Estimation of prediction error variances via Monte Carlo sampling methods using different formulations of the prediction error variance

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Abstract
Calculation of the exact prediction error variance covariance matrix is often computationally too demanding, which limits its application in REML algorithms, the calculation of accuracies of estimated breeding values and the control of variance of response to selection. Alternatively Monte Carlo sampling can be used to calculate approximations of the prediction error variance, which converge to the true values if enough samples are used. However, in practical situations the number of samples, which are computationally feasible, is limited. The objective of this study was to compare the convergence rate of different formulations of the prediction error variance calculated using Monte Carlo sampling. Four of these formulations were published, four were corresponding alternative versions, and two were derived as part of this study. The different formulations had different convergence rates and these were shown to depend on the number of samples and on the level of prediction error variance. Four formulations were competitive and these made use of information on either the variance of the estimated breeding value and on the variance of the true breeding value minus the estimated breeding value or on the covariance between the true and estimated breeding values.

Introduction
In quantitative genetics the prediction error variance-covariance matrix is central to the calculation of accuracies of estimated breeding values (\( \hat{u} \)) [e.g. [1]], to REML algorithms for the estimation of variance components [2], to methods which restrict the variance of response to selection [3], and can be used to explore trends in Mendelian sampling deviations over time [4]. The mixed model equations (MME) for most national genetic evaluations range from 100,000 to 20,000,000 equations and inversion of systems of equations of this size is generally not possible because of their magnitude or because of loss of
numerical precision [5]. Methods that approximate the prediction error variances (PEV) and calculate the accuracy of provide biased estimates in some circumstances by ignoring certain information [e.g. [6]]. Variance components upon which genetic evaluations of large populations are based are generally estimated using reduced data sets. The use of reduced data sets may create bias in the estimates as REMEL only provides unbiased estimates of variance components when all the data on which selection has taken place is included in the analysis [7]. Variance of response to selection is generally not controlled in breeding programs although it might be a risk to them [3].

Approximations of the PEV without needing to invert the coefficient matrix or to delete data, can be obtained by comparing Monte Carlo samples of the data and successive solutions of the mixed model equations of this data.

However different formulations have been presented to approximate the PEV in this way [8-11]. Approximations of the PEV using these formulations converge to the exact PEV (PEVexact) as the number of Monte Carlo samples increases, but the number of samples is generally limited by computational requirements in practice [e.g. [12]]. Also, differences in the rates of convergence have been shown to depend on the level of PEVexact for a given genetic variance (σ^2_g) [10]. Consequently, when finding the optimal number of iterations required, both the different formulations, and the level of PEVexact need to be taken into account. Some of the formulations are weighted averages of other formulations, with the weighting depending on the sampling variances of these. Garcia-Cortes et al. [10] use asymptotic approximations of these sampling variances. Alternative weighting strategies could use empirically approximated sampling variances based on independent replicates of samples or using leave-one-out Jackknife procedures [13,14].

The objective of this study was to compare the convergence to PEVexact of ten different formulations of the PEV, using simulations based on data and pedigree from a commercial population containing animals with different levels of PEV and using different numbers of samples (n = 50, 100, ..., 950, 1000). Four of the formulations were previously published, four were alternative versions of these, and two were derived as part of this study.

**Methods**

**Monte Carlo sampling procedure for calculating PEV**

The Monte Carlo sampling procedure for calculating the sampled PEV has been described extensively elsewhere for single breed [8-10] and multiple breed scenarios [12]. Assuming a simple additive genetic animal model without genetic groups y = Xb + Zu + e, where the distribution of random variables is y ~ N(Xb, ZGZ’ + R), u ~ N(0, G), and e ~ N(0, R), the three steps involved in calculating the sampled PEV are as follows: 1. Simulate n samples of y and u using the pedigree and the distributions of the original data, modified to account for the fact that the expectation of Xb does not affect the distribution of random variables [15,16] thus the samples of y can be simulated using random normal deviates from N(0, ZGZ’ + R) instead of N(Xb, ZGZ’ + R). 2. Set up and solve the mixed model equations for the data set using the n simulated samples of y instead of the true y. This accounts for the fixed effects structure of the real data. 3. Calculate the sampled PEV for some formulation.

