

A comparison of alternative random regression and reaction norm models for whole genome predictions¹

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ABSTRACT: Whole genome prediction (WGP) based on high density SNP marker panels is known to improve the accuracy of breeding value (BV) prediction in live-stock. However, these accuracies can be compromised when genotype by environment interaction ($G \times E$) exists but is not accounted for. Reaction norm (RN) and random regression (RR) models have proven to be useful in accounting for $G \times E$ in pre-WGP evaluations by modeling BV as linear or higher order functions of environmental or temporal covariates. We extend these RR/RN models based on several alternative specifications for SNP-specific intercepts and linear slopes on environmental covariates. One specification is based on bivariate normality (BVN) of SNP-specific intercepts and slopes, whereas 2 others, IW-BayesA and based on inverted Wishart (IW) extensions IW-BayesB, are, respectively, bivariate Student t extensions of currently popular models without (BayesA) or with (BayesB) variable selection. We highlight alternative specifications based on the square root free Cholesky decomposition (CD) of SNP-specific variance-covariance (VCV) matrices in an attempt to better differentially model

environmentally sensitive from environmentally robust QTL. Two CD specifications were considered with (CD-BayesB) or without (CD-BayesA) any variable selection on intercept and slope effects. We compared each of the 5 models based on an RN simulation study. Six scenarios were considered based on differences in overall genetic correlations between SNP-specific intercept and slope effects as well as on heritabilities and numbers of environmentally robust versus sensitive QTL. In most scenarios, IW-BayesA had the greatest accuracy, whereas CD-BayesB exhibited the greatest accuracy in low complexity architectures (i.e., low number of QTL). In an RR application of a Duroc $\times$ Pietrain resource population at Michigan State University, 5,271 SNP markers and 928 F2 animals with known pedigree were analyzed for backfat thickness at wk 10, 13, 16, 19, and 22. SNP-based RR methods had a 2.5% greater ($P < 0.0001$) cross-validation accuracy for predicting phenotypes than the SNP-based conventional BayesA/BayesB and/or pedigree based RR BLUP; however, none of the proposed RR models had performances that were different from each other.

Key words: environmentally robust, environmentally sensitive, hierarchical Bayesian analysis, whole-genome prediction

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INTRODUCTION

Whole genome prediction (WGP) using high density SNP markers has revolutionized genetic selection

of animals and plants for economically important traits. Genotype by environment ($G \times E$) interaction characterizes how genotypes influence phenotypes differentially in different environments (Falconer, 1952). Recently, it has been inferred that some SNP have differential effects across environments (Lillehammer et al., 2009). If $G \times E$ is present but is not considered in WGP models, then selection of animals for specific environments could be suboptimal and further complicate cross-validation strategies.

Random regression (RR) and reaction norm (RN) models have played an important role in detecting $G \times E$ of a linear or even higher order nature (Calus

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et al., 2002; Berry et al., 2003; Calus and Veerkamp, 2003; Cardoso and Tempelman, 2012; Streit et al., 2012). With increasing availability of high density marker panels for WGP, genomic RR/RN models can be developed by specifying SNP effects as random intercept and linear functions of age or environmental covariates (Streit et al., 2013; Jarquin et al., 2014; Silva et al., 2014). In “Bayesian alphabet” WGP models like BayesA or BayesB (Meuwissen et al., 2001), alternative distributional assumptions on SNP specific genetic variances have been used to generate alternative heavy tailed or variable selection specifications. We similarly propose alternative augmented specifications for the 2×2 genetic variance-covariance (VCOV) matrices pertaining to SNP-specific intercepts and slopes in an attempt to provide greater flexibility in RR/RN WGP models. The objectives of this study were to compare various alternative RR/RN WGP specifications to each other and to 2 conventional models (BayesA and BayesB) for assessing the accuracy of breeding value (BV) prediction in WGP using a focused simulation study and application to backfat thickness in pigs.

MATERIALS AND METHODS

Random Regression and Reaction Norm Models

The RR model for WGP can be written as follows:

$$y_{ik} = \mathbf{x}'_{ik}\boldsymbol{\beta} + \mathbf{z}'_i(\mathbf{g}_1 + d_{ik}\mathbf{g}_2) + a_i + e_{ik} \quad [1]$$

where y_{ik} is the phenotypic record k on animal i ($k = 1, 2, \dots, t_i$; $i = 1, 2, \dots, n$) having t_i records; $\boldsymbol{\beta}$ is the vector of fixed effects, $\mathbf{x}'_{ik}$ is the incidence row vector connecting elements of $\boldsymbol{\beta}$ to record k of animal i ; $\mathbf{z}'_i = [z_{i1} \ z_{i2} \ z_{i3} \ \dots \ z_{im}]$ is the vector of genotypes coded as 0, 1, or 2 copies of the minor allele on SNP for animal i ; $\mathbf{g}_1 = \{g_{1j}\}_{j=1}^m$ is the vector of SNP-specific intercept effects; $\mathbf{g}_2 = \{g_{2j}\}_{j=1}^m$ is the vector of SNP-specific temporal slope effects; d_{ik} is the temporal covariate for record k on animal i ; and e_{ik} is the random residual. Finally, a_i is the random effect of animal i characterized by a variance component σ_a^2 . This particular random effect may be either a specification on residual polygenic or permanent environmental effects or both; nevertheless, it is required in addition to the other terms in Eq. [1] when there are repeated records per animal as inherent with RR models. In Eq. [1], one could further write the BV for animal i at covariate d_{ik} as $\mathbf{z}'_i(\mathbf{g}_1 + d_{ik}\mathbf{g}_2)$, which, in turn, is a function of an intercept BV $\mathbf{z}'_i\mathbf{g}_1$ and a slope BV $\mathbf{z}'_i\mathbf{g}_2$. So $\mathbf{z}'_i\mathbf{g}_1$ is a measure of genetic merit (assuming d_{ik} is recentered to a mean of 0) at

the temporal or environmental midpoint for animal i whereas $\mathbf{z}'_i\mathbf{g}_2$ is the genetic merit of that same animal's environmental sensitivity (i.e., the greater the absolute value of $\mathbf{z}'_i\mathbf{g}_2$, the greater the sensitivity of that animal's genetic merit at different times or environments as represented by different values of d_{ik}).

We further rewrite Eq. [1] in matrix notation as follows:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{g}_1 + \mathbf{DZ}\mathbf{g}_2 + \mathbf{W}\mathbf{a} + \mathbf{e} \quad [2]$$

where $\mathbf{e} = \{e_{ik}\}$, $\mathbf{D}$ is a diagonal matrix of dimension $\sum_{i=1}^n t_i$ with the environmental covariates $\{d_{ik}\}$ along the diagonal, $\mathbf{X} = \{\{\mathbf{x}'_{ik}\}_{k=1}^{t_i}\}_{i=1}^n$, and $\mathbf{Z} = \{\mathbf{z}'_i \otimes \mathbf{1}_{t_i \times 1}\}_{i=1}^n$ with $\otimes$ denoting the Kronecker product. We assume $\mathbf{e} \sim N(\mathbf{0}, \mathbf{R} = \mathbf{I}\sigma_e^2)$ in this paper, although generalizations to heterogeneous residual variances over time are possible, too. Also, we might specify arbitrarily informative or diffuse priors $p(\boldsymbol{\beta})$ on “fixed effects” $\boldsymbol{\beta}$, $p(\sigma_e^2)$ on σ_e^2 , and $p(\sigma_a^2)$ on σ_a^2 .

Reaction norm models could be considered special cases of RR models as typically only 1 phenotypic record (y_i) is observed per animal (i.e., $t_i = 1 \ \forall i$), although the environmental (rather than temporal as typical with RR models) covariate d_i unique to animal i may vary substantially across animals. Furthermore, these covariates may need to be inferred (Su et al., 2006), but for the purposes of this study, we will consider d_i as known. The RN model can then be written as

$$y_i = \mathbf{x}'_i\boldsymbol{\beta} + \mathbf{z}'_i(\mathbf{g}_1 + d_i\mathbf{g}_2) + e_i \quad [3]$$

As with the RR model in Eq. [1] and [2], we could add animal effects or, equivalently, residual polygenic effects based on a known correlation (i.e., numerator relationship) matrix $\mathbf{A}$ between animals if the number of SNP is not considered to be large enough to model genetic variability.

Conventional BayesA and BayesB

Conventional WGP models do not include SNP-specific temporal slope effects ($\mathbf{g}_2$). BayesB specifies a mixture prior to a point mass at zero with non-association probability $(1 - \pi)$ and a Student t density with degrees of freedom ν and scale parameter s^2 with association probability π . BayesA is a special case of BayesB when $\pi = 1$ (Meuwissen et al., 2001). Note that Meuwissen et al. (2001) defined π as the non-association probability whereas we prefer the definition of π used most commonly in the variable selection literature (O'Hara and Sillanpaa, 2009). Priors such as $p(\nu)$, $p(s^2)$, and/or $p(\pi)$ can be specified on these hyper-

parameters for BayesA or BayesB to properly “tune” them or account for their uncertainty, as we and others have done previously (Yi and Xu, 2008; Technow et al., 2012; Yang and Tempelman, 2012) and strongly advocated (Jia and Jannink, 2012; Gianola, 2013).

