio *et al.*, 2019; Tolhurst *et al.*, 2019; Martini *et al.*, 2020). Notably, modelling non-additive variation has been shown to improve the estimation of additive values in certain cases (Varona *et al.*, 2018).

A challenge with modelling non-additive variation is that it is difficult to separate non-additive variation from additive and environmental variation even when large datasets are available (e.g., Misztal, 1997; Zhu *et al.*, 2015; de los Campos *et al.*, 2019). This suggests that genomic models should be *robust* in the sense that spurious non-additive values are not estimated. One way to handle partially confounded sources of variation is to include expert knowledge on their absolute or relative sizes. For small datasets, it is particularly important to supplement the limited information in the data with expert knowledge to achieve robustness.

There is ample information about the relative magnitude of the sources of phenotypic variation that has been collated since the seminal work of Fisher (1918). The magnitude of genetic variation for a range of traits is well known (e.g., Houle, 1992; Falconer and Mackay, 1996; Lynch *et al.*, 1998). Data and theory indicate that the majority of genetic variation is captured by additive values (Hill *et al.*, 2008; Mäki-Tanila and Hill, 2014), while the magnitude of variation in dominance and epistasis values varies considerably due to a range of factors. For example, there is no dominance variation between inbred individuals by definition. Further, model specification has a strong effect on the resulting estimates (e.g., Huang and Mackay, 2016; Martini *et al.*, 2017; Vitezica *et al.*, 2017; Martini *et al.*, 2020). With common model specifications, additive values capture most of the genetic variation because they capture the main effects (in the statistical sense), while dominance and epistasis values capture interaction deviations from the main effects (Hill *et al.*, 2008; Mäki-Tanila and Hill, 2014; Hill and Mäki-Tanila, 2015; Huang and Mackay, 2016).

In a Bayesian setting, expert knowledge on the different sources of variation can be included in the model through prior distributions (e.g., Sorensen and Gianola, 2007). Prior distributions reflect beliefs and uncertainties about unknown quantities of a model and should be elicited from an expert in the field of interest

(O'Hagan *et al.*, 2006; Farrow, 2013). However, the ability to use external information with the Bayesian approach is seldomly exploited or even discouraged. One reason is the lack of intuitive methods that could utilize the elicited information in an analysis. Here, we show how to use the recently developed penalized complexity (PC) prior framework (Simpson *et al.*, 2017) to facilitate robust modelling, and the hierarchical decomposition (HD) prior framework (Fuglstad *et al.*, 2020) to incorporate the wealth of knowledge about the magnitude of genetic and environmental variation as well as of additive and non-additive variation in an intuitive way. An advantage of these prior frameworks over the standard priors used in quantitative genetics (e.g., Sorensen and Gianola, 2007) is that both use simple rules to choose priors on the scale of the expert knowledge.

The aim of this paper is to introduce the penalized complexity and hierarchical decomposition prior frameworks for robust genomic modelling and to evaluate the potential impact of using these priors along with expert knowledge in plant breeding with a simulated case study. We compare settings with different models and different priors incorporating varying amounts of expert knowledge, and evaluate their effect on the robustness of estimation, accuracy of selecting the genetically best individuals, accuracy of estimating the different genetic values, and accuracy of estimating variance parameters.

We first describe the genomic model and how to incorporate the expert knowledge in this model using the penalized complexity and hierarchical decomposition prior frameworks, followed by a description of the simulated case-study, model fitting and analysis. Our key focus is to demonstrate how an analyst can take advantage of expert knowledge from literature or domain experts to enable robust genomic modelling of additive and non-additive variation. This focus involves specifying and visualizing the expert knowledge in an intuitive way. We then present the results and discuss the relevance of our work.

Materials and Methods

Genomic model

We model observed phenotypic values of n individuals $\boldsymbol{y} = (y_1, \ldots, y_n)$ with the aim to estimate their genetic values and their additive and non-additive components. To this end we use the genomic information about the individuals contained in the observed single nucleotide polymorphism (SNP) matrix $\boldsymbol{Z}$, where row i contains SNP marker genotypes for individual i coded additively with $0, 1, 2$. We let $\boldsymbol{Z}_{\mathrm{a}}$ be the column-centered $\boldsymbol{Z}$ where we have removed markers with low minor allele frequency, and let $\boldsymbol{Z}_{\mathrm{d}}$ be the column-centered matrix obtained from $\boldsymbol{Z}$ after setting heterozygote genotypes to 1 and homozygote genotypes to 0.

We model the phenotypic observation y_i of individual i as

$$y_i = \mu + g_i + e_i, \quad i = 1, \ldots, n, \tag{1}$$

where μ is an intercept, g_i is genetic value and e_i environmental residual. We model the environmental residual as an independently and identically distributed Gaussian random variable, $\boldsymbol{e} = (e_1, \ldots, e_n) \sim \mathcal{N}(\boldsymbol{0}, \sigma_{\mathrm{e}}^2 \mathbf{I}_n)$, where σ_{e}^2 is the environmental variance and $\mathbf{I}_n$ is the $n \times n$ identity matrix.

Let $\boldsymbol{a} = (a_1, \ldots, a_n)$, $\boldsymbol{d} = (d_1, \ldots, d_n)$ and $\boldsymbol{x} = (x_1, \ldots, x_n)$ be vectors of the additive, the dominance and the epistasis values for the individuals, respectively. We consider the simple additive model where $g_i = a_i$ (*Model A*) and the comprehensive additive and non-additive model where $g_i = a_i + d_i + x_i$ (*Model ADX*). We model these values as $\boldsymbol{a} \sim \mathcal{N}(\boldsymbol{0}, \sigma_{\mathrm{a}}^2 \boldsymbol{A})$, $\boldsymbol{d} \sim \mathcal{N}(\boldsymbol{0}, \sigma_{\mathrm{d}}^2 \boldsymbol{D})$ and $\boldsymbol{x} \sim \mathcal{N}(\boldsymbol{0}, \sigma_{\mathrm{x}}^2 \boldsymbol{X})$, where σ_{a}^2, σ_{d}^2 and σ_{x}^2 are the additive, dominance and epistasis variances, respectively. We specify the covariance matrices as $\boldsymbol{A} = \boldsymbol{Z}_{\mathrm{a}} \boldsymbol{Z}_{\mathrm{a}}^T / S_{\mathrm{a}}$, $\boldsymbol{D} = \boldsymbol{Z}_{\mathrm{d}} \boldsymbol{Z}_{\mathrm{d}}^T / S_{\mathrm{d}}$ and $\boldsymbol{X} = \boldsymbol{A} \odot \boldsymbol{A} / S_{\mathrm{x}}$ (we consider only additive-by-additive epistatis), where $\odot$ is the Hadamard product (Horn, 1990; Vitezica *et al.*, 2017). The scaling factors S_{a}, S_{d}, and S_{x} are selected such that the mean of the diagonal of each covariance matrix is 1, which means that the variance parameters describe the *typical* variances of the random variables (Legarra, 2016; Vitezica *et al.*, 2017; Sørbye and Rue, 2018; Fuglstad *et al.*, 2020). Finally, phenotypic variance is $\sigma_{\mathrm{p}}^2 = \sigma_{\mathrm{g}}^2 + \sigma_{\mathrm{e}}^2 = \sigma_{\mathrm{a}}^2 + \sigma_{\mathrm{d}}^2 + \sigma_{\mathrm{x}}^2 + \sigma_{\mathrm{e}}^2$.

Expert knowledge about variance components

As highlighted in the introduction, we have ample prior information about the relative magnitude of the genetic and environmental variation and the relative magnitude of the additive, dominance and epistasis variation that can guide the construction of prior distributions. We can summarize this expert knowledge in a hierarchical manner:

EK1 Proportion of genetic to phenotypic variation is $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 1 - R_{\frac{\mathrm{e}}{\mathrm{g+e}}}$

EK2 Proportion of non-additive to genetic variation is $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 1 - R_{\frac{\mathrm{a}}{\mathrm{g}}}$

EK3 Proportion of epistasis to non-additive variation is $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} = 1 - R_{\frac{\mathrm{d}}{\mathrm{d+x}}}$

Values for the relative magnitudes R_* will vary between study systems and traits in line with the expert knowledge. In this study we assume $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$ (so $R_{\frac{\mathrm{e}}{\mathrm{g+e}}} = 0.75$), $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 0.15$ (so $R_{\frac{\mathrm{a}}{\mathrm{g}}} = 0.85$), and $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} =\sim 0.33$ (so $R_{\frac{\mathrm{d}}{\mathrm{d+x}}} =\sim 0.67$, $R_{\frac{\mathrm{d}}{\mathrm{g}}} =\sim 0.15 \cdot 0.67 =\sim 0.10$ and $R_{\frac{\mathrm{x}}{\mathrm{g}}} =\sim 0.15 \cdot 0.33 =\sim 0.05$). We emphasise that we use this information to construct prior distributions, i.e., these relative magnitudes are only taken as a guide and not as the exact magnitude of variance components.

