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Accuracy of additive models under epistatic genetic architectures

K. Razi[1*] and C. Gondro[1]

[1]*Michigan State University, East Lansing, USA;* [*]*Corresponding author: razikay1@msu.edu*

Introduction

Genomic prediction using genetic markers to predict breeding values has become a central tool in selection programs (VanRaden, 2008). Methods such as genomic best linear unbiased prediction (GBLUP) assume an additive infinitesimal genetic architecture and exploit linkage disequilibrium (LD) between markers and causal loci to capture genetic effects. While these approaches often achieve high prediction accuracy within a closely related population, prediction accuracies decay across generations (Habier et al., 2010) as the population becomes less related due to recombination, drift and LD changes (Goddard and Hayes, 2009). The extent of this decay depends on several factors, including trait heritability, population size, mating design, and most importantly, the underlying number and distribution of causal variants (Goddard and Hayes, 2009). Traits with a more discreet genetic architecture differ fundamentally from highly polygenic traits, where genetic variance is distributed across thousands of loci. In addition, non-additive genetic effects such as epistasis further complicate prediction, as standard additive kernels may fail to capture interaction-driven variance even when broad sense heritability is high (Carlborg and Haley, 2004). Despite extensive theoretical work, the relative contributions of causal signals versus marker-based LD to long-term prediction accuracy are still not fully quantified. It still remains unclear to what extent genomic prediction models learn true biological effects as opposed to population-specific LD patterns that deteriorate over time.

Mechanistic simulations allow explicit control of varying genetic architectures and generational structures which provide a useful platform to study genomic prediction models. In this study, we use large-scale forward simulations to evaluate the decay of genomic prediction accuracy across multiple generations under varying numbers of QTL, heritability levels, and additive versus epistatic genetic architectures. By contrasting prediction models based on all genome-wide markers with models using only true causal loci, we aim to clarify the role of LD-driven versus causal information in sustaining predictive performance across generations. This work provides insights into the limitations of standard genomic prediction models and highlights conditions under which long-term prediction remains reliable.

Materials & Methods

Genotypes from real cattle data were processed using PLINK2 (Chang et al., 2015): SNPs were filtered for MAF between 0.2 and 0.8, pruned for linkage disequilibrium (100 kb window, $r^2 < 0.4$), and thinned to a minimum physical distance of 8,000 bp. Final dataset: 110,219 SNPs and 60,000 individuals

QTL sets of 10, 100, 1,000 and 10,000 were randomly selected from the SNPs (subsets of the largest set). Incidence matrices were constructed for k-way epistasis (k = 2, 4, 6), where each interaction involved exactly k QTLs in non-overlapping groups. Simulations were performed with the *epinetr* package (Detterer et al., 2017) over 11 generations, using phenotypic variance of 50 and genomic selection based on EBV ranking (gBLUP). Truncation selection used the top 10% sires and 70% dams, with 10 dams per sire, sires used for up to 3 rounds, dams up to 4 rounds, and litter distribution c(0,1). The following scenarios were simulated by varying broad-sense heritability (H^2), narrow-sense heritability (h^2), and epistatic interaction order (k).

Simulation scenarios. We evaluated nine genetic architectures across four QTL densities (10, 100, 1,000, and 10,000 QTLs), resulting in 36 simulation conditions. Parameter combinations for each QTL density are summarized below.

Table 1. Simulation scenarios

Architecture type	H^2	h^2	k	Description
Control	0	0	0	No genetic effects
Additive	1	1	0	Additive, high heritability
Additive	0.5	0.5	0	Additive, moderate heritability
Epistatic	0.5	0	2	Epistasis, moderate H^2
Epistatic	0.5	0	4	Epistasis, moderate H^2
Epistatic	0.5	0	6	Epistasis, moderate H^2
Epistatic	1	0	2	Epistasis, high H^2
Epistatic	1	0	4	Epistasis, high H^2
Epistatic	1	0	6	Epistasis, high H^2

Four variants of genomic relationship matrices (G) were constructed and evaluated using GBLUP:

1- **Full marker G**: The standard genomic relationship matrix calculated using all available SNP markers across the genome.
2- **Full marker without causal QTLs**: The G matrix constructed using all markers excluding the simulated causal quantitative trait loci (QTLs), to assess prediction accuracy relying solely on linkage disequilibrium (LD) with QTLs.
3- **QTL-only G**: The G matrix built using only the simulated causal QTLs as markers, representing an idealized scenario where causal variants are known.
4- **Additive-by-additive (G × G) matrix**: An epistatic extension computed as the Hadamard product of the standard full marker G matrix with itself, to partially capture additive × additive interaction effects.