Alternative Distributional Specifications for RR/RN Models

Bivariate Normality. The simplest specification for SNP-effects and slopes might be based on multivariate normality. Suppose we reorder $\mathbf{g} = [\mathbf{g}'_1 \ \mathbf{g}'_2]'$ instead as $\mathbf{g}^* = [g_{11} \ g_{21} \ g_{12} \ g_{22} \ \dots \ g_{1m} \ g_{2m}]' = [\mathbf{g}'_1 \ \mathbf{g}'_2 \ \dots \ \mathbf{g}'_m]'$, where $\mathbf{g}'_j = [g_{1j} \ g_{2j}]'$ represents the random intercept and slope effects of SNP j . In other words, $\mathbf{g}^*$ is ordered by traits within SNP whereas $\mathbf{g}$ is ordered by SNP within traits. Here each $\mathbf{g}_j$ is specified to be independently multivariate normal with null mean vector and common variance covariate matrix Σ_g where

$$\Sigma_g = \begin{bmatrix} \sigma_{g_1}^2 & \sigma_{g_1 g_2} \\ \sigma_{g_1 g_2} & \sigma_{g_2}^2 \end{bmatrix} \quad [4]$$

One can specify a subjective conjugate inverted Wishart (IW) prior on Σ_g ; i.e., $\Sigma_g \sim IW(v_0, \mathbf{S}_0)$. We denote this extension as bivariate normality (BVN).

Bivariate Student t Model With or Without Variable Selection. We consider an extension to BVN, whereby elements of $\mathbf{g}$ are specified to have heterogeneous VCV matrices across SNP. For SNP j , we specify $\mathbf{g}_j$ to be conditionally bivariate normal with SNP-specific covariance matrix Σ_j ; i.e.,

$$\mathbf{g}_{\cdot j} \sim \mathbf{N} \left(\mathbf{0}_{2 \times 1}, \Sigma_j = \begin{bmatrix} \sigma_{g_{1j}}^2 & \sigma_{g_{1j} g_{2j}} \\ \sigma_{g_{1j} g_{2j}} & \sigma_{g_{2j}}^2 \end{bmatrix} \right) \quad [5]$$

We then specify each Σ_j to have exchangeable independent conjugate inverted Wishart prior densities; i.e., $\Sigma_j \sim IW[v_g, \Sigma_g(v_g - 3)]$ characterized by a degrees of freedom parameter v_g and scale matrix

$$\Sigma_g = \begin{bmatrix} \sigma_{g_1}^2 & \sigma_{g_1 g_2} \\ \sigma_{g_1 g_2} & \sigma_{g_2}^2 \end{bmatrix} \text{ such that } \mathbf{E}(\Sigma_j) = \Sigma_g. \text{ We denote}$$

this specification as **IW-BayesA**, noting the obvious bivariate extension to BayesA as first proposed by Meuwissen et al. (2001). Note that as $v_g \rightarrow \infty$, $\Sigma_j = \Sigma_g \forall j$ such that IW-BayesA then reverts back to BVN. We specify a prior $p(v_g)$ on v_g and a conjugate Wishart

(W) prior $\Sigma_g \sim W(v_0, \frac{\mathbf{S}_0}{v_0})$ on Σ_g such that $\mathbf{E}(\Sigma_g) = \mathbf{S}_0$.

Mirroring the variable selection extension of BayesA to BayesB by Meuwissen et al. (2001), we also further modified IW-BayesA by specifying a mixture prior on Σ_j such that $\Sigma_j = \mathbf{0}_{2 \times 2}$ with probability $(1 - \pi)$, and $\Sigma_j \sim IW[v_g, \Sigma_g(v_g - 3)]$ with probability π . We name this procedure **IW-BayesB**, specifying a prior $p(\pi)$ on π .

Cholesky Decomposition Specification Including Variable Selection. We conjectured that specification of inverted Wishart prior densities on Σ_j might be rather inflexible, as such specifications either imply that all SNP have either nonzero effects for both intercept and slope (IW-BayesA, BVN), or, if they do not, both effects are 0 (i.e., IW-BayesB), thereby not allowing for the possibility that some SNP effects are important over all environments (i.e., nonzero intercept) but environmentally robust (i.e., 0 slope). Furthermore, these IW specifications are additionally inflexible in that the heterogeneity of each single component of Σ_j is controlled by a single parameter v_g .

Hence, we developed a potentially more flexible parameterization based on the square root free Cholesky decomposition (**CD**) of Σ_j following our previous work (Bello et al., 2010) by specifying

$$\mathbf{g}_2 = \Psi \mathbf{g}_1 + \mathbf{g}_{2|1} \quad [6]$$

Here $\mathbf{g}_{2|1} = \{g_{2|1,j}\}$ is the vector of SNP-specific slope effects conditional on intercept effects, whereas $\Psi = \text{diag}\{\phi_j\}_{j=1}^m$ represents a diagonal matrix of SNP-specific associations between intercept and slope effects. Hence, we can rewrite the RN/RR model (Eq. [2]) as

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{g}_1 + \mathbf{DZ}(\Psi \mathbf{g}_1 + \mathbf{g}_{2|1}) + \mathbf{e} \quad [7a]$$

or equivalently as

$$\mathbf{y} = \mathbf{X}\beta + (\mathbf{Z} + \mathbf{DZ}\Psi)\mathbf{g}_1 + \mathbf{DZ}\mathbf{g}_{2|1} + \mathbf{e} \quad [7b]$$

Note for SNP j that if $\phi_j \approx 0$, intercept effects are nearly independent of slope effects. If $g_{2|1,j} \approx 0$ and $\phi_j \neq 0$, then intercept and slope effects are nearly perfectly correlated. If $g_{2|1,j} \approx 0$ and/or $\phi_j \approx 0$, then $g_{2j} \approx 0$ such that the SNP is said to be environmentally robust.

For SNP j , we specify $g_{1j} \sim N(0, \sigma_{g_{1j}}^2)$ with $\sigma_{g_{1j}}^2 \sim \chi^{-2}(v_1, v_1 s_1^2)$ such that $\mathbf{E}(\sigma_{g_{1j}}^2) = \frac{v_1 s_1^2}{v_1 - 2}$ whereas

$g_{2|1,j} \sim N(0, \sigma_{g_{2|1,j}}^2)$ with $\sigma_{g_{2|1,j}}^2 \sim \chi^{-2}(v_{2|1}, v_{2|1} s_{2|1}^2)$. In essence, these 2 mixtures specify 2 separate univariate Student t densities for elements of $\mathbf{g}_1$ and $\mathbf{g}_{2|1}$. Furthermore, we specify independent normal priors on SNP-specific association parameters between intercept and slope effects; that is, $\phi_j \sim N(\mu_\phi, \sigma_\phi^2) \forall j$. We label

Table 1. Summary of 6 scenarios in simulation study

Scenario	Number of QTL for both intercept and slope (M_{both})	Number of QTL for intercept only (M_{int})	Overall genetic correlation ($\bar{\rho}_{g,g_2}$) (and range across replicates)	Average h^2
1	100	0	0 (−0.07, 0.07)	0.5
2	100	0	0.5 (0.39, 0.61)	0.5
3	100	0	0.8 (0.68, 0.85)	0.5
4	50	50	0.5 (0.40, 0.66)	0.5
5	50	50	0.5 (0.40, 0.66)	0.2
6	20	20	0.5 (0.37, 0.71)	0.5

this model as **CD-BayesA**. Alternatively, we also consider a variable selection extension of CD-BayesA such that $\sigma_{g_{1j}}^2$ and $\sigma_{g_{2lj}}^2$ have these same respective inverted chi-square priors but with respective probabilities π_1 and π_{2l} such that $\sigma_{g_{1j}}^2 = 0$ and $\sigma_{g_{2lj}}^2 = 0$ with probabilities $1 - \pi_1$ and $1 - \pi_{2l}$. For obvious reasons then, we label this model as **CD-BayesB**. In both models, we might typically specify arbitrarily informative priors on μ_ϕ and on σ_ϕ^2 .

Bayesian Inference

To conduct fully Bayesian inference using Markov Chain Monte Carlo (MCMC) methods, it is necessary to derive the full conditional densities (**FCD**) for each unknown parameter to be inferred. For each of the aforementioned RN/RR models, we present these FCD in the Supplementary Web File based on the description of other prior specifications described in a subsequent section *Priors and Number of MCMC Samples Used for Data Analyses*.