We present two approaches for constructing a prior that includes EK1, EK2 and EK3: independently for each variance parameter – component-wise (CW) prior – and jointly for all variance parameters – model-wise (MW) prior. We contrast these two priors, which includes the expert knowledge (exp), against default priors (def) that do not use any expert knowledge. The default priors are priors from the literature, which are not specific for the problem at hand. For the component-wise expert knowledge prior we need additional information on the expected magnitude of the phenotypic variance V_{p}. We summarize the resulting priors in Table 1 and describe them in detail in the next sections.

We do not include expert knowledge about the intercept because it is typically well-identified from the data, and we specify the nearly translation-invariant prior $\mu \sim \mathcal{N}(0, 1000)$. For the same reason, we do not include expert knowledge about the total variance (corresponding to the phenotypic variance) in the model-wise priors, and we use the non-informative and scale-invariant Jeffreys' prior $\sigma_{\mathrm{p}}^2 \sim 1/\sigma_{\mathrm{p}}^2$.

We use the penalized complexity (PC) prior framework of Simpson *et al.* (2017) where the prior is intuitive and shrinks the parameters of a complex model to a simpler (base) model unless the data provides other information. In this framework, the prior on a parameter is controlled by two elements: a preferred parameter value and an idea on how strongly we believe in this preferred value. This parameter could be either a standard deviation or variance, a proportion of variances, or other parameters such as correlations (Guo *et al.*, 2017).

In our component-wise prior we use a PC prior for each variance parameter in the model. These PC priors shrink towards variance equal to 0, i.e., towards a simpler model without the corresponding effect. The PC prior for a standard deviation is denoted as $\sigma \sim \text{PC-SD}_0(\sqrt{V}, \alpha)$ and the analyst has to specify an upper variance value V and a tail probability α such that the upper-tail probability $\mathrm{P}(\sigma > \sqrt{V}) = \alpha$. We use an expert-expected value for V and $\alpha = 0.25$ so the prior distributions are weakly-informative towards the expert knowledge, but prefers variance equal to zero unless the data informs otherwise. See examples below. The PC prior for a variance parameter corresponds to an exponential distribution on standard deviation.

In our model-wise prior we use the hierarchical decomposition (HD) prior framework of Fuglstad *et al.* (2020). The HD prior is constructed hierarchically following a *tree structure*, where we use expert knowledge to attribute the total variance in the model to the different effects. We can do this with splits at one or more levels in the tree structure where we attribute the proportion of variance p to different effects. See Figure 3, and Fuglstad *et al.* (2020) for examples. We can choose to be ignorant about splits or to provide expert knowledge. We specify ignorance between splits among the m model components by using a symmetric Dirichlet prior $\boldsymbol{p} \sim \text{Dirichlet}(m)$.

In the HD prior framework, we can use expert knowledge in two different ways. We can prefer one effect to the others, or we can prefer a specific proportion of variance attributed to each effect. The use of PC

Table 1: Summary of the prior distributions. $\sigma \sim \text{PC-SD}_0(\sqrt{V}, \alpha)$ describes a penalized complexity (PC) prior for a standard deviation where $\text{P}(\sigma > \sqrt{V}) = \alpha$. $p \sim \text{PC-P}_0(R_*)$ describes a PC prior for a variance proportion that has median equal to R_* and a preference for the variance proportion being equal to 0. $p \sim \text{PC-P}_\text{M}(R_*)$ describes a PC prior for a variance proportion with median R_* and a preference for the variance proportion being equal to R_*, and 75% probability in $[\text{logit}(R_*)-1, \text{logit}(R_*)+1]$ around the median on logit-scale. The tree structure for the model-wise (MW) priors is shown in Figure 3. The dependence of the MW priors on this structure is suppressed in the notation. The values for A-CW-def are taken from Simpson *et al.* (2017).

	Additive (Model A, $g_i = a_i$)		**Additive and non-additive (Model ADX, $g_i = a_i + d_i + x_i$)**
	Default (def)	*Expert (exp)*	*Expert (exp)*
Component-wise (CW)	A-CW-def: $\sigma_\text{e} \sim \text{PC-SD}_0\,(0.968, 0.01)$ $\sigma_\text{a} \sim \text{PC-SD}_0\,(0.968, 0.01)$	A-CW-exp: $\sigma_\text{e} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{e}}{\text{g+e}}} V_\text{p}}, 0.25\right)$ $\sigma_\text{a} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{g}}{\text{g+e}}} V_\text{p}}, 0.25\right)$	ADX-CW-exp: $\sigma_\text{e} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{e}}{\text{g+e}}} V_\text{p}}, 0.25\right)$ $\sigma_\text{a} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{a}}{\text{g}}} R_{\frac{\text{g}}{\text{g+e}}} V_\text{p}}, 0.25\right)$ $\sigma_\text{d} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{d}}{\text{g}}} R_{\frac{\text{g}}{\text{g+e}}} V_\text{p}}, 0.25\right)$ $\sigma_\text{x} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\text{x}}{\text{g}}} R_{\frac{\text{g}}{\text{g+e}}} V_\text{p}}, 0.25\right)$
Model-wise (MW)	A-MW-def: $p_{\frac{\text{g}}{\text{g+e}}} \sim \text{Dirichlet}\,(2)$ $\sigma_\text{p}^2 \sim$ Jeffreys'	A-MW-exp: $p_{\frac{\text{g}}{\text{g+e}}} \sim \text{PC-P}_0\left(R_{\frac{\text{g}}{\text{g+e}}}\right)$ $\sigma_\text{p}^2 \sim$ Jeffreys'	ADX-MW-exp: $p_{\frac{\text{g}}{\text{g+e}}} \sim \text{PC-P}_0\left(R_{\frac{\text{g}}{\text{g+e}}}\right)$ $p_{\frac{\text{d+x}}{\text{g}}} \sim \text{PC-P}_\text{M}\left(R_{\frac{\text{d+x}}{\text{g}}}\right)$ $p_{\frac{\text{d}}{\text{d+x}}} \sim \text{PC-P}_\text{M}\left(R_{\frac{\text{x}}{\text{d+x}}}\right)$ $\sigma_\text{p}^2 \sim$ Jeffreys'

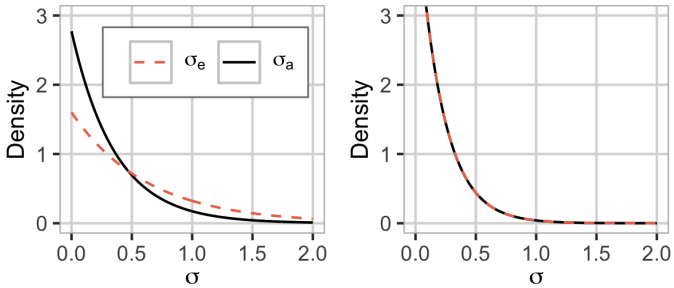


Figure 1: The prior used for the A-CW-exp (left) and A-CW-def (right) settings. For A-CW-exp, we use $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$. We have plotted the priors for $V_\mathrm{p} = 1$. For A-CW-def, additive and environmental variances have the same prior.

priors will then shrink the model towards the preferred effect or preferred attribution of variance to the effects.

For a variance proportion with shrinkage towards one of the effects, we denote the PC prior as $p \sim \text{PC-P}_0(R)$, where R encodes the expert knowledge about the relative magnitude of variances such that R is the median ($\mathrm{P}(p > R) = 0.5$)). For a variance proportion with shrinkage towards a specific proportion of variance assigned to each effect, we denote the PC prior as $p \sim \text{PC-P}_\mathrm{M}(R)$, where R has the same interpretation as for $\text{PC-P}_0(R)$, but in addition encodes the preferred variance attribution (see examples below). For $\text{PC-P}_\mathrm{M}(R)$, we need to specify how concentrated the distribution is on logit-scale in the interval $[\mathrm{logit}(R) - 1, \mathrm{logit}(R) + 1]$ around the median (see Fuglstad *et al.* (2020) for details). We allocated 75% probability to this interval.

The PC prior for a variance proportion depends on the structure of the two effects through their covariance matrices. We omit this in the notation for simplicity, and to emphasize that the priors on proportions are independent of each other. As the PC prior on proportions depends on the covariance matrix structure, it is application specific, and the priors do not correspond to common families of distributions such as the exponential or normal distributions (see Fuglstad *et al.* (2020) for more details).