For each variant, genomic estimated breeding values (GEBVs) were predicted using a standard GBLUP model (Van Raden, 2008):

$$\mathbf{y} = \mathbf{1}\mu + \mathbf{Z}\mathbf{g} + \mathbf{e} \quad (1)$$

where $\mathbf{y}$ is the vector of phenotypes, μ is the overall mean, $\mathbf{g}$ is the vector of random genomic effects, $\mathbf{Z}$ is the incidence matrix, and $\mathbf{e}$ is the residual (Su et al., 2012). Prediction accuracies were calculated as the correlation between GEBVs and phenotypes in validation generations.

Results

Overall performance of GBLUP across genetic architectures. GBLUP performance was evaluated across 36 simulation scenarios spanning additive, epistatic, and control genetic architectures, varying QTL number, heritability components, and epistasis order. Prediction accuracy, and accuracy decay was quantified as the proportional loss from the first to the last generation. Additive scenarios consistently yielded high initial prediction accuracies with moderate decay, epistatic scenarios showed substantially reduced accuracy accompanied by rapid decay, and control scenarios confirmed the absence of any meaningful genetic signal.

Additive genetic architecture (k = 0; n = 8). Under purely additive architectures, GBLUP aligned well with the simulated genetic model. Using the full marker set, the mean initial accuracy was 0.895, with values approaching unity in high-heritability and low-QTL scenarios. Despite recombination and

drift, prediction accuracy showed moderate persistence across generations, with a mean decay of 38.5%. Removing QTLs from the marker panel resulted in only a minor reduction in initial accuracy (0.891), but substantially increased decay (58.3%). This indicates that GBLUP can capture family relationship and co-segregation in the short term (Habier at al., 2007), but this signal decays rapidly across generations due to recombination. When prediction relied exclusively on QTLs, initial accuracy remained high (mean 0.860) and decay was minimal (10.8%), particularly under complete heritability ($H^2 = h^2 = 1$), where accuracy remained stable across generations. In contrast, the additive-by-additive epistatic kernel (G×G) yielded considerably lower initial accuracy (0.533) and offered no improvement in additive scenarios.

Epistatic genetic architecture ($k > 0$; $n = 24$). In the presence of epistasis, GBLUP performance deteriorated markedly. Using all markers, the mean initial accuracy dropped to 0.368, accompanied by severe generational decay averaging 85.7%. Prediction accuracy declined systematically with increasing epistasis order, demonstrating limited robustness of additive models under non-additive genetic control. Excluding QTLs produced similar results (0.385 initial accuracy; 87.3% decay), indicating that marker-based LD alone was insufficient to capture epistatic signal over generations. Using only QTLs further reduced initial accuracy (0.291) and produced highly variable decay, including values exceeding 100%, reflecting instability and sign reversals in prediction. While standard GBLUP still captured some of the epistatic effects in the base population, the G×G kernel failed to improve performance (0.182) and its lower proportional decay (81.9%) is mainly a floor effect due to very low baseline accuracy.

Control scenarios ($H^2 = h^2 = 0$; $n = 4$). Control scenarios confirmed the absence of genetic signal, with low initial accuracies (0.069–0.133) across all G matrices that rapidly decayed to random expectation, validating the simulation framework.

Effects of QTL number and epistasis order. Across all architectures, QTL number influenced both initial accuracy and persistence. Scenarios with few QTLs (10) achieved higher initial accuracy but experienced rapid decay, whereas increasingly polygenic architectures showed more stable performance across generations. This trend was most pronounced under epistatic control, where higher epistasis orders led to monotonic reductions in accuracy and increased decay.

Discussion

GBLUP showed strong and persistent performance under additive genetic architectures, consistent with its modeling assumptions. In contrast, epistatic architectures exhibited substantially reduced prediction accuracy and accelerated decay across generations, even when the broad-sense heritability was high, indicating a failure of additive models to capture non-additive genetic effects. The additive-by-additive (G×G) kernel provided only limited improvement, suggesting that pairwise interactions alone are insufficient for complex epistasis. Polygenic architectures exhibited greater stability across generations, highlighting the buffering effect of many small-effect loci on genomic prediction. If a trait is largely regulated by epistatic effects, the additive models can still linearize a proportion of the true genetic variance with less complex levels of interaction. However, while GBLUP is extremely efficient for selection, it only provides limited insights into the underlying genetic architecture of a trait.

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