Simulation Study

To help discern the ability of the proposed models to differentially fit various simply defined genetic architectures, we conducted a simulation study. We targeted 6 specific scenarios as outlined in Table 1. Key specifications were based on an overall or average genetic correlation ($\bar{\rho}_{g,g_2}$) between intercept and slope, as further described in Appendix 1, targeting values of $\bar{\rho}_{g,g_2} = 0$, $\bar{\rho}_{g,g_2} = 0.5$, and $\bar{\rho}_{g,g_2} = 0.8$. We also investigated the influence of the number of QTL influencing both intercept and slope ($M_{both} = 20, 50$, or 100), the number of QTL influencing the intercept only ($M_{int} = 20, 50$), and the h^2 ($h^2 = 0.20$ or 0.50). One may think of M_{int} as the number of environmentally robust QTL (i.e., consistent genetic effects across environments), whereas M_{both} denotes the number of environmentally sensitive QTL, that is, QTL whose effects are modulated by environmental effects. The first 3 scenarios (Scenarios 1 to 3) all entailed $M_{both} = 100$ and $h^2 = 0.50$, characterizing situations that seemingly best agreed with an IW-BayesB or a CD-BayesB situation, i.e., $m \gg M_{both}$

and $M_{int} = 0$. The key differences between each of these 3 scenarios were differences in $\bar{\rho}_{g,g_2}$. Scenarios 4 to 6 seemingly best agreed with the CD-BayesB specification (i.e., $m \gg M_{both} + M_{int}$ and $M_{int} > 0$) and were studied to assess the effect of h^2 (0.5 vs. 0.2 for Scenarios 4 vs. 5) and M_{int} and M_{both} (50 vs. 20 for Scenarios 4 vs. 6). Analytical results are further provided in Appendix 2 to illustrate the nature of genetic correlation generated between, as well as the heterogeneity of genetic variation across, different environmental covariate values.

Twenty replicated datasets were generated under each of the 6 different scenarios. For each replicate, we used the R package HaploSim (Coster and Bastiaansen, 2009) to generate 6,000 historical generations based on a constant population size of 100 animals. The genome was composed of 1 chromosome with 1 morgan in length and having 100,000 equally spaced loci. For 20,000 of these loci, the biallelic minor allele frequency (**MAF**) was 0.5, whereas the remaining loci (i.e., 80,000) were specified to be monomorphic in the base population. The number of recombinations for each meiosis event was drawn from a Poisson distribution with mean 1 whereas genomic positions for recombination were randomly chosen from a uniform distribution. For the 6,000 historical generations, we specified the recurrent mutation rate for all loci as 10^{-5} per locus per generation. After 6,000 generations, 2 additional generations, 6,001 and 6,002, were generated to expand to randomly mated population sizes of $n = 2,000$ animals each.

For each replicate, we deleted SNP with $MAF < 0.05$ in Generation 6,001 such that the number of SNP ranged from 2,167 to 2,516 across replicates after data editing. The genotype matrix **Z** for this generation was then based on the number of minor alleles (0, 1, or 2) at each locus for each animal. We randomly chose M_{int} of these SNP to be environmentally robust QTL and M_{both} to be environmentally sensitive QTL within each scenario. Variances for QTL-specific intercept effects $\sigma_{g_{1j}}^2$ were drawn from scaled inverted chi-square distributions with scale $s_1^2 = 2$ and degrees of freedom $\nu_1 = 5$. Variances for any QTL-specific slope effects conditional on intercept effects (i.e., $\sigma_{g_{2lj}}^2$) for each of M_{both} QTL were also drawn from scaled

inverted chi-square densities always with $v_{2|l} = 5$ and with $s_{2|l}^2 = 2$ ($\bar{\rho}_{g_1g_2} = 0$), $s_{2|l}^2 = 1.5$ ($\bar{\rho}_{g_1g_2} = 0.5$), or $s_{2|l}^2 = 0.72$ ($\bar{\rho}_{g_1g_2} = 0.8$). Quantitative trait locus effects for intercepts $\{g_{QTL,1j}\}_{j=1}^{j=M_{both}+M_{int}}$ and conditional slopes $\{g_{QTL,1j}\}_{j=1}^{j=M_{both}}$ were then independently generated from normal distributions with null means and their corresponding variances $\sigma_{g_{1j}}^2$ and $\sigma_{g_{2|j}}^2$. Hence, QTL effects for $\{g_{QTL,1j}\}_{j=1}^{j=M_{both}+M_{int}}$ and $\{g_{QTL,1j}\}_{j=1}^{j=M_{both}}$ were each Student t -distributed.

The association parameters $\{\phi_{QTL,1j}\}_{j=1}^{j=M_{both}}$ between intercept and slope for each of M_{both} QTL were generated from independent normal distributions, always with variance $\sigma_{QTL,\phi}^2 = 0.05$ but with mean $\mu_{QTL,\phi} = 0$ for $\bar{\rho}_{g_1g_2} = 0$, $\mu_{QTL,\phi} = 0.5$ for $\bar{\rho}_{g_1g_2} = 0.5$, and $\mu_{QTL,\phi} = 0.8$ for $\bar{\rho}_{g_1g_2} = 0.8$. Subsequently, the slope effect for QTL j was determined to be $g_{QTL,2j} = g_{QTL,1j} + \phi_{QTL,j}g_{QTL,2|j}$, $j = 1, 2, \dots, M_{both}$. An environmental covariate d_i , unique to each animal, was randomly drawn from $N(0, \sigma_d^2 = 0.36)$. Writing $\mathbf{Z}_{QTL,int}$ as the subset of the $n \times M_{int}$ SNP genotypes in $\mathbf{Z}$ that were designated to be environmentally robust QTL and $\mathbf{Z}_{QTL,both}$ as the subset of the $n \times M_{both}$ SNP genotypes in $\mathbf{Z}$ that were designated to be environmentally sensitive QTL, the true breeding value $\{TBV_i\}_{i=1}^{i=n}$ in each of generations 6,001 and 6,002 were generated using

$$\begin{aligned} \{TBV_i\}_{i=1}^{i=n} = & \mathbf{Z}_{QTL,both} \{g_{QTL,1j}\}_{j=1}^{j=M_{both}} \\ & + \mathbf{Z}_{QTL,int} \{g_{QTL,1j}\}_{j=M_{both}+1}^{j=M_{both}+M_{int}} \\ & + \text{diag}(d_i) \mathbf{Z}_{QTL,both} \{g_{QTL,2j}\}_{j=1}^{j=M_{both}} \end{aligned} \quad [8]$$

For each record on each animal, residuals (e_i) were independently drawn from $N(0, \sigma_e^2)$ as dependent on h^2 , i.e.,

$$\sigma_e^2 = \frac{\text{var}\left(\{TBV_i\}_{i=1}^{i=n}\right)(1-h^2)}{h^2} \quad [9]$$

Hence, phenotypic records were generated as $y_i = TBV_i + e_i$.

Since the existence of G×E would imply that genetic merit depends on environmental conditions, we compared the accuracy of predicting TBV among the 5 aforementioned RN models as well as the 2 conventional models (BayesA, BayesB) at 3 environmental covariate values: $d = -1.2$, $d = 0.0$, and $d = 1.2$ (i.e., $-2, 0$, and $+2\sigma_d$). Accuracy at a particular value of d was defined as the correlation between $\{TBV_{i,d}\}_{i=1}^{i=n}$ and $\{EBV_{i,d}\}_{i=1}^{i=n}$ for generation 6,002 animals where $\{TBV_{i,d}\}$ is based on Eq. [8] but with all $d_i = d$ and $EBV_{i,d} = \mathbf{z}'_i \hat{\mathbf{g}}_1 + d \mathbf{z}'_i \hat{\mathbf{g}}_2$. Here, $\mathbf{z}'_i$ were the SNP genotypes for animal i in Generation 6,002, whereas $\hat{\mathbf{g}}_1$

and $\hat{\mathbf{g}}_2$ were the respective posterior means for SNP-specific intercepts and slopes from the analysis of only generation 6,001 phenotypes. For each of the 5 RR/RN models, we also assessed the relative accuracy of predicting the components of the BV, due to intercept and slope, separately in all 6 scenarios among the 5 models. Intercept BV accuracy was determined as the correlation between true intercept BV (first 2 expressions on the right side of Eq. [8]) and estimated intercept BV ($\mathbf{Z} \hat{\mathbf{g}}_1$), whereas slope BV accuracy was determined as the correlation between true slope BV ($\mathbf{Z}_{QTL,both} \{g_{QTL,2j}\}_{j=1}^{j=M_{both}}$) and estimated slope BV ($\mathbf{Z} \hat{\mathbf{g}}_2$). We compared prediction accuracy of BV using a Wilcoxon signed rank test between each pair of the RR/RN and conventional models.

Michigan State University Pig Resource Population Data

The genotypes used for this analysis were based on a commercial platform for low density genotyping (8,434 SNP) in swine marketed as the Neogen Porcine GeneSeek Genomic Profiler LD (version 1; GeneSeek, a Neogen Company, Lincoln, NE; Badke et al., 2013). We received complete phenotype and genotype information on 928 F2 animals derived from a Duroc × Pietrain resource population at Michigan State University (Edwards et al., 2008; Choi et al., 2010). Any SNP with MAF < 0.01 were deleted. For adjacent SNP in complete linkage disequilibrium (LD) with pairwise $r^2 = 1$, we deleted 1 SNP at random from each pair. Then we excluded SNPs having P values < 10^{-4} for the Hardy Weinberg equilibrium test. Genotypes for the remaining 5,271 SNP were standardized using $(z_{ij} - 2p_j) / \sqrt{2p_j(1-p_j)}$ where z_{ij} is the genotype of SNP j on animal i , and p_j is the allele frequency of the reference allele for SNP j (de los Campos et al., 2013). Pedigree information was available for the 928 F2 animals including their parents and grandparents. There were 140 unique full-sib families in total among the 928 F2 animals. The average full-sib family size was around 6. Map information was available on SNP for each of the 18 autosomes from Duarte et al. (2013).