**Formulations of PEV**

Ten formulations of the sampled PEV are shown in Table 1. The first three formulations (PEVGC1, PEVGC2, and PEVGC3) were outlined by Garcia-Cortes et al. [10] and the fourth formulation (PEVFL) was outlined by Fouilloux and Laloë [8]. PEVAF1, PEVAF2, PEVAF3, and PEVAF4 are alternative versions of these formulations, which rescale the formulations from the Var (u) and to the σ^2_g in order to account for the effects of sampling on the Var(u). Two new formulations of the sampled PEV (PEVNF1, and PEVNF2) are also given in Table 1. The ten formulations differ from each other in the way in which they compare information relating to the Var(u), the Var( u’), the Var (u’), and the Cov(u, u’).

**Approximation of sampling variance of PEV**

Formulæ, based on Taylor series approximations, to predict the asymptotic sampling variances for each of the ten formulations of sampled PEV at different levels of PEVexact are given in Table 1. The sampling variance can also be approximated stochastically using a number (e.g. 100) of independent replicates of the n samples or by applying a leave-one-out Jackknife [13,14] to the n samples.

**Application to test data set**

**Data and model**

A data set containing 32,128 purebred Limousin animals with records for a trait (height) and a corresponding pedigree of 50,435 animals was extracted from the Irish Cattle Breeding Federation database. In the simulations the trait
Table 1: Previously published, alternative, and new formulations of the prediction error variance for a random effect $u$ with $\sigma_g^2$, the assumptions pertinent to each formulation, the information used in each formulation, and the asymptotic sampling variances of each formulation

| Formulation | Assumptions | Uses information on | Asymptotic sampling variance |
|-------------|-------------|---------------------|-------------------------------|
| $1 \text{PEVGC}_1 = \sigma_g^2 - \text{Var}(\hat{u})$ | $\text{Cov}(u, \hat{u}) = \text{Var}(\hat{u})$ | $\hat{u}$ | $2A \sigma_g^4 / n$ |
| $2 \text{PEVGC}_2 = \text{Var}(u - \hat{u})$ | $11 \text{Cov}(u, \hat{u}) \neq \text{Var}(\hat{u})$ | $u - \hat{u}$ | $2(1-r)^2 \sigma_g^2 / n$ |
| $3 \text{PEVGC}_3 = \left( \frac{\text{PEVGC}_1}{\text{Var(PEVGC}_1)} \right)^4 + \left( \frac{\text{PEVGC}_2}{\text{Var(PEVGC}_2)} \right)^4$ | $\text{Cov}(u - \hat{u}, \hat{u}) = 0$ | $\hat{u}, u - \hat{u}$ | $\left( \frac{24(1-r)^2}{(1-(r)^2)+r^4} \right) \sigma_g^4 / n$ |
| $4 \text{PEVFL} = \sigma_g^2 - \text{Cov}(u, \hat{u})$ | $\text{Cov}(u, \hat{u}) = \text{Var}(\hat{u})$ | $\hat{u}$ | $\sigma_g^2 / n$ |
| $5 \text{PEVAF}_1 = \sigma_g^2 - \left[ \text{Var}(\hat{u}) \right] \sigma_g^2$ | $\text{Cov}(u, \hat{u}) = \text{Var}(\hat{u})$ | $\hat{u}, u$ | $4\sigma_g^4 (1-r)^2 / n$ |
| $6 \text{PEVAF}_2 = \left[ \text{Var}(u - \hat{u}) \right] \sigma_g^2$ | $11 \text{Cov}(u, \hat{u}) \neq \text{Var}(\hat{u})$ | $u - \hat{u}, u$ | $4\sigma_g^4 (1-r)^2 / n$ |
| $7 \text{PEVAF}_3 = \left( \frac{\text{PEVAF}_1}{\text{Var(PEVAF}_1)} \right)^4 + \left( \frac{\text{PEVAF}_2}{\text{Var(PEVAF}_2)} \right)^4$ | $\text{Cov}(u - \hat{u}, \hat{u}) = 0$ | $\hat{u}, u - \hat{u}, u$ | $4\sigma_g^4 (1-r)^2 / n$ |
| $8 \text{PEVAF}_4 = \sigma_g^2 - \left[ \text{Cov}(u, \hat{u}) \right] \sigma_g^2$ | $\text{Cov}(u, \hat{u}) = \text{Var}(\hat{u})$ | $\hat{u}, u$ | $\sigma_g^2 / n$ |
| $9 \text{PEVAF}_5 = \left[ 1 - \text{Cov}(u, \hat{u}) \right] / \left( \text{Var}(u) \times \text{Var}(\hat{u}) \right)$ | $\text{Var}(u) \neq \sigma_g^2$ | $\sigma_g^2$ | $4\sigma_g^4 (1-r)^2 / n$ |
| $10 \text{PEVAF}_6 = \left[ \text{Var}(u - \hat{u}) / \text{Var}(\hat{u}) + \text{Var}(u - \hat{u}) \right] \sigma_g^2$ | $\text{Cov}(u - \hat{u}, \hat{u}) = 0$ | $\hat{u} \text{ and } u - \hat{u}$ | $4\sigma_g^4 (1-r)^2 / n$ |