Component-wise prior

We first calculate the empirical phenotypic variance (total variance) V_p from a separate dataset, which is a trial study or a study believed to exhibit similar phenotypic variance as the study at hand. In this study, we use $V_p = 1.86$. This empirical phenotypic variance is combined with the expert knowledge in EK1, EK2 and EK3 to compute expected variances for the model effects. Following EK1 we expect genetic variance around $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} V_\mathrm{p}$ and environmental variance around $R_{\frac{\mathrm{e}}{\mathrm{g+e}}} V_\mathrm{p}$. Following EK2 and EK3 we expect additive variance around $R_{\frac{\mathrm{a}}{\mathrm{g}}} R_{\frac{\mathrm{g}}{\mathrm{g+e}}} V_\mathrm{p}$, dominance variance around $R_{\frac{\mathrm{d}}{\mathrm{g}}} R_{\frac{\mathrm{g}}{\mathrm{g+e}}} V_\mathrm{p}$ and epistasis variance around $R_{\frac{\mathrm{x}}{\mathrm{g}}} R_{\frac{\mathrm{g}}{\mathrm{g+e}}} V_\mathrm{p}$. We use this expert knowledge in the PC prior by setting the upper variance values. For example, for Model A we get $\sigma_\mathrm{a} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\mathrm{g}}{\mathrm{g+e}}} V_\mathrm{p}}, 0.25\right)$ and $\sigma_\mathrm{e} \sim \text{PC-SD}_0\left(\sqrt{R_{\frac{\mathrm{e}}{\mathrm{g+e}}} V_\mathrm{p}}, 0.25\right)$ (Table 1).

Combining the above expert knowledge procedure with the two different genomic models (Model A and Model ADX) gave us settings we denote as A-CW-exp and ADX-CW-exp. We have contrasted these settings with a default PC prior proposed by Simpson *et al.* (2017) with $U = 0.968$ and $\alpha = 0.01$ on all variances, which gave us settings denoted as A-CW-def and ADX-CW-def. Preliminary analyses showed that the inference for ADX-CW-def is not robust and we do not present results from this setting. The priors for A-CW-exp and A-CW-def are plotted in Figure 1 and for ADX-CW-exp in Figure 2, using $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$, $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 0.15$, $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} =\sim 0.33$ and $V_\mathrm{p} = 1$. If V_p takes another value, we simply rescale the x- and y-axes; the shape of the prior stays the same.

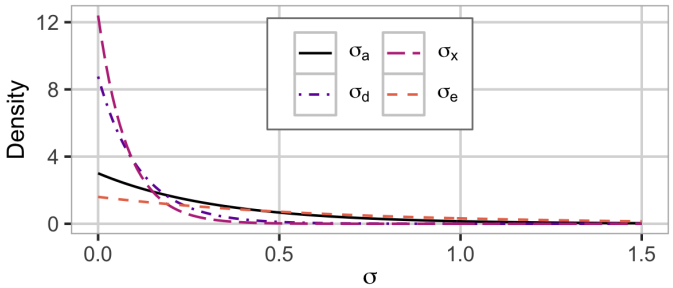


Figure 2: The prior used for the ADX-CW-exp setting. We use $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$, $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 0.15$, and $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} =\sim 0.33$. We have plotted the priors for $V_{\mathrm{p}} = 1$.

Model-wise prior

To incorporate the expert knowledge in a model-wise way we utilize the expert knowledge in a hierarchical manner following the tree structure in Figure 3. We can now assume the scale of the phenotype is unknown. To construct the HD prior we follow the tree structure from the bottom nodes and continue in a conditional fashion upwards in the tree (Fuglstad *et al.*, 2020). In this study we assumed that at the top level model shrinks the genetic effect unless the data indicates otherwise to reduce overfitting. Further, at the lower levels the model shrinks towards the expert knowledge EK2 and EK3. Note that we could have chosen different assumptions. To obtain a prior fulfilling our assumptions, we follow four steps:

1. we use a PC-$\mathrm{P_M}$ prior for the proportion of epistasis to non-additive variance with median of $R_{\frac{\mathrm{x}}{\mathrm{d+x}}}$ (EK3),
2. we use a PC-$\mathrm{P_M}$ prior for the proportion of non-additive to genetic variance with median of $R_{\frac{\mathrm{d+x}}{\mathrm{g}}}$ (EK2),
3. we use a PC-$\mathrm{P_0}$ prior for the proportion of genetic to phenotypic variance with the median of $R_{\frac{\mathrm{g}}{\mathrm{g+e}}}$ (EK1), and
4. we achieve scale-independence through a scale-invariant prior for phenotypic variance (defined before).

This differs from the component-wise prior where we need to use a dataset to inform about the scale of variances, and that we now use parameters on the same scale as the expert knowledge. This construction gives the joint prior $\pi(\sigma_{\mathrm{p}}^2, p_{\frac{\mathrm{g}}{\mathrm{g+e}}}, p_{\frac{\mathrm{d+x}}{\mathrm{g}}}, p_{\frac{\mathrm{x}}{\mathrm{d+x}}}) = \pi(\sigma_{\mathrm{p}}^2)\pi(p_{\frac{\mathrm{g}}{\mathrm{g+e}}})\pi(p_{\frac{\mathrm{d+x}}{\mathrm{g}}})\pi(p_{\frac{\mathrm{x}}{\mathrm{d+x}}})$. We show this prior in Figure 4 for $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$, $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 0.15$ and $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} =\sim 0.33$ and denote this setting as ADX-MW-exp. Note that the model-wise priors with expert knowledge are dependent on the covariance matrices of the modelled effects and are therefore dataset specific (Fuglstad *et al.*, 2020), and the plots of these priors thus pertain to one specific dataset. The spike at $p = 1$ for $p_{\frac{\mathrm{g}}{\mathrm{g+e}}}$ in Figure 4 is an artifact of the parameterization chosen for visualization and does not induce overfitting; see Fuglstad *et al.* (2020) for details.

We explored the influence of alternative expert knowledge. In addition to the previously stated EK1, EK2 and EK3 we also tested $R_{\frac{\mathrm{g}}{\mathrm{g+e}}} = 0.25$ (so $R_{\frac{\mathrm{e}}{\mathrm{g+e}}} = 0.75$), $R_{\frac{\mathrm{d+x}}{\mathrm{g}}} = 0.95$ (so $R_{\frac{\mathrm{a}}{\mathrm{g}}} = 0.05$), and $R_{\frac{\mathrm{x}}{\mathrm{d+x}}} =\sim 0.89$ (so $R_{\frac{\mathrm{d}}{\mathrm{d+x}}} =\sim 0.11$, $R_{\frac{\mathrm{d}}{\mathrm{g}}} =\sim 0.95 \cdot 0.11 =\sim 0.10$ and $R_{\frac{\mathrm{x}}{\mathrm{g}}} =\sim 0.95 \cdot 0.89 =\sim 0.85$). The constructions follows the description above but with these medians instead. We denote this setting as ADX-MW-opp, as it expresses almost opposite or "wrong" beliefs compared to ADX-MW-exp setting, and show the prior in Figure S1 in File S1 in the Supplemental materials.

For Model A the genetic variance is not decomposed to different sources and the distribution of the phenotypic variance can be visualized using the top split in Figure 3. We use the expert knowledge in EK1 to construct a prior for the proportion of genetic to phenotypic variance and denote this setting as A-MW-exp. We show this prior in Figure 5.

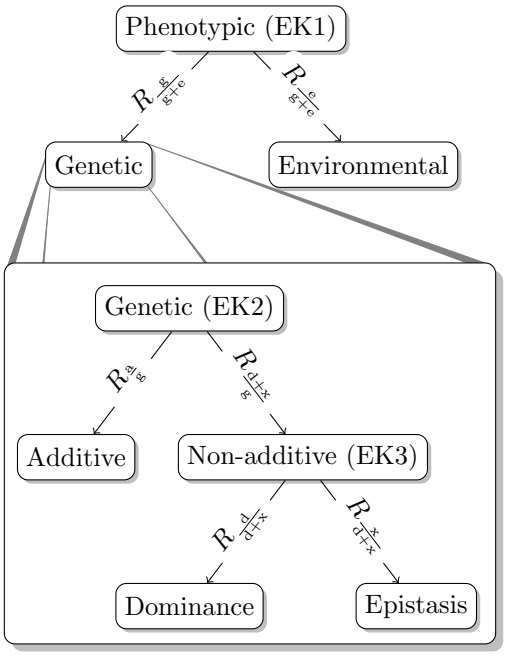


Figure 3: Tree structure describing the expert knowledge on the decomposition of phenotypic variance used in the HD prior. Edge labels indicate the expert motivated relative magnitude of variances used as a median proportion of the variance in the parent node attributed to each child node. For the top split we use the PC-P_0 prior (shrinking to environmental noise), while for splits two and three we use the PC-P_M prior.

We compared the model-wise prior with expert knowledge to a prior with no expert knowledge by constructing an HD prior using the exchangeable Dirichlet prior on the proportion of phenotypic variance attributed to each of the sources of variance following Fuglstad *et al.* (2020). For Model A we use a uniform prior, which is a special case of the symmetric Dirichlet(m) prior with $m = 2$, on the proportion of genetic to phenotypic variance $p_{\frac{g}{g+e}}$ and denote this setting as A-MW-def (see Figure 5). For Model ADX we use a Dirichlet(4) prior on the proportions, and denote this ADX-MW-def. Due to the lack of expert knowledge this model was not robust and we do not show results from this setting. The tree structure and prior for ADX-MW-def can be seen in Figures S2 and S3 in File S1, respectively.