We focused on backfat thickness as our response variable. Backfat thickness was measured at the 10th rib by B-mode ultrasound at wk 10, 13, 16, 19, and 22 (Edwards et al., 2008). We used the following RR model for data analysis:

$$\begin{aligned} y_{ijkl} = & \mu + \sum_{p=1}^4 \beta_p d_i^p + \text{sex}_j + \sum_{p=1}^4 (\text{sex}_j \times \beta_p d_i^p) \\ & + \text{litter}_k + u_{il} + d_i u_{2l} + \mathbf{z}'_i (\mathbf{g}_1 + d_i \mathbf{g}_2) + e_{ijkl} \end{aligned} \quad [10]$$

Here, μ is the overall mean, d_i^p is the p th order power or polynomial ($p = 1, 2, 3, 4$) on wk i with β_p being the corresponding partial regression coefficient, sex_j is the fixed effect of sex j , $(sex_j \times \beta_p d_i^p)_j$ is the fixed effect of the interaction between d_i^p and sex j , $litter_k$ is the random effect for litter k , u_{1l} is the permanent environmental intercept effect for animal l , u_{2l} is the permanent environmental slope effect for animal l , $\mathbf{z}_l' = [z_{l1} \ z_{l2} \ z_{l3} \ \dots \ z_{lm}]$ is the vector of genotypes on animal l , $\mathbf{g}_1$ is the vector of SNP-specific intercept effects, $\mathbf{g}_2$ is the vector of SNP-specific slope effects, d_i is the recoded covariate for wk i , and e_{ijkl} is the residual effect on y_{ijkl} . We coded d_i as $-1, -0.5, 0, 0.5$, and 1 for wk 10, 13, 16, 19, and 22.

Random effect distributional specifications were as follows. Litter effects were presumed to be normally and independently distributed with null mean and variance component σ_{litter}^2 . We decided not to fit polygenic effects since they were strongly confounded with both litter effects and the genotype-based linear combination of SNP effects and hence would otherwise severely impede MCMC performance. The permanent environmental effects $\mathbf{u} = [\mathbf{u}_1' \ \mathbf{u}_2']'$ for $\mathbf{u}_1 = \{u_{1l}\}$ and $\mathbf{u}_2 = \{u_{2l}\}$ were assumed to be multivariate normal with null mean vector and VCV matrix $\Sigma_u \otimes \mathbf{I}$ where $\mathbf{I}$ is the identity matrix and Σ_u is the 2×2 unstructured covariance matrix between permanent environmental intercepts and slopes.

We also applied a conventional polygenic model (RR-BLUP) as a control-based comparison for the genomic (i.e., SNP) based RR models. Fixed effects, random litter effects, and permanent environmental effects were defined the same as in Eq. [10], except that we replaced SNP effects by polygenic effects for both intercept and slope as follows:

$$y_{ijkl} = \mu + \sum_{p=1}^4 \beta_p d_i^p + sex_j + \sum_{p=1}^4 (sex_j \times \beta_p d_i^p) + litter_k + u_{1l} + d_i u_{2l} + a_{1l} + d_i a_{2l} + e_{ijkl} \quad [11]$$

We assumed that the polygenic effects $\mathbf{a} = [\mathbf{a}_1' \ \mathbf{a}_2']'$ for intercept $\mathbf{a}_1 = \{a_{1l}\}$ and slope $\mathbf{a}_2 = \{a_{2l}\}$ have a joint multivariate normal distribution with null mean vector and VCV matrix $\Sigma_a \otimes \mathbf{A}$, where $\mathbf{A}$ is the numerator relationship matrix and Σ_a is the 2×2 unstructured covariance matrix between polygenic intercept and slope effects.

All of the 5 aforementioned RR models along with RR-BLUP were compared to conventional WGP specifications (i.e., BayesA and BayesB) based on 20 random across-litter cross-validation splits of the data. This cross-validation split strategy was adapted to minimize the effect on predictive accuracy of close full sib relationships between individuals in the training with those in the validation splits. Furthermore, we wanted to avoid having an animal's own records to be split between the

training and validation sets, as any 2 records on an animal would otherwise provide excellent extrapolation for the remaining 3 records, for example. So, for each split, data on all individuals from 126 (90%) litters were randomly chosen as the training data, whereas the data on all subjects in the remaining 14 (10%) litters were chosen to be validation data. In this cross validation, hyperparameters and variance components were fixed to posterior means derived from analyses of all of the data. To expedite analyses under the RR-BLUP model, we used ASReml 3.0 (Gilmour et al., 2009) to provide analytical BLUP solutions based on REML estimates of variance components rather than using MCMC, noting that conditionally on variance components, these MCMC and BLUP inferences are identical. For all 8 models, the Pearson correlation between predictions of validation data, based on estimates derived from training data and the validation genotypes, with the actual validation data was used as a measure of performance of the competing models. A Wilcoxon signed rank test was used to draw conclusions on differences in these correlations between models across the 20 data splits.

Priors and Number of MCMC Samples Used for Data Analyses

Diffuse or noninformative priors were chosen for hyperparameters wherever possible to minimize the influence of prior assignments on their estimates and comparisons between models. For all conventional BayesA analyses, we specified a vaguely informative prior $v \sim p(v) \propto (v+1)^{-2}$. Furthermore, we specified the noninformative Gelman prior $s^2 \sim \text{Gamma}(0.5, 0) \propto (s^2)^{-1/2}$ (Gelman, 2006) for conventional BayesA and $s^2 \sim \text{Gamma}(0.1, 0.1) \propto (s^2)^{-0.9} e^{-0.1s^2}$ and $\pi \sim p(\pi) = \text{Beta}(1, 8)$ for conventional BayesB based on our previous experience that at least diffusely informative priors on s^2 are required in BayesB implementations (Yang and Tempelman, 2012). For BVN, a noninformative inverted Wishart prior was specified on Σ_g with $\Sigma_g \sim IW(v_0 = -3, S_0 = \mathbf{0}_{2 \times 2}) \propto 1$. For IW-BayesA and IW-BayesB, we specified the prior $p(v_g) \propto (v_g + 1)^{-2}$ on v_g and a mildly informative conjugate Wishart prior on Σ_g ; i.e., $\Sigma_g \sim W[v_0 = 4, S_0 = \text{diag}(0.2)] \propto |\Sigma_g|^{-2} \exp[-10 \text{trace}(\Sigma_g)]$. Also $\pi \sim \text{Beta}(\alpha_\pi = 1, \beta_\pi = 8)$ was specified in IW-BayesB.

In CD-BayesA and CD-BayesB, we used the same noninformative priors $p(v_1) \propto (v_1 + 1)^{-2}$ and $p(v_{2l}) \propto (v_{2l} + 1)^{-2}$. In addition, Gelman's prior $s_1^2 \sim \text{Gamma}(\alpha_1 = 0.5, \beta_1 = 0) \propto (s_1^2)^{-1/2}$ and $s_{2l}^2 \sim \text{Gamma}(\alpha_{2l} = 0.5, \beta_{2l} = 0) \propto (s_{2l}^2)^{-1/2}$ were used in CD-BayesA, while $s_1^2 \sim \text{Gamma}(\alpha_1 = 0.1, \beta_1 = 0.1) \propto (s_1^2)^{-0.9} e^{-0.1s_1^2}$ and $s_{2l}^2 \sim \text{Gamma}(\alpha_{2l} = 0.1, \beta_{2l} = 0.1) \propto (s_{2l}^2)^{-0.9} e^{-0.1s_{2l}^2}$ were

Table 2. Average posterior means of key hyperparameters ($\pm$ SD) using Cholesky decomposition (CD)-BayesA and CD-BayesB models across 20 replicated datasets and 6 scenarios in simulation study