1Garcia-Cortes et al. (1995) formulation
2Garcia-Cortes et al. (1995) formulation 2
3Garcia-Cortes et al. (1995) formulation 3
4Fouilloux and Laloe (2001) formulation
5Corrects PEVGC1 for $\text{Var}(u) \neq \sigma_g^2$ and corresponds to Lidauer et al. (2007)
6Corrects PEVGC2 for $\text{Var}(u) \neq \sigma_g^2$
7Corrects PEVGC3 for $\text{Var}(u) \neq \sigma_g^2$
8Corrects PEVFL for $\text{Var}(u) \neq \sigma_g^2$
9Based on the classical formulation of the accuracy of an EBV
10Implicitly weights information on $\text{Var}(\hat{u})$ and $\text{Var}(u, \hat{u})$ and corrects for $\text{Var}(u) \neq \sigma_g^2$
11No assumption made about the relationship between $\text{Var}(\hat{u})$ and $\text{Cov}(u, \hat{u})$
was assumed to have a $\sigma_g^2$ of 1.0 and residual variance $\sigma_r^2$ of 3.0. Fixed effects were contemporary group, technician who scored the animal, parity of dam, age of animal at scoring and sex.

**Calculation of exact PEV**
The PEV$\text{exact}$ were calculated for the extracted data set by setting up and solving the MME, with fixed effects of contemporary group, technician who scored the animal, parity of dam, and a second order polynomial of age of animal at scoring nested within sex, and random animal and residual effects, using the BLUP option in ASReml [17] which fully inverts the left hand side of the MME.

**Sampled PEV**
Following the Monte Carlo sampling procedure described above, 100,000 samples of the extracted data set were simulated assuming a $\sigma_g^2$ of 1.0 and $\sigma_r^2$ of 3.0. For each of the simulated data sets MME, using the same design matrix (X) as used when estimating the PEV$\text{exact}$ were set up and solved using MiX99 [18]. The sampled PEV of the $\hat{u}$ for each animal in the pedigree was approximated using the formulations of the sampled PEV described in Table 1 using $n$ samples ($n = 50, 100, ..., 950, 1000$).

Stochastic approximations of the sampling variance of the sampled PEV were calculated using 100 independent replicates of the $n$ samples, and using the leave-one-out Jackknife on $n$ samples, for the different formulations, with the exception of PEV$_{GC3}$ and PEV$_{AF3}$. To calculate the sampling variance for PEV$_{GC3}$ and PEV$_{AF3}$ using $n$ independent replicates would have required more than 100,000 samples (due to the need to generate sampling variances of component formulations) generated for this study so therefore these were not considered. Asymptotic sampling variances for all ten formulations were calculated using the formulae in Table 1.

**Alternative weighting strategies**
Of the formulations presented in Table 1, PEV$_{GC3}$ and PEV$_{AF3}$ are weighted averages of PEV$_{GC1}$ and PEV$_{GC2}$ and of PEV$_{AF1}$ and PEV$_{AF2}$ respectively with the weighting dependent on the sampling variances of the component formulations. Garcia-Cortes et al. [10] suggest weighting by asymptotic approximations of the sampling variances. The sampling variances could also be approximated empirically using independent replicates of $n$ samples or by leave-one-out Jackknife procedures [13,14]. These alternative weighting strategies were compared by calculating sampling variances using 100 independent replicates of the $n$ samples, using the $n$ samples and a leave-one-out Jackknife procedure [14], and using the asymptotic