Simulation case-study and experimental setup

We applied the described genomic model (1) with different priors to a simulated case study that mimics a wheat breeding program. We simulated the breeding program using the R package AlphaSimR (Faux *et al.*, 2016; Gaynor, 2019) and closely following descriptions of Gaynor *et al.* (2017) and Selle *et al.* (2019).

Specifically, we simulated a wheat-like genome with 21 chromosomes, selected at random, $1,000$ SNP markers and $1,000$ causal loci from each chromosome and used this genome to initiate a breeding program with breeding individuals. Every year we have used 50 fully inbred parents to initiate a new breeding cycle with 100 random crosses. In each cross we have generated 10 progenies and selfed them to generate $1,000$ F2 individuals, which were selfed again to generate $10,000$ F3 individuals. We reduced the $10,000$ F3 individuals in four successive selection stages (headrow, preliminary yield trial, advanced yield trial and elite yield trial) with 10% selection intensity in each stage. In the headrow stage, we simulated a visual selection on a phenotype with the heritability of 0.03. For the preliminary, advanced and elite yield trials we respectively simulated selection on phenotype with heritability 0.25, 0.45 and 0.62. We used the 50 individuals with the highest phenotype values from the last three selection stages as parents for the next breeding cycle.

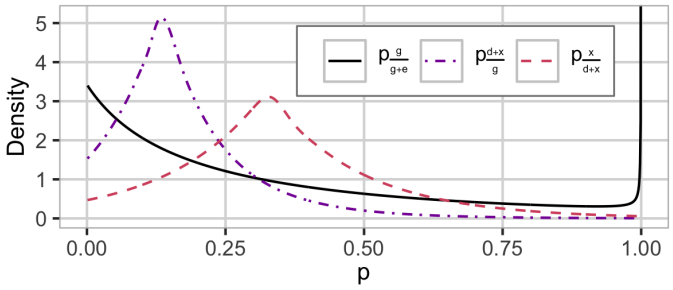


Figure 4: The HD prior used in the ADX-MW-exp setting with the proportion of genetic to phenotypic variance $p_{\frac{g}{g+e}}$, non-additive to genetic variance $p_{\frac{d+x}{g}}$, and epistasis to non-additive variance $p_{\frac{x}{d+x}}$. We use $R_{\frac{g}{g+e}} = 0.25$, $R_{\frac{d+x}{g}} = 0.15$, and $R_{\frac{x}{d+x}} =\sim 0.33$. This is a dataset specific prior.

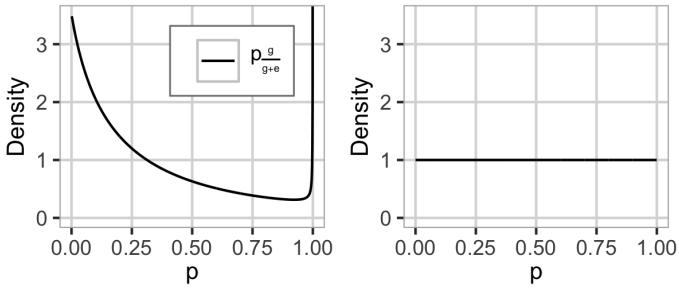


Figure 5: The prior for the proportion of genetic to phenotypic variance $p_{\frac{g}{g+e}}$ for the A-MW-exp (left) and A-MW-def (right) settings. We use $R_{\frac{g}{g+e}} = 0.25$. A-MW-exp is a dataset specific prior.

We ran the simulation for 30 years. At year 1, we set the following variances for the population of the 50 parents: additive variance of 1.0, dominance variance of 0.5, and epistasis variance of 0.1. We set the environmental variance to 6.0 for all stages and years. We ran the simulation for 20 years as a "burn-in" to obtain realistic breeding data under selection. We then ran the simulation for another 10 years with selection on phenotype and evaluated the fit of the models at the third selection stage. We did not use the models for selection. At this stage we had 100 individuals each with five replicates and the goal was to select the 10 genetically best individuals for the fourth, last, stage. Prior to fitting the models we removed the SNP markers with minor allele frequency below 5%.

Model fit and analysis

We fitted the models with a Bayesian approach (for the {A,ADX}-{CW,MW}-{def,exp,opp} settings) through the R package RStan (Carpenter *et al.*, 2017; Stan Development Team, 2019) that uses the No-U-Turn sampler, a variant of Hamiltonian Monte Carlo. Sampling methods such as Markov Chain Monte Carlo and Hamiltonian Monte Carlo have guaranteed asymptotic accuracy as the number of drawn samples go to infinity. However, in an applied context with finite computational resources, it is hard to assess this accuracy. Betancourt (2016) developed a diagnostic metric for the Hamiltonian Monte Carlo, called divergence, that indicates the robustness of a model fit to a specific dataset. This metric indicates whether the sampler is able to explore the posterior effectively or not, where in the latter case the results might be biased (we show an example on this in the results).

We also fitted Model A and Model ADX with the maximum likelihood (ML) approach using the low-

storage BFGS algorithm through the R package nloptr (Nocedal, 1980; Liu and Nocedal, 1989; Johnson, 2020). These approaches do not use priors. We denote them as A-ML and ADX-ML and use them as a base-line for comparison because maximum likelihood is a common approach in the literature. Inference for ADX-ML was, just like for ADX-MW-def and ADX-CW-def, not robust, and we do not present results from this setting. At last, we compared the model results to the performance of selection based solely on phenotype.

We ran the breeding program simulation 4,000 times and fitted the model and prior settings in each of the last 10 years of simulation (40,000 model fits in total), and evaluated the fits against the true (simulated) values. For each model fit we evaluated: (i) robustness, (ii) the accuracy of selecting the genetically best individuals, (iii) the accuracy of estimating the different genetic values and (iv) the accuracy of estimating the variance parameters.

For the robustness of the Bayesian approach we used the proportion of datasets that had robust inference (which we define as at least 99% non-divergent samples) for each model and prior setting. For the robustness of the maximum likelihood approach we used the proportion of datasets where the optimizer converged.

For the accuracy of selecting the genetically best individuals we ranked the best 10 individuals based on the estimated genetic value or estimated additive value, and counted how many were among the true genetically best 10 individuals based on the true genetic value or true additive value. We used the posterior mean of the effects as estimated values for ranking. Selection on the genetic value indicated selection of new varieties, while the selection on the additive value indicated selection of new parents.

For the accuracy of estimating the different genetic values we used Pearson correlation and continuous rank probability score (CRPS, Gneiting and Raftery, 2007). With the correlation we measured how well posterior means correlated with true values (high value is desired). This metric works with point estimates and ignores uncertainty of inferred posterior distributions of each individual genetic value. With the CRPS we measured a combination of bias and sharpness of the posterior distribution (Gneiting and Raftery, 2007) compared to true values (low value is desired). For the CRPS we used the posterior distribution of the estimated genetic values. In the case of phenotypic selection, we have a point estimate, and the CRPS reduces to the mean absolute error between the true genetic values and the phenotype. We extract the true genetic, additive, dominance and epistasis values from the breeding program and compare with the corresponding estimates from the models.

For the accuracy of estimating the variance parameters we compared estimated variance components to true values. We collected posterior medians and divided them by true genetic variances for each of the 10 years from the simulated breeding program (a value close to 1 is desired). This is not done for phenotype selection.

We provide example code to fit the models presented in this paper together with an example dataset (this dataset is not used in the analysis); see File S2 in the Supplemental materials for details.

Data availability

All data used in the case study is simulated according to the previous description, and are available upon request. One example data set is included in File S2 the Supplemental materials, but we do not include all datasets due to the size required to store them. The Supplemental materials are available at figshare: https://doi.org/10.6084/m9.figshare.12040716.v2.

Results

In the case study the model-wise priors and expert knowledge improved the robustness of non-additive models and the selection of the genetically best individuals, but did not improve the accuracy of estimating different genetic values for all individuals or for variance components.

The model-wise priors combined with expert knowledge improved robustness of the non-additive model to the level of robustness of the additive model and phenotypic selection. We show this in Table 2 with

Table 2: Robustness by model and prior setting.