Scenario	Model	s_1^2	$s_{2 1}^2$	μ_ϕ	σ_ϕ^2	v_1	$v_{2 1}$	π_1	$\pi_{2 1}$
1	CD-BayesA	0.03 $\pm$ 0.02	0.03 $\pm$ 0.02	0.01 $\pm$ 0.19	0.57 $\pm$ 0.35	2.4 $\pm$ 1.1	3.9 $\pm$ 1.8	NA ¹	NA
	CD-BayesB	1.31 $\pm$ 0.33	1.22 $\pm$ 0.28	0.01 $\pm$ 0.18	0.62 $\pm$ 0.28	10 $\pm$ 5.1	9.4 $\pm$ 3.9	0.09 $\pm$ 0.03	0.06 $\pm$ 0.02
2	CD-BayesA	0.02 $\pm$ 0.02	0.02 $\pm$ 0.01	0.49 $\pm$ 0.14	0.52 $\pm$ 0.35	2.0 $\pm$ 0.6	4.5 $\pm$ 1.6	NA	NA
	CD-BayesB	1.57 $\pm$ 0.37	1.12 $\pm$ 0.26	0.50 $\pm$ 0.14	0.56 $\pm$ 0.32	9.5 $\pm$ 4.4	10.1 $\pm$ 3.2	0.07 $\pm$ 0.02	0.06 $\pm$ 0.02
3	CD-BayesA	0.02 $\pm$ 0.01	0.02 $\pm$ 0.01	0.80 $\pm$ 0.10	0.25 $\pm$ 0.21	2.0 $\pm$ 0.8	4.8 $\pm$ 1.5	NA	NA
	CD-BayesB	1.52 $\pm$ 0.59	0.96 $\pm$ 0.27	0.80 $\pm$ 0.10	0.30 $\pm$ 0.24	8.8 $\pm$ 3.3	11.2 $\pm$ 2.8	0.07 $\pm$ 0.02	0.05 $\pm$ 0.02
4	CD-BayesA	0.01 $\pm$ 0.01	0.01 $\pm$ 0.01	0.36 $\pm$ 0.10	0.33 $\pm$ 0.14	1.8 $\pm$ 0.2	5.6 $\pm$ 0.9	NA	NA
	CD-BayesB	1.60 $\pm$ 0.48	0.84 $\pm$ 0.14	0.36 $\pm$ 0.12	0.37 $\pm$ 0.20	9.1 $\pm$ 3.5	11.4 $\pm$ 1.6	0.07 $\pm$ 0.02	0.04 $\pm$ 0.02
5	CD-BayesA	0.07 $\pm$ 0.05	0.02 $\pm$ 0.01	0.34 $\pm$ 0.15	0.24 $\pm$ 0.17	4.5 $\pm$ 1.9	5.7 $\pm$ 0.7	NA	NA
	CD-BayesB	1.27 $\pm$ 0.31	0.88 $\pm$ 0.10	0.36 $\pm$ 0.18	0.33 $\pm$ 0.22	12 $\pm$ 4.7	11.6 $\pm$ 1.3	0.11 $\pm$ 0.04	0.05 $\pm$ 0.01
6	CD-BayesA	0.002 $\pm$ 0.002	0.003 $\pm$ 0.002	0.41 $\pm$ 0.16	0.45 $\pm$ 0.24	1.3 $\pm$ 0.2	5.2 $\pm$ 1.2	NA	NA
	CD-BayesB	1.46 $\pm$ 0.62	0.85 $\pm$ 0.24	0.40 $\pm$ 0.17	0.47 $\pm$ 0.27	6.7 $\pm$ 4.4	10.3 $\pm$ 2.9	0.03 $\pm$ 0.02	0.03 $\pm$ 0.01

¹ NA = not available.

specified in CD-BayesB. For CD-BayesB, we specified the proper priors $\pi_1 \sim \text{Beta}(\alpha_1 = 1, \beta_1 = 8)$ and $\pi_{2|1} \sim \text{Beta}(\alpha_{2|1} = 1, \beta_{2|1} = 8)$. For both CD-BayesA and CD-BayesB, we specified $p(\mu_\phi) = N(\tau = 0, \zeta^2 = 1)$ and $p(\sigma_\phi^2) = \chi^{-2}(v_\phi = -1, s_\phi^2 = 0) \propto (s_\phi^2)^{-1/2}$, which is an alternative form of the Gelman prior but written in a way that reflects the fact that the scaled inverted chi-square distribution is conjugate for σ_ϕ^2 . Finally, $\sigma_e^2 \sim \chi^{-2}(v_e = -1, s_e^2 = 0) \propto (\sigma_e^2)^{-1/2}$ was specified in all cases whereas $\Sigma_a \sim IW(v_0 = -3, S_0 = \mathbf{0}_{2 \times 2}) \propto 1$ was used in the pig data analysis.

The total number of MCMC cycles for all analyses in this paper was 350,000, deleting the first 50,000 as burn-in and saving every 10th sample after burn-in for 30,000 saved samples.

RESULTS

Simulation Study

Average posterior means of the competing RN genomic models are provided in Table 2 for CD-BayesA and CD-BayesB and in Table 3 for BVN, IW-BayesA, and IW-BayesB. Note that the simulation process best matched CD-BayesB in all 6 scenarios, especially for the last 3. However, the average posterior means using CD-BayesB did not necessarily match the true values for many of the hyperparameters as given in the simulation study. This phenomenon is most likely due to the distortion provided by the presence of LD among markers in the vicinity of QTL and its effect on determinedness as further discussed in a much more general sense by Wimmer et al. (2013). However, note that average posterior means of μ_ϕ , v_1 , $v_{2|1}$, π_1 , and $\pi_{2|1}$ did track reasonably well with “true” values using CD-BayesB; note, in particular, that estimates of π_1 , and

$\pi_{2|1}$ were smallest in Scenario 6, which was the simplest genetic architecture simulated (i.e., half as many QTL as the other 5 scenarios). Also CD-BayesA estimates of s_1^2 and $s_{2|1}^2$ were much smaller than the corresponding CD-BayesB estimates, as expected since s_1^2 and $s_{2|1}^2$ define “typical” values of SNP-specific variances across SNP specified to have nonzero effects (Yang and Tempelman, 2012; Yang et al., 2015); hence the estimates of s_1^2 and $s_{2|1}^2$ would need to be distributed about a much larger number of SNP markers in CD-BayesA relative to CD-BayesB. For the same reasons, IW-BayesA led to smaller estimates of elements of Σ_g compared to IW-BayesB (see Table 3).

Comparisons of the accuracies for each of the 7 competing models at each of 3 different environmental covariate values: $d = -1.2$, 0, and 1.2 for each of the 6 scenarios are presented in Fig. 1. Recall that the simulated genetic architecture in Scenarios 1 to 3 specified situations where all QTL were environmentally sensitive (i.e., $M_{int} = 0$). When $\bar{\rho}_{g_1g_2} = 0$ (Fig. 1a), there were differences ($P < 0.05$) in accuracy of nearly 30 percentage points at the 2 extreme d values in favor of each of the 5 RN models over the 2 conventional models (BayesA/BayesB). Such differences were also significant ($P < 0.05$) at $\bar{\rho}_{g_1g_2} = 0.5$ (Fig. 1b) and at $\bar{\rho}_{g_1g_2} = 0.8$ (Fig. 1c) although these differences became increasingly asymmetric between $d = -1.2$ (i.e., progressively larger) and $d = 1.2$ (i.e., progressively smaller) as $\bar{\rho}_{g_1g_2}$ increased. For each of these 3 scenarios, IW-BayesA had the highest accuracy relative to all other models in $d = -1.2$ and 1.2 ($P < 0.05$). Accuracy differences were unimportant between all RN and conventional models at $d = 0$.

We further compared accuracies at $d = -1.2$, 0, and 1.2 in Scenarios 4, 5, and 6 where the simulated genetic architecture seemed even more congruent with a

Table 3. Average posterior means of key hyperparameters ($\pm$ SD) using bivariate normality (BVN), Inverted-Wishart (IW)-BayesA, and IW-BayesB models across 20 replicated datasets and 6 scenarios in simulation study

Scenario	Model	$\sigma_{g_1}^2$	$\sigma_{g_1g_2}$	$\sigma_{g_2}^2$	v_g	π
1	BVN	0.15 $\pm$ 0.03	-0.01 $\pm$ 0.02	0.17 $\pm$ 0.05	NA ¹	NA
	IW-BayesA	0.20 $\pm$ 0.04	0.00 $\pm$ 0.02	0.21 $\pm$ 0.06	4.66 $\pm$ 4.42	NA
	IW-BayesB	0.66 $\pm$ 0.14	0.01 $\pm$ 0.12	0.53 $\pm$ 0.12	1.78 $\pm$ 0.04	0.018 $\pm$ 0.002
2	BVN	0.15 $\pm$ 0.04	0.08 $\pm$ 0.03	0.18 $\pm$ 0.07	NA	NA
	IW-BayesA	0.19 $\pm$ 0.04	0.09 $\pm$ 0.03	0.22 $\pm$ 0.05	4.14 $\pm$ 2.76	NA
	IW-BayesB	0.64 $\pm$ 0.14	0.30 $\pm$ 0.10	0.54 $\pm$ 0.11	1.79 $\pm$ 0.04	0.017 $\pm$ 0.002
3	BVN	0.14 $\pm$ 0.04	0.12 $\pm$ 0.04	0.17 $\pm$ 0.05	NA	NA
	IW-BayesA	0.19 $\pm$ 0.03	0.15 $\pm$ 0.03	0.21 $\pm$ 0.04	4.0 $\pm$ 2.70	NA
	IW-BayesB	0.66 $\pm$ 0.14	0.51 $\pm$ 0.12	0.64 $\pm$ 0.11	1.82 $\pm$ 0.05	0.017 $\pm$ 0.002
4	BVN	0.15 $\pm$ 0.04	0.06 $\pm$ 0.02	0.08 $\pm$ 0.03	NA	NA
	IW-BayesA	0.23 $\pm$ 0.04	0.08 $\pm$ 0.03	0.13 $\pm$ 0.03	4.99 $\pm$ 5.81	NA
	IW-BayesB	0.97 $\pm$ 0.18	0.29 $\pm$ 0.10	0.37 $\pm$ 0.09	1.89 $\pm$ 0.08	0.017 $\pm$ 0.002
5	BVN	0.15 $\pm$ 0.05	0.05 $\pm$ 0.03	0.09 $\pm$ 0.04	NA	NA
	IW-BayesA	0.18 $\pm$ 0.04	0.06 $\pm$ 0.03	0.11 $\pm$ 0.03	13.52 $\pm$ 11.78	NA
	IW-BayesB	0.66 $\pm$ 0.11	0.19 $\pm$ 0.12	0.31 $\pm$ 0.05	1.85 $\pm$ 0.06	0.013 $\pm$ 0.002
6	BVN	0.08 $\pm$ 0.05	0.04 $\pm$ 0.03	0.05 $\pm$ 0.03	NA	NA
	IW-BayesA	0.20 $\pm$ 0.03	0.07 $\pm$ 0.03	0.13 $\pm$ 0.03	3.07 $\pm$ 0.03	NA
	IW-BayesB	0.81 $\pm$ 0.13	0.26 $\pm$ 0.13	0.38 $\pm$ 0.10	1.96 $\pm$ 0.13	0.013 $\pm$ 0.002

¹ NA = not available.

CD-BayesB like specification (i.e., $M_{int} > 0$) based on $\bar{\rho}_{g_1g_2} = 0.5$. In Scenario 4 (Fig. 1d) where $M_{both} = M_{int} = 50$ and $h^2 = 0.5$, both conventional BayesA and BayesB were inferior ($P < 0.05$) to all RN models at both $d = -1.2$ and 1.2 as expected. However, IW-BayesA surprisingly outperformed ($P < 0.05$) all other RN models at both $d = -1.2$ and 1.2 even though such differences were small (i.e., < 2 to 3%). Differences between all models were trivial at $d = 0$. The specification for Scenario 5 (Fig. 1e) differed only from Scenario 4 due to a lower $h^2 = 0.2$ vs. $h^2 = 0.5$. In that case, IW-BayesA also had higher ($P < 0.05$) accuracy compared to other RN models at $d = -1.2$ and $d = +1.2$ except for CD-BayesB at $d = +1.2$. At $d = 0$, CD-BayesB outperformed ($P < 0.05$) all other models although all differences were very small. The final Scenario 6 (Fig. 1f) differed only from Scenario 4 by lower numbers of QTL (i.e., $M_{both} = M_{int} = 20$). Not only was BVN then significantly much lower in accuracy compared to all other RN models at all 3 values of d , it was even lower in accuracy compared to conventional (i.e., BayesA and BayesB) models at $d = 0$. CD-BayesB had the highest accuracy among the 5 RN models at each value of d , although its differences with IW-BayesA and IW-BayesB were not important at $d = -1.2$.

We attempted to better understand these results by focusing on which of the RN models performed best for inferring on the intercept component of the BV and the slope component of the BV. For all 6 simulation scenarios, we found that CD-BayesB always had the

highest accuracy ($P < 0.05$) for intercept BV compared to all other RN models (Fig. 2a), whereas BVN and IW-BayesB were generally among the worst. For slope BV accuracy, there was no evidence of differences between any of the models at the low h^2 scenario 5 (Fig. 2b). However, IW-BayesA did outperform other RN models in Scenarios 1 to 4 for slope BV except for Scenario 3 with respect to CD-BayesB. In Scenario 6, IW-BayesA only outperformed BVN for slope BV. Bivariate normality and IW-BayesB had generally the lowest slope BV accuracy although CD-BayesA was poorest in Scenario 4. Hence the general advantages for predicting environment-specific BV for CD-BayesB appeared to accrue from its greater accuracy on inferring intercept components of genetic merit whereas that for IW-BayesA appeared to accrue from inferring the slope components.

Michigan State University Pig Resource Population Data

Predictive ability was calculated as the correlation between observed phenotypes y_{ijkl} in the validation dataset and their predicted values based on inferences from the training dataset. The predictive abilities for each of the 8 models for each of the 20 different cross-validation sets are illustrated in Fig. 3. The 5 RR Bayesian models had ~ 2.5 percentage points higher ($P < 0.0001$) cross-validation predictive performance compared to BayesA, BayesB, and RR-BLUP.

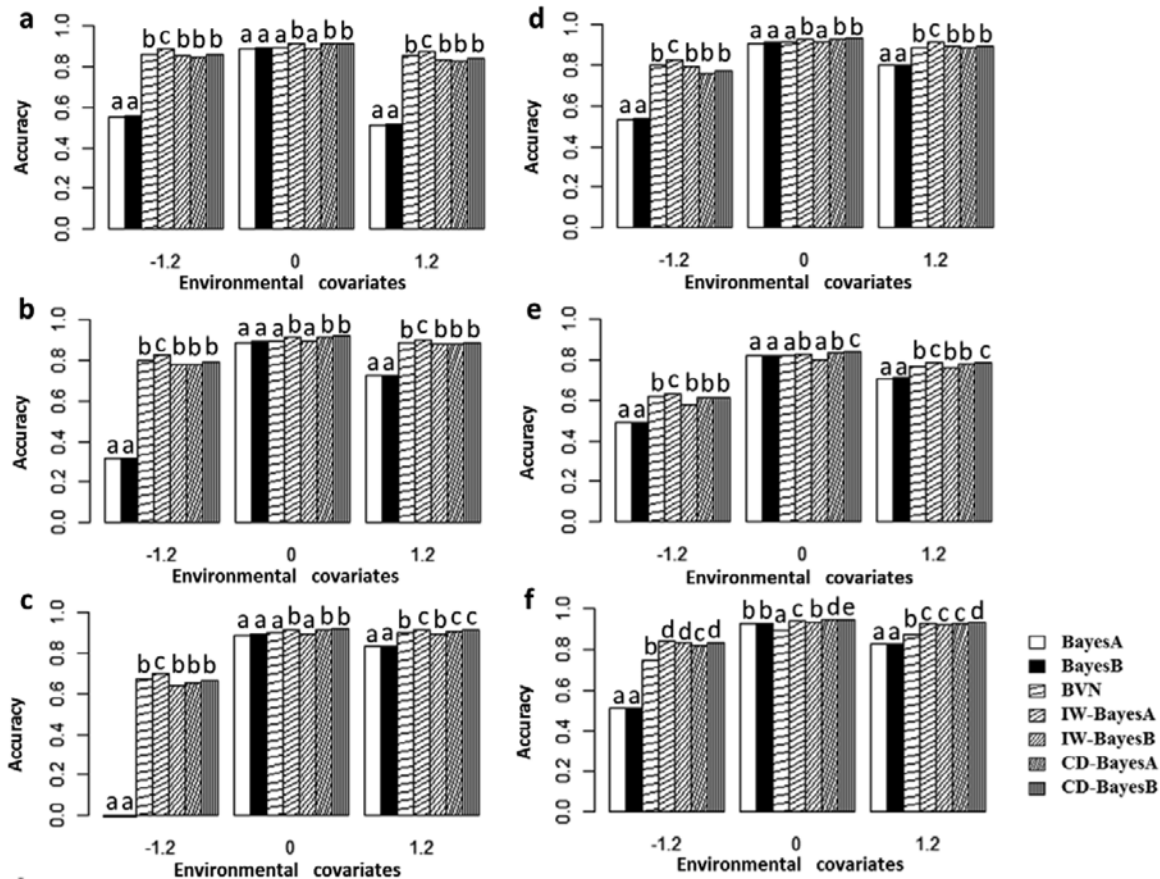


Figure 1. Average accuracy of breeding value prediction for 7 models (BayesA, BayesB, Inverted-Wishart (IW)-BayesA, IW-BayesB, bivariate normality [BVN], Cholesky decomposition [CD]-BayesA, and CD-BayesB) at 3 environmental covariates in 6 scenarios, i.e., A) $M_{both} = 100$, $M_{int} = 0$, $\rho_{g_1g_2} = 0$, $h^2 = 0.5$; B) $M_{both} = 100$, $M_{int} = 0$, $\rho_{g_1g_2} = 0.5$, $h^2 = 0.5$; C) $M_{both} = 100$, $M_{int} = 0$, $\rho_{g_1g_2} = 0.8$, $h^2 = 0.5$; D) $M_{both} = 50$, $M_{int} = 50$, $\rho_{g_1g_2} = 0.5$, $h^2 = 0.5$; E) $M_{both} = 50$, $M_{int} = 50$, $\rho_{g_1g_2} = 0.5$, $h^2 = 0.2$; F) $M_{both} = 20$, $M_{int} = 20$, $\rho_{g_1g_2} = 0.5$, $h^2 = 0.5$. Different letters indicate significant difference at $P < 0.05$.

However, no significant differences in predictive ability were found among the 5 RR genomic models.

DISCUSSION

Although RR and RN models have been extensively used for modeling G×E in classical polygenic models (Cardoso and Tempelman, 2012), they are just starting to be adapted for WGP models (Streit et al., 2012, 2013; Jarquin et al., 2014; Silva et al., 2014). Several efforts have been made to infer on G×E using RN models in QTL mapping and genome wide association studies (Lillehammer et al., 2007a, 2007b, 2008, 2009).