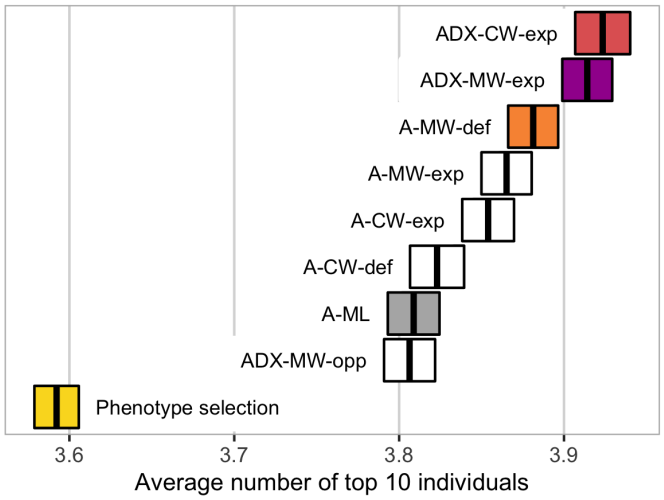
Setting	Robustness
Phenotype selection	1.00
A-MW-exp	1.00
A-MW-def	0.99
ADX-MW-exp	0.98
A-ML	0.94
A-CW-exp	0.94
A-CW-def	0.86
ADX-MW-opp	0.86
ADX-CW-exp	0.80
ADX-ML	0.76
ADX-MW-def	0.23
ADX-CW-def	0.04

the proportion of robust model fits by model and prior setting. Phenotypic selection does not depend on a model fit to a dataset and therefore had the highest robustness by definition. This maximum level of robustness was matched by fitting the simple additive model and model-wise prior with and without using expert knowledge (A-MW-exp and A-MW-def). This high model robustness was followed closely by fitting the more complicated non-additive model with model-wise prior and expert knowledge (ADX-MW-exp) as well as fitting the simple additive model with the standard maximum-likelihood approach (A-ML) and with the Bayesian approach using component-wise priors with and without expert knowledge (A-CW-exp and A-CW-def). The proportion of robust model fits then started to decrease for the other settings. For the non-additive model the standard maximum-likelihood approach (ADX-ML) was improved by using the Bayesian approach with either the component-wise prior with expert knowledge (ADX-CW-exp) or the model-wise prior with wrong/opposite expert knowledge (ADX-MW-opp). Literature default priors used with the non-additive model (ADX-MW-def and ADX-CW-def) had the lowest robustness.

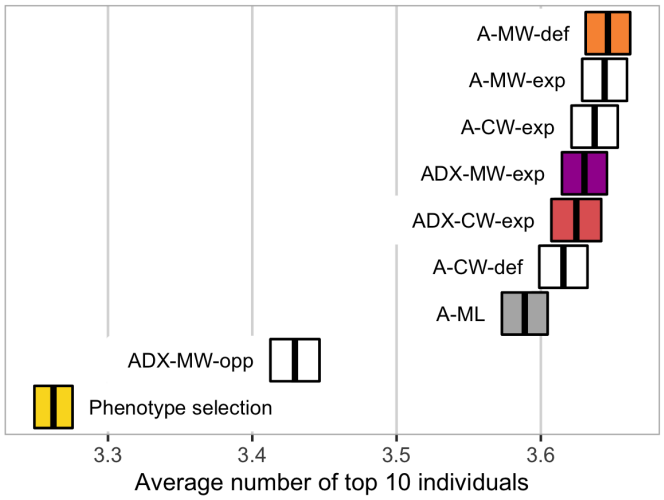
The reason for deteriorated robustness of some model and prior settings is that genetic and environmental effects can be partially confounded, which limits the exploration of the posterior when using the Bayesian approach or limits convergence of mode-seeking algorithms when using the maximum likelihood approach. We show the partial confounding with images of the covariance matrices for additive, dominance, epistasis and environmental sources of variation for one dataset in Figure S4 in File S1 in the Supplemental materials. In Figure S5 we show joint posterior samples for the epistasis and environmental variance for the ADX-MW-def and ADX-MW-exp settings for one dataset. We see that without a robust model (this includes both the likelihood and the prior), the posterior becomes difficult to explore, and this is also supported by the divergence diagnostics (Table 2). The posterior of the model-wise prior without expert knowledge (ADX-MW-def) is bimodal and the sampler has not been able to sample with convergence due to confounding.

Due to the lack of robust inference with the ADX-CW-def, ADX-MW-def and ADX-ML settings we do not present their results in the following.

The model-wise priors exploiting expert knowledge improved the selection of the genetically best individuals significantly, and the model choice was important for different breeding aims. We show this in Figure 6 where we display the accuracy of selecting individuals with the highest genetic value (variety selection, Figure 6a) and with the highest additive value (parent selection, Figure 6b). The settings with the non-additive model and expert knowledge (ADX-CW-exp and ADX-MW-exp) performed significantly better for selection of new varieties than the others, which followed in order from A-MW-def, A-MW-exp, A-CW-exp, A-CW-def, A-ML to ADX-MW-opp. The differences between these settings were small, but they all performed significantly better than sole phenotype selection, which is sensitive to environmental noise. For the selection of new parents the simpler additive model performed the best and model-wise priors improved its performance (A-MW-def, A-MW-exp and A-CW-exp). Wrong expert knowledge harmed the parent selection



(a) Genetic value (variety selection).



(b) Additive value (parent selection).

Figure 6: Accuracy of selecting individuals with the highest (a) genetic value (for variety selection) and (b) additive value (for parent selection) by model and prior setting - measured with the number of the top 10 true best individuals among the top 10 selected individuals (average ± two standard errors over replicates).

(ADX-MW-opp), but it still outperformed sole phenotype selection.

In the following we focus only on results for ADX-MW-exp, ADX-CW-exp, A-MW-def, A-ML and phenotype selection, and show the result of the remaining settings in the File S1 of the Supplemental materials (Figures S6-S8).

While using the model-wise priors and expert knowledge significantly improved the selection of the genetically best individuals compared to the maximum-likelihood approach, it did not significantly improve the accuracy of estimating different genetic values across all individuals. We show this in Figure 7 with the correlation between the true values and corresponding posterior means and in Figure 8 with the continuous rank probability score (CRPS) between the true values and corresponding posterior distributions. We show this for the genetic, additive, dominance and epistasis values separately. While there was a tendency of more

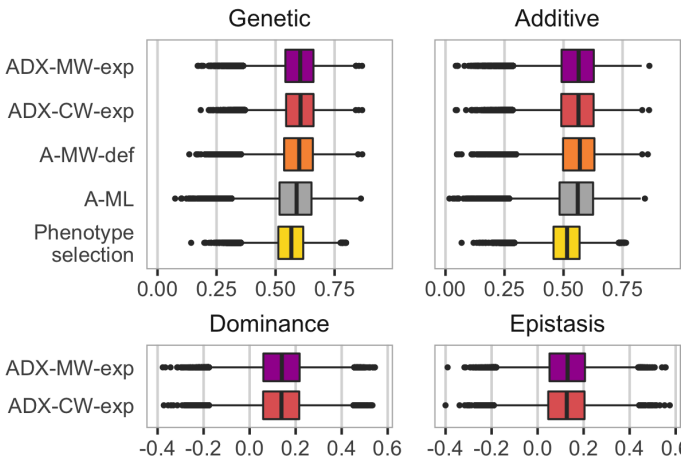


Figure 7: Accuracy of estimating the different genetic values for all individuals by model and prior setting - correlation (high value is desired, boxplots show variation over replicates). Genetic (upper left) means the sum of estimated additive, dominance and epistasis values for Model ADX, and estimated additive values for Model A.

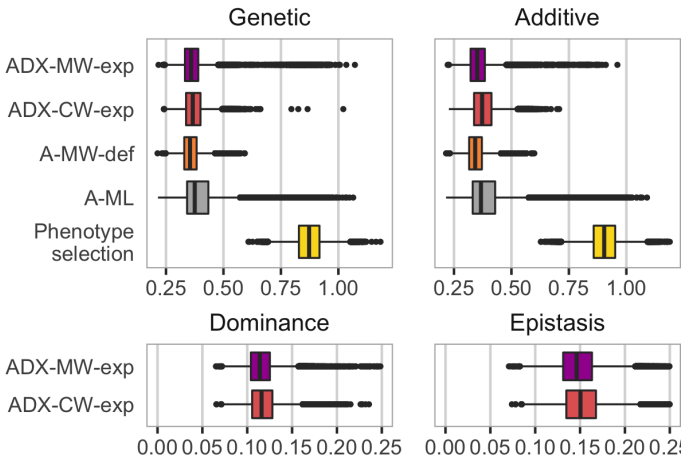
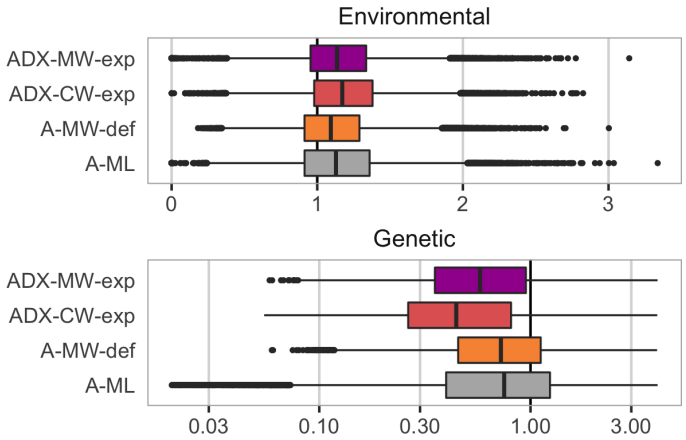


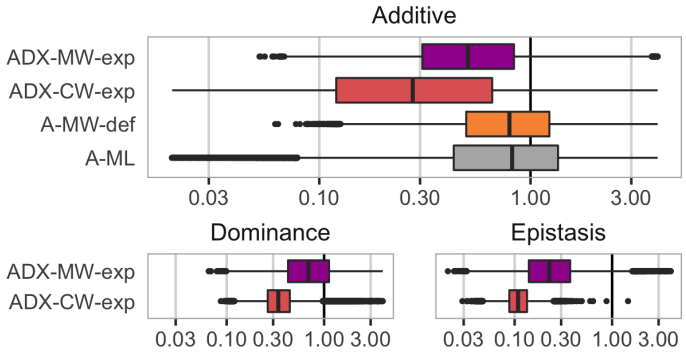
Figure 8: Accuracy of estimating the different genetic values for all individuals by model and prior setting - continuous rank probability score (CRPS; low value is desired, boxplots show variation over replicates). Genetic (upper left) means the sum of estimated additive, dominance and epistasis values for Model ADX, and estimated additive values for Model A.

favourable correlation and CRPS for certain model and prior settings, the variation between replicates was much larger than variation between the model and prior settings. The model-wise prior tended to perform better than the component-wise prior, expert knowledge tended to perform better than the default non-informative prior knowledge and use of prior knowledge via the Bayesian approach tended to perform better than the maximum likelihood. All models performed better in estimating the genetic and additive values, especially in the terms of CRPS, than the phenotype selection.