We consider both RR and RN WGP models in this paper since the modeling issues are virtually identical, albeit the circumstances are rather different. Reaction norm models are intended for those situations where there is typically 1 measure per animal and animal BV might be characterized by linear functions of environmental covariates (de Jong, 1995). Random regression models are intended for longitudinal data collection in the sense that there are repeated measurements for each animal over time, such as backfat thickness in pigs as analyzed

in this paper. Because of this repeated measures dynamic, it becomes even more imperative to model animal effects (i.e., additive genetics and/or permanent environmental effects) in RR genomic models relative to RN models. Furthermore, depending on how many repeated records are available per animal, it may be more feasible to explore nonlinear QTL effects in RR specifications as opposed to RN specifications as datasets for RN modeling tend to be data poor on a per animal basis.

The simplest RN/RR specification that we considered was BVN, which was essentially identical to a classical mixed model specification. Unlike any of the other 4 RR/RN specifications, BVN assumes all pairs of SNP-specific intercept and slope effects to be normally distributed, whereas each of the other models specify either t -distributed or mixtures thereof with null effects. Being simpler, the only hyperparameters requiring inference in BVN are variance components. This feature of BVN is not trivial given the difficulty for inferring degrees of freedom, for example, in Student t specifications (Habier et al., 2011). In fact, BVN is identical in principle to a classical RR or RN approach for mixed effects modeling of animal-specific intercept and slope

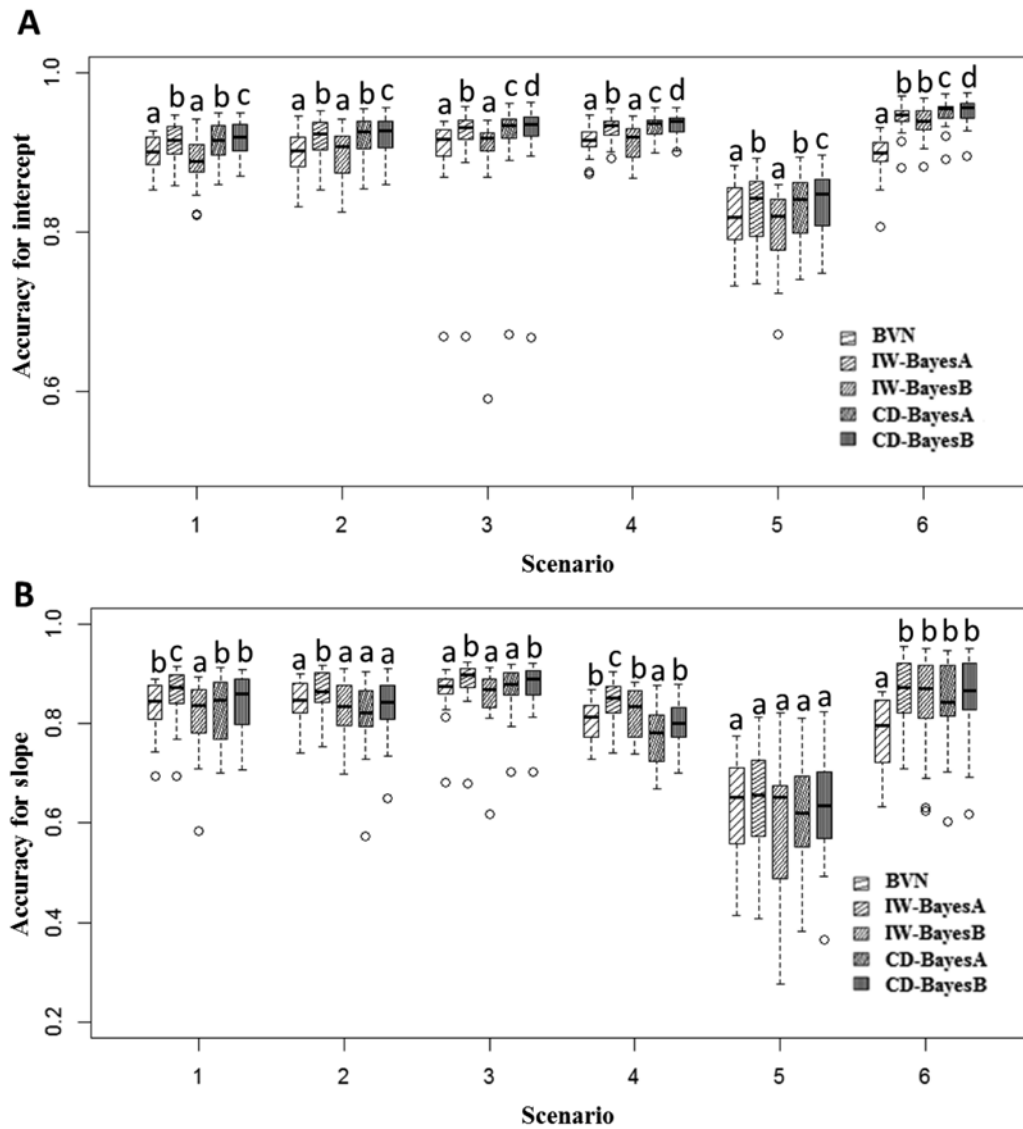


Figure 2. Accuracy of A) intercept and B) slope breeding value prediction for 5 reaction norm models (Inverted Wishart [IW]-BayesA, IW-BayesB, bivariate normality [BVN], Cholesky decomposition [CD]-BayesA, CD-BayesB) under 6 scenarios: 1) $M_{both} = 100$, $M_{int} = 0$, $\bar{\rho}_{g_1g_2} = 0$, $h^2 = 0.5$; 2) $M_{both} = 100$, $M_{int} = 0$, $\bar{\rho}_{g_1g_2} = 0.5$, $h^2 = 0.5$; 3) $M_{both} = 100$, $M_{int} = 0$, $\bar{\rho}_{g_1g_2} = 0.8$, $h^2 = 0.5$; 4) $M_{both} = 50$, $M_{int} = 50$, $\bar{\rho}_{g_1g_2} = 0.5$, $h^2 = 0.5$; 5) $M_{both} = 50$, $M_{int} = 50$, $\bar{\rho}_{g_1g_2} = 0.5$, $h^2 = 0.2$; 6) $M_{both} = 20$, $M_{int} = 20$, $\bar{\rho}_{g_1g_2} = 0.5$, $h^2 = 0.5$. Different letters indicate significant difference at $P < 0.05$.

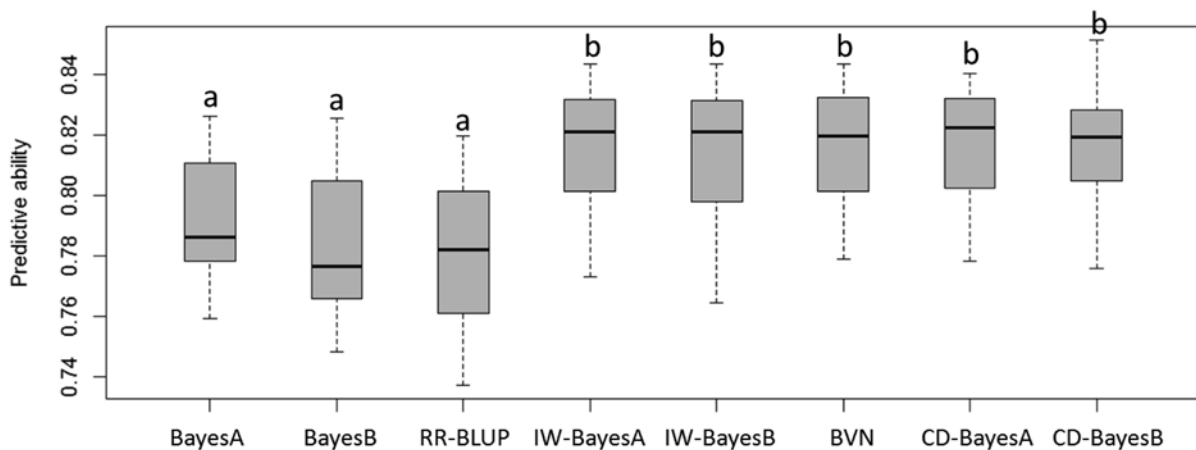


Figure 3. Predictive ability for 8 models (BayesA, BayesB, random regression [RR]-BLUP, Inverted Wishart [IW]-BayesA, IW-BayesB, bivariate normality [BVN], Cholesky decomposition [CD]-BayesA, and CD-BayesB) from cross-validation analysis using backfat thickness in Michigan State University Pig Resource Population data. Different letters indicate significant difference at $P < 0.0001$.

effects using a genomic relationship matrix (Silva et al., 2014) rather than modeling QTL effects directly.