Variance component estimates varied considerably around the true values for all models and prior settings, but the estimates from the Bayesian inference showed slightly larger biases and smaller variances than maximum likelihood estimates. We show this in Figure 9 with the ratio of estimated to true variances (value



(a) Environmental and genetic variance.



(b) Additive, dominance and epistasis variance.

Figure 9: Accuracy of estimating (a) environmental and genetic variance and (b) additive, dominance and epistasis variance by model and prior setting - expressed as the estimated posterior median divided by the true value (a value close to 1 is desired, boxplots show variation over replicates, x-axes have a log-scale (except for environmental variance) and is focused on area around 1 with some outliers excluded).

close to 1 is desired and values below/above 1 denote underestimation/overestimation). Of the model and prior settings in Figure 9, the maximum likelihood approach (A-ML) was the closest to the true value on average in estimating the genetic variance, but also had the largest variation between replicates. Bayesian analysis with the additive model, model-wise prior and non-informative knowledge (A-MW-def) reduced variance between replicates, but did not improve bias. The non-additive model and expert knowledge (ADX-CW-exp and ADX-MW-exp) further increased the bias (underestimation) compared to A-ML and A-MW-def, and the model-wise prior (ADX-MW-exp) tended to perform better than the component-wise prior (ADX-CW-exp). When estimating dominance and epistasis variance the model-wise prior (ADX-MW-exp) tended to perform better than component-wise prior (ADX-CW-exp). Estimates for epistasis variance were considerably more underestimated than for the dominance variance.

Discussion

In this study we have introduced new priors for robust genomic modelling of additive and non-additive variation based on the penalized complexity prior (Simpson *et al.*, 2017) and hierarchical decomposition prior (Fuglstad *et al.*, 2020) frameworks. In the case study, the new priors enabled straightforward use of

expert knowledge, which in turn improved the robustness of genomic modelling and the selection of the genetically best individuals in a breeding program. However, it did not improve the overall accuracy of estimating genetic values for all individuals or for variance components. These results highlight three points for discussion: (i) expert-knowledge priors for genomic modelling, (ii) the importance of priors for breeding and (iii) limitations of our work.

Expert-knowledge priors for genomic modelling

Genomic modelling is challenging due to inherent high-dimensionality and pervasive correlations between loci and therefore requires substantial amounts of information for robust estimation. Most genomes harbour millions of segregating loci that are highly or mildly correlated. While estimating additive effects at these loci is a challenging task in itself (e.g., Visscher *et al.*, 2017; Young, 2019), estimating dominance and epistasis effects is an even greater challenge (e.g., Misztal, 1997; Zhu *et al.*, 2015; de los Campos *et al.*, 2019). One challenge in estimating the interactive dominance and epistasis effects is that they are correlated with the main additive effects and all these effects are further correlated across nearby loci (Mäki-Tanila and Hill, 2014; Hill and Mäki-Tanila, 2015; Vitezica *et al.*, 2017). Information to estimate all these locus effects and corresponding individual values has to inherently come from the data, but could also come in a limited extent from the expert knowledge. There is a wealth of expert knowledge in genetics (e.g., Houle, 1992; Falconer and Mackay, 1996; Lynch *et al.*, 1998), however, this expert knowledge is seldom used because it is not clear how to use it in a credible and a consistent manner.

We showed how to use the expert knowledge about the magnitude of different sources of variation by leveraging two recently introduced prior frameworks (Simpson *et al.*, 2017; Fuglstad *et al.*, 2020). While the penalized complexity priors are parsimonious and intuitive, they require absolute prior statements when used in a component-wise approach, which are challenging to elicit for multiple effects. The hierarchical decomposition framework imposes a tree structure according to a domain model, and the intuitive penalized complexity prior can be used in the hierarchical decomposition prior framework to ensure robust modelling. This model-wise approach enables the use of relative prior statements, which are less challenging to elicit than the absolute prior statements. The presented priors therefore pave a way for a fruitful elicitation dialogue between a geneticist and a statistician (Farrow, 2013). In particular, the hierarchical decomposition prior framework provides both a method for prior construction and a platform for communication among geneticists and statisticians. Further, the graphical representation allows a description of a joint prior in a visual way with minimal statistical jargon (Figure 3).

The hierarchical decomposition prior framework enabled us to use expert knowledge on relative additive and non-additive variation. In the simulated case study this information improved the robustness of the Bayesian approach over the maximum likelihood approach and improved the selection of the genetically best individuals. This improvement was due the additional information that alleviated the strong confounding between the non-additive (particularly epistasis) and environmental variation.

The hierarchical decomposition prior framework is also useful when expert knowledge is only available on parts of the model. For example, an expert may not have a good intuition about the level of broad-sense heritability, say for a new trait, but will likely have a good intuition on how the genetic variance decomposes into additive, dominance and epistasis components, simply due to the model specification (Hill *et al.*, 2008; Mäki-Tanila and Hill, 2014; Hill and Mäki-Tanila, 2015; Huang and Mackay, 2016). In those cases, we can use weakly-informative default priors on the parts of the model where expert knowledge is missing, and priors based on expert knowledge for the rest of the model. The component-wise specification of expert knowledge with the standard (Sorensen and Gianola, 2007) or the penalized complexity (Simpson *et al.*, 2017) priors is infeasible in this context, and does not admit a simple visualization of the implied assumptions on the decomposition of the phenotypic variance. Further, the component-wise specification of expert knowledge is particularly challenging when phenotypic variance is unknown or when collected observations are influenced by a range of effects which can inflate sample phenotypic variance. The model-wise approach with the hierarchical decomposition prior can address these situations.

There exists previous work on penalized estimation of genetic covariances (e.g., Meyer, 2016, 2019) that

also uses Bayesian principles and scale-free penalty functions to reduce variation of the estimates from small datasets and for large numbers of traits. Our proposed priors and expert knowledge also reduced variation of estimates in the simulated case study. However, our estimates were biased, which is expected given the small sample size and that the Bayesian approach induced bias towards a lower variance (e.g, Sorensen and Gianola, 2007). It is worth noting that the maximum likelihood estimates of genetic variance also were largely underestimated, which we believe is due to the small sample size and a large number of parameters to estimate. Further, for some datasets we could not obtain the maximum likelihood estimates, while priors robustified the modelling. We note, however, that genomic models are inherently misspecified by trying to estimate the effect of causal loci through correlated marker loci (Gianola *et al.*, 2009; de los Campos *et al.*, 2015).

Future research could expand the hierarchical decomposition prior framework to other settings. For example, to multiple traits or modelling genotype-by-environment interactions, which are notoriously noisy, and we aim to find parsimonious estimates (e.g., Meyer, 2016, 2019; Tolhurst *et al.*, 2019). Also, expand to model macro- and micro-environmental effects (e.g., Selle *et al.*, 2019) and to model multiple layers of sparse, yet high-dimensional, "omic" data from modern biological experiments using network-like models (Damianou and Lawrence, 2013).

Importance of priors for breeding

Robust genomic modelling of non-additive variation is important for breeding programs. There is substantial literature indicating sizeable non-additive genetic variation (e.g., Oakey *et al.*, 2006; Muñoz *et al.*, 2014; Bouvet *et al.*, 2016; Varona *et al.*, 2018; de Almeida Filho *et al.*, 2019; Santantonio *et al.*, 2019; Tolhurst *et al.*, 2019), but robust modelling of this variation is often challenging. We have shown how to achieve this robust modelling with the proposed priors and expert knowledge. We evaluated this approach with a simulated wheat breeding program where we assessed the ability to select the genetically best individuals on their genetic value (variety selection) and additive value (parent selection). The results showed that the proposed priors and the expert knowledge improved variety and parent selection. We observed more improvement in the variety selection, which is expected because there is more variation in genetic values than its first-order approximation additive values. However, this additional non-additive variation is hard to model due to a small signal from the data relative to environmental variation and confounding with the environmental variation. The proposed priors and the expert knowledge helped us to model the non-additive variation in a robust way.

Importantly, all models improved upon sole phenotypic selection, which shows the overall importance of genomic modelling. While the differences between the different models and priors were small, the improved genomic modelling can contribute to the much needed improvements in plant breeding (Ray *et al.*, 2013; Asseng *et al.*, 2015). Also, even a small improvement in the variety selection has a huge impact on production, because varieties are used extensively (Acquaah, 2009). In the terms of model complexity, the answer to whether to use the additive model or the non-additive model depended on the aim of the analysis. The non-additive model was the best in selecting the genetically best individuals on genetic value, whereas the additive model performed best in selecting the genetically best individuals on additive value. The reason for this is likely the small sample size and large number of parameters to estimate with the non-additive model (Varona *et al.*, 2018).

Of note is the observation that the proposed priors and the expert knowledge improved the selection of the genetically best individuals, but not the estimation of the different genetic values. We did not expect this difference. In principle both of these metrics are important, but for breeding the ability to select the genetically best individuals is more important (de los Campos *et al.*, 2013). A possible explanation for the difference between the two metrics is that the top individuals deviated more from the overall distribution and the overall metrics do not capture well the tail-behaviour.

The importance of the proposed priors and the expert knowledge will likely vary with the stage and size of a breeding program. Prior importance is known to decrease as the amount of data increases (Sorensen and Gianola, 2007), but the required amount of data for accurate estimation of non-additive effects is

huge compared to the size of most breeding programs. Therefore the proposed penalized complexity and hierarchical decomposition priors could be helpful also in large breeding programs as they enforce shrinkage according to the expert knowledge unless the data indicates otherwise, reducing the risk of estimating spurious effects.

Limitations of our work

The aim of this paper was to describe the use of the expert knowledge to improve genomic modelling, which we achieved through two recently introduced prior frameworks (Simpson *et al.*, 2017; Fuglstad *et al.*, 2020), and demonstrated their use in a simulated case study of a wheat breeding program. There are multiple other possible uses of the proposed priors in genomic modelling. The case study is small with only 100 individuals in the advanced stages of a wheat breeding program. We have chosen this stage for computationally simplicity and speed because we evaluate the robustness of estimation over many replicates. Also, a small number of individuals and a limited genetic variation at this stage made a good case study to test the importance of priors. Finally, we could have tested more prior options, in particular the shrinkage of the non-additive values towards the additive values, i.e., the PC-P_0 versus the PC-P_M prior. More research is needed in the future to see how the expert knowledge can improve genetic modelling further.

Interesting areas for future research are also in other breeding domains with the recent rise in volumes of individual genotype and phenotype data, which provide power for estimating dominance and epistasis values (e.g., Alves *et al.*, 2020; Joshi *et al.*, 2020). The ability to estimate the non-additive values would be very beneficial in breeding programs that aim to exploit biotechnology (e.g., Gottardo *et al.*, 2019). Finally, an exciting area for estimating non-additive individual values is in the area of personalized human medicine (Mackay and Moore, 2014; Sackton and Hartl, 2016; de los Campos *et al.*, 2018; Begum, 2019).

The proposed priors are novel and require further computational work to facilitate widespread use. The penalized complexity priors (Simpson *et al.*, 2017) are increasingly used in the R-INLA software (Rue *et al.*, 2009, 2017), while hierarchical decomposition priors (Fuglstad *et al.*, 2020) have been implemented with the general purpose Bayesian software Stan (Carpenter *et al.*, 2017; Stan Development Team, 2019). However, this implementation is technical. We are currently developing an R package that facilitates the prior specification and estimation using Stan and INLA. This will ease the use of the prior, and INLA will speed up the computations. The goal is to provide a simple graphical interface that can be used both by non-statisticians and statisticians. However, further work is needed to enable Bayesian treatment of large genomic models fitted to massive datasets.

Conclusion

In conclusion, we have presented how to use the expert knowledge on relative magnitude of genetic variation and its additive and non-additive components in the context of a Bayesian approach with two novel prior frameworks. We believe that when modelling a phenomenon for which there exists a lot of knowledge, we should employ methods that are able to take advantage of this resource. We have demonstrated with a simulated case study that such methods are important and helpful in the breeding context, and they might have potential also in other areas that use genomic modelling.

References

Acquaah, G., 2009 *Principles of Plant Genetics and Breeding*. John Wiley & Sons.

Alves, K., L. F. Brito, C. F. Baes, M. Sargolzaei, J. A. B. Robinson, *et al.*, 2020 Estimation of additive and non-additive genetic effects for fertility and reproduction traits in North American Holstein cattle using genomic information. Journal of Animal Breeding and Genetics **00**: 1–15.

Asseng, S., F. Ewert, P. Martre, R. P. Rötter, D. B. Lobell, *et al.*, 2015 Rising temperatures reduce global wheat production. Nature climate change **5**: 143–147.

Begum, R., 2019 A decade of Genome Medicine: toward precision medicine. Genome Med **11**: 13.

Belamkar, V., M. J. Guttieri, W. Hussain, D. Jarquín, I. El-basyoni, *et al.*, 2018 Genomic Selection in Preliminary Yield Trials in a Winter Wheat Breeding Program. G3: Genes, Genomes, Genetics **8**: 2735–2747.

Betancourt, M., 2016 Diagnosing Suboptimal Cotangent Disintegrations in Hamiltonian Monte Carlo. arXiv preprint arXiv:1604.00695 .

Bouvet, J.-M., G. Makouanzi, D. Cros, and P. Vigneron, 2016 Modeling additive and non-additive effects in a hybrid population using genome-wide genotyping: prediction accuracy implications. Heredity **116**: 146–157.

Carpenter, B., A. Gelman, M. D. Hoffman, D. Lee, B. Goodrich, *et al.*, 2017 Stan : A Probabilistic Programming Language. Journal of Statistical Software **76**.

Damianou, A. and N. Lawrence, 2013 Deep Gaussian Processes. In *Artificial Intelligence and Statistics*, pp. 207–215.

de Almeida Filho, J. E., J. F. R. Guimarães, F. Fonsceca e Silva, M. D. Vilela de Resende, P. Muñoz, *et al.*, 2019 Genomic Prediction of Additive and Non-additive Effects Using Genetic Markers and Pedigrees. G3: Genes, Genomes, Genetics **9**: 2739–2748.

de los Campos, G., J. M. Hickey, R. Pong-Wong, H. D. Daetwyler, and M. P. L. Calus, 2013 Whole-Genome Regression and Prediction Methods Applied to Plant and Animal Breeding. Genetics **193**: 327–345.

de los Campos, G., D. Sorensen, and D. Gianola, 2015 Genomic Heritability: What Is It? PLOS Genetics **11**.

de los Campos, G., D. A. Sorensen, and M. A. Toro, 2019 Imperfect Linkage Disequilibrium Generates Phantom Epistasis (& Perils of Big Data). G3: Genes, Genomes, Genetics **9**: 1429–1436.

de los Campos, G., A. I. Vazquez, S. Hsu, and L. Lello, 2018 Complex-Trait Prediction in the Era of Big Data. Trends in Genetics **34**: 746–754.

Falconer, D. S. and T. F. C. Mackay, 1996 *Introduction to Quantitative Genetics*. Longman Group, Harlow, fourth edition.

FAO, IFAD, UNICEF, WFP, and WHO, 2019 *The State of Food Security and Nutrition in the World 2019*. FAO, Rome.

Farrow, M., 2013 Prior elicitation. In *Encyclopedia of Systems Biology*, edited by W. Dubitzky, O. Wolkenhauer, K.-H. Cho, and H. Yokota, pp. 1743–1743, Springer New York, New York, NY.

Faux, A.-M., G. Gorjanc, R. C. Gaynor, M. Battagin, S. M. Edwards, *et al.*, 2016 AlphaSim: Software for Breeding Program Simulation. The Plant Genome **9**: 1–14.

Fisher, R. A., 1918 The correlation between relatives on the supposition of mendelian inheritance. Earth and Environmental Science Transactions of the Royal Society of Edinburgh **52**: 399–433.

Fuglstad, G.-A., I. G. Hem, A. Knight, H. Rue, and A. Riebler, 2020 Intuitive Joint Priors for Variance Parameters. Bayesian Anal. Advance publication.

Gaynor, C., 2019 *AlphaSimR: Breeding Program Simulations*. R package version 0.10.0.

Gaynor, R. C., G. Gorjanc, A. R. Bentley, E. S. Ober, P. Howell, *et al.*, 2017 A Two-Part Strategy for Using Genomic Selection to Develop Inbred Lines. Crop Science **57**: 2372–2386.

General Assemby of the United Nations, 2015 Resolution adopted by the General Assembly on 25 September 2015 A/RES/70/1.