One objective of this paper was to develop and compare 5 alternative RR/RN models against each other and 2 conventional WGP models BayesA and BayesB. In the simulation study, we first investigated the effect of an average genetic correlation ($\bar{\rho}_{g_1g_2}$) between intercept and slope. In Scenarios 1 to 3 of the simulation study, we considered 3 different levels of $\bar{\rho}_{g_1g_2}$ representing low, medium, and high positive genetic correlations between traits. We furthermore compared accuracies of genomic prediction in low, average, and high environmental levels. As expected, we found significantly higher accuracies for the 5 RN models compared to the 2 conventional WGP models at the extreme environments ($d = -1.2$ and $d = 1.2$) at all specifications of $\bar{\rho}_{g_1g_2}$. We found the difference in accuracies between the RN vs. the conventional models became greater with increasing $\bar{\rho}_{g_1g_2}$ at $d = -1.2$, whereas we found the converse trends at $d = 1.2$. This can be explained as follows. Recall that the intercept is defined at $d = 0$. Hence, positive genetic correlations between intercept and slope would create positive associations between genomic evaluations at $d = 0$ with those genomic evaluations based on $d \geq 0$ with the nature of that association progressively increasing with higher values of $\bar{\rho}_{g_1g_2}$. Conversely, negative associations would be expected between genomic evaluations at $d = 0$ and those genomic evaluations at increasingly negative values of d . In other words, one would expect to see SNP and, hence, animal-specific RN lines “crisscross” each other when $d < 0$, with this characteristic becoming increasingly more dramatic with higher values of $\bar{\rho}_{g_1g_2}$. Of course, if we had specified $\bar{\rho}_{g_1g_2}$ to be negative, we would have found the opposite trends in RR genomic accuracies, i.e., positive associations between genomic predictions based on $d = 0$ with those based on $d < 0$.

We found that IW-BayesA tended to have significantly greater accuracies in scenarios 1 to 3 than all other RN models at $d = 1.2$ and $d = -1.2$. This was initially surprising to us; however, we would note 2 considerations. First, the degrees of freedom specification were the same for QTL effects for both intercept and in slope, i.e., $v_1 = v_{2|1} = 5$. Hence, CD-BayesA or CD-BayesB might confer little or no advantage to IW-BayesA then because of the greater parsimony of a single degrees of freedom specification of the latter. Second, with data simulated based on LD, one might anticipate that the assumption of independence between effects of adjacent SNP markers is somewhat distorted (Yang and Tempelman, 2012), although independence is assumed for every model in this study. It may be rather difficult to predict the relative performance of WGP models under LD since the true model cannot be specified parametrically under LD, even when QTL effects are generated from known distributions as we did

in our simulation study. In fact, we conducted a separate simulation study (results not shown) whereby the data generation strategy exactly matches the assumptions of either of the 2 models, CD-BayesA and IW-BayesA, without generation of any LD between the SNP markers. In those comparisons, CD-BayesA did outperform IW-BayesA when the data generation model was based on a CD-BayesA model and vice versa. Recently, Wimmer et al. (2013) determined that the presence of high levels of LD, high levels of complexity [$(M_{both} + M_{int})/m$] of genetic architecture and low levels of determinedness (n/m) will tend to mute differences in performance between various Bayesian alphabet models. The level of determinedness is arguably much worse in RN and RR models compared to conventional models like BayesA or BayesB since twice as many SNP effects need to be inferred for the same amount of data; i.e., determinedness = $n/(2m)$ in an RR/RN WGP model.

Scenarios 4 to 6 in the simulation study were intended to more intensely mimic a CD-BayesB-like process whereby only a fraction of the QTL effects have environmentally robust effects (i.e., intercept only) with the remaining QTL having environmental sensitivity (i.e., nonzero slope effects). Scenario 4 ($h^2 = 0.5$) and Scenario 5 ($h^2 = 0.2$) were the same in that half of the 100 QTL were environmentally sensitive. Due to this h^2 difference, all RN models had lower accuracy in Scenario 5 than in Scenario 4, as expected. Somewhat surprisingly, however, IW-BayesA, a procedure not intended to separate environmentally sensitive from environmentally robust QTL, still generally maintained its advantage over all models in both of these scenarios.

Realizing that the total number of QTL have also been known to influence prediction accuracy comparisons between conventional BayesA and BayesB (Meuwissen and Goddard, 2010), we considered Scenario 6, which involved a total of 40 QTL, $M_{int} = 20$ environmentally robust QTL, and $M_{both} = 20$ environmentally sensitive QTL, 2/5 of that specified in Scenario 4 with everything else being the same. As anticipated, CD-BayesB finally started to emerge as the most accurate of the 4 RN models particularly at $d = 0$ and $d = 1.2$. Again, these results are in agreement with Wimmer et al. (2013) who determined that variable selection models (like BayesB or, in our case, CD-BayesB), perform best under genetic architectures with low complexities. Conversely, it was this scenario where the performance of BVN started to plummet, even being inferior to conventional BayesA/BayesB analyses at $d = 0$. Of course, we should then quickly note that QTL effects were simulated from heavy-tailed t -distributions, perhaps thereby further stacking the odds against BVN.

A particularly odd result was that the comparisons on accuracies did not necessarily match up with comparisons on accuracies of predicting their components,

i.e., intercept and slope BV. That is, CD-BayesB was among the best for inferring on intercept BV in Fig. 2a, whereas IW-BayesA was typically among the best for inferring on slope BV in Fig. 2b. Nevertheless, this does somewhat help explain why IW-BayesA was often the best for inferring on genomic BV at $d = -1.2$ and $d = 1.2$ and why CD-BayesB generally dominated at $d = 0$.

Our simulation study was based on arbitrary specifications of genetic architecture based on $(M_{both} + M_{int})$ QTL randomly located on a 1M chromosome. Based on arguments provided by Meuwissen and Goddard (2010), one might, albeit roughly, extrapolate these simulation results to the case of $n_{chr} \times (M_{both} + M_{int})$ QTL for an n_{chr} M genome based on n_{chr} chromosomes and a sample size of $n_{chr} \times n$ and the number of SNP markers being $n_{chr} \times m$. We further realize that other determinants, such as marker density, can also influence the comparisons among the 5 RN WGP models. Furthermore, if we had specified even greater $M_{both} + M_{int}$ QTL, the more complex genetic architecture might then better reflect the BVN assumptions ($\pi_g = 1$, $v_g \rightarrow \infty$, such that $\Sigma_j = \Sigma_g \forall j$), such that its relative performance would further improve.

Given our simulation results, it perhaps then was not too surprising that we did not observe any meaningful differences between the various models with an application to data from a pig resource population. First, the model applied was an RR rather than a RN model implying that there is greater phenotypic information provided on each individual by the repeated records in a RR context, thereby potentially muting any real differences between the various candidate models. Furthermore, the genetic architecture of the trait analyzed may have been far more complex and the level of determinedness far less than anything considered in the simulation study.

Conclusions

Five RR/RN models have been developed in this paper under the framework of WGP. Based on an RN simulation study and RR data analysis in pigs, RR/RN WGP models provide greater accuracies in genomic evaluations compared to more conventional WGP models. We believe that it is important to account for SNP-specific intercept and slope effects in RN or RR data situations where SNP genotypes are available. Nevertheless, differences in predictive performance between the various RR/RN WGP models were not overwhelming such that simpler specifications such as IW-BayesA, and perhaps even BVN, may be suitable for analyses that involve high degrees of genetic complexity or low levels of determinedness as previously suggested by Wimmer et al. (2013). Conversely, based on our simulation results, we anticipate that CD-BayesB might show greater promise

when marker density is large relative to the number of QTL (i.e., low degree of complexity).

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APPENDIX 1

Derivation of an Overall Genetic Correlation Between Intercept and Slope in RR/RN WGP Models

Given the RR/RN model

$$y_i = \mathbf{x}_i' \boldsymbol{\beta} + \sum_{j=1}^m z_{ij} (g_{1j} + d_i g_{2j}) + e_i; i = 1, 2, \dots, n \quad [\text{A1.1}]$$

the genetic variance at environmental covariate d_i for animal i with genotype z_{ij} at locus j can be defined as,

$$\text{var} \left[\sum_{j=1}^m z_{ij} (g_{1j} + d_i g_{2j}) \right] = \sum_{j=1}^m z_{ij}^2 (\sigma_{g_{1j}}^2 + d_i^2 \sigma_{g_{2j}}^2 + 2d_i \sigma_{g_{1j}g_{2j}}) = \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}}^2 + \sum_{j=1}^m z_{ij}^2 d_i^2 \sigma_{g_{2j}}^2 + \sum_{j=1}^m z_{ij}^2 2d_i \sigma_{g_{1j}g_{2j}} \quad [\text{A1.2}]$$

Thus, for any environmental covariate d , we can define the genetic variance as follows,

$$\text{var} \left[\sum_{j=1}^m z_{ij} (g_{1j} + d g_{2j}) \right] = \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}}^2 + d^2 \sum_{j=1}^m z_{ij}^2 \sigma_{g_{2j}}^2 + \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}g_{2j}} \quad [\text{A1.3}]$$

Using de los Campos et al. (2013), we can compute the overall genetic variance across all animals as follows:

$$V_g = n^{-1} \sum_{i=1}^n \left(\sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}}^2 + d^2 \sum_{j=1}^m z_{ij}^2 \sigma_{g_{2j}}^2 + 2d \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}g_{2j}} \right) = n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}}^2 + d^2 n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{2j}}^2 + 2d n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}g_{2j}} \quad [\text{A1.4}]$$

where $n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}}^2$ is the overall genetic variance for intercept across animals, $n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{2j}}^2$ is the overall genetic variance for slope across animals, and $n^{-1} \sum_{i=1}^n \sum_{j=1}^m z_{ij}^2 \sigma_{g_{1j}g_{2j}}$ is the overall genetic covariance between intercept