Gianola, D., G. de los Campos, W. G. Hill, E. Manfredi, and R. Fernando, 2009 Additive Genetic Variability and the Bayesian Alphabet. Genetics **183**: 347–363.

Gneiting, T. and A. E. Raftery, 2007 Strictly Proper Scoring Rules, Prediction, and Estimation. Journal of the American Statistical Association **102**: 359–378.

Gottardo, P., G. Gorjanc, M. Battagin, R. C. Gaynor, J. Jenko, *et al.*, 2019 A Strategy To Exploit Surrogate Sire Technology in Livestock Breeding Programs. G3: Genes, Genomes, Genetics **9**: 203–215.

Guo, J., A. Riebler, and H. Rue, 2017 Bayesian bivariate meta-analysis of diagnostic test studies with interpretable priors. Statistics in Medicine **36**: 3039–3058.

Hill, W. and A. Mäki-Tanila, 2015 Expected influence of linkage disequilibrium on genetic variance caused by dominance and epistasis on quantitative traits. Journal of Animal Breeding and Genetics **132**: 176–186.

Hill, W. G., M. E. Goddard, and P. M. Visscher, 2008 Data and Theory Point to Mainly Additive Genetic Variance for Complex Traits. PLOS Genetics **4**: e1000008.

Horn, R. A., 1990 The Hadamard Product. In *Proc. Symp. Appl. Math*, volume 40, pp. 87–169.

Houle, D., 1992 Comparing evolvability and variability of quantitative traits. Genetics **130**: 195–204.

Huang, W. and T. F. C. Mackay, 2016 The Genetic Architecture of Quantitative Traits Cannot Be Inferred from Variance Component Analysis. PLOS Genetics **12**: 1–15.

Johnson, S. G., 2020 *The NLopt nonlinear-optimization package*. http://ab-initio.mit.edu/nlopt.

Joshi, R., T. H. Meuwissen, J. A. Woolliams, and H. M. Gjøen, 2020 Genomic dissection of maternal, additive and non-additive genetic effects for growth and carcass traits in Nile tilapia. Genetics Selection Evolution **52**: 1.

Legarra, A., 2016 Comparing estimates of genetic variance across different relationship models. Theoretical Population Biology **107**: 26–30.

Liu, D. C. and J. Nocedal, 1989 On the limited memory BFGS method for large scale optimization. Mathematical Programming **45**: 503–528.

Lynch, M., B. Walsh, *et al.*, 1998 *Genetics and analysis of quantitative traits*, volume 1. Sinauer Sunderland, MA.

Mackay, I., A. Horwell, J. Garner, J. White, J. McKee, *et al.*, 2011 Reanalyses of the historical series of UK variety trials to quantify the contributions of genetic and environmental factors to trends and variability in yield over time. Theoretical and Applied Genetics **122**: 225–238.

Mackay, T. F. and J. H. Moore, 2014 Why epistasis is important for tackling complex human disease genetics. Genome Medicine **6**: 42.

Mäki-Tanila, A. and W. G. Hill, 2014 Influence of Gene Interaction on Complex Trait Variation with Multilocus Models. Genetics **198**: 355–367.

Martini, J. W., N. Gao, D. F. Cardoso, V. Wimmer, M. Erbe, *et al.*, 2017 Genomic prediction with epistasis models: on the marker-coding-dependent performance of the extended GBLUP and properties of the categorical epistasis model (CE). BMC Bioinformatics **18**: 3.

Martini, J. W., F. H. Toledo, and J. Crossa, 2020 On the approximation of interaction effect models by Hadamard powers of the additive genomic relationship. Theoretical Population Biology **132**: 16–23.

Meuwissen, T. H. E., B. J. Hayes, and M. E. Goddard, 2001 Prediction of total genetic value using genome-wide dense marker maps. Genetics **157**: 1819–1829.

Meyer, K., 2016 Simple Penalties on Maximum-Likelihood Estimates of Genetic Parameters to Reduce Sampling Variation. Genetics **203**: 1885–1900.

Meyer, K., 2019 "Bending" and beyond: Better estimates of quantitative genetic parameters? Journal of Animal Breeding and Genetics **136**: 243–251.

Misztal, I., 1997 Estimation of Variance Components with Large-Scale Dominance Models. Journal of Dairy Science **80**: 965–974.

Muñoz, P. R., M. F. R. Resende, S. A. Gezan, M. D. V. Resende, G. de los Campos, *et al.*, 2014 Unraveling Additive from Nonadditive Effects Using Genomic Relationship Matrices. Genetics **198**: 1759–1768.

Nocedal, J., 1980 Updating quasi-Newton matrices with limited storage. Mathematics of Computation **35**: 773–782.

Oakey, H., A. Verbyla, W. Pitchford, B. Cullis, and H. Kuchel, 2006 Joint modeling of additive and non-additive genetic line effects in single field trials. Theoretical and Applied Genetics **113**: 809–819.

O'Hagan, A., C. E. Buck, A. Daneshkhah, J. R. Eiser, P. H. Garthwaite, *et al.*, 2006 *Uncertain Judgements: Eliciting Experts' Probabilities*. John Wiley & Sons.

Ray, D. K., N. D. Mueller, P. C. West, and J. A. Foley, 2013 Yield Trends Are Insufficient to Double Global Crop Production by 2050. PLOS ONE **8**: 1–8.

Rife, T. W., R. A. Graybosch, and J. A. Poland, 2019 A Field-Based Analysis of Genetic Improvement for Grain Yield in Winter Wheat Cultivars Developed in the US Central Plains from 1992 to 2014. Crop Science **59**: 905–910.

Rue, H., S. Martino, and N. Chopin, 2009 Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. Journal of the Royal Statistical Society: Series B **71**: 319–392.

Rue, H., A. Riebler, S. H. Sørbye, J. B. Illian, D. P. Simpson, *et al.*, 2017 Bayesian computing with INLA: A review. Annual Review of Statistics and Its Application **4**: 395–421.

Sackton, T. B. and D. L. Hartl, 2016 Genotypic Context and Epistasis in Individuals and Populations. Cell **166**: 279–287.

Santantonio, N., J.-L. Jannink, and M. Sorrells, 2019 Prediction of Subgenome Additive and Interaction Effects in Allohexaploid Wheat. G3: Genes, Genomes, Genetics **9**: 685–698.

Selle, M. L., I. Steinsland, J. M. Hickey, and G. Gorjanc, 2019 Flexible modelling of spatial variation in agricultural field trials with the R package INLA. Theoretical and Applied Genetics **132**: 3277–3293.

Shewry, P. R. and S. J. Hey, 2015 The contribution of wheat to human diet and health. Food and Energy Security **4**: 178–202.

Simpson, D., H. Rue, A. Riebler, T. G. Martins, and S. H. Sørbye, 2017 Penalising Model Component Complexity: A Principled, Practical Approach to Constructing Priors. Statistical Science **32**: 1–28.

Sørbye, S. H. and H. Rue, 2018 Fractional Gaussian noise: Prior specification and model comparison. Environmetrics **29**: e2457, e2457 env.2457.

Sorensen, D. and D. Gianola, 2007 *Likelihood, Bayesian, and MCMC methods in Quantitative Genetics*. Springer Science & Business Media.

Stan Development Team, 2019 RStan: the R interface to Stan. R package version 2.19.2.

Sweeney, D. W., J. Sun, E. Taagen, and M. E. Sorrells, 2019 Genomic selection in wheat. In *Applications of Genetic and Genomic Research in Cereals*, edited by T. Miedaner and V. Korzun, Woodhead Publishing Series in Food Science, Technology and Nutrition, pp. 273–302, Woodhead Publishing.

Tolhurst, D. J., K. L. Mathews, A. B. Smith, and B. R. Cullis, 2019 Genomic selection in multi-environment plant breeding trials using a factor analytic linear mixed model. Journal of Animal Breeding and Genetics **136**: 279–300.

Varona, L., A. Legarra, M. A. Toro, and Z. G. Vitezica, 2018 Non-additive Effects in Genomic Selection. Frontiers in Genetics **9**: 78.

Visscher, P. M., N. R. Wray, Q. Zhang, P. Sklar, M. I. McCarthy, *et al.*, 2017 10 Years of GWAS Discovery: Biology, Function, and Translation. The American Journal of Human Genetics **101**: 5–22.

Vitezica, Z. G., A. Legarra, M. A. Toro, and L. Varona, 2017 Orthogonal Estimates of Variances for Additive, Dominance, and Epistatic Effects in Populations. Genetics **206**: 1297–1307.

Wittenburg, D., N. Melzer, and N. Reinsch, 2011 Including non-additive genetic effects in Bayesian methods for the prediction of genetic values based on genome-wide markers. BMC genetics **12**: 74.

Young, A. I., 2019 Solving the missing heritability problem. PLOS Genetics **15**: 1–7.

Zhu, Z., A. Bakshi, A. A. Vinkhuyzen, G. Hemani, S. H. Lee, *et al.*, 2015 Dominance Genetic Variation Contributes Little to the Missing Heritability for Human Complex Traits. The American Journal of Human Genetics **96**: 377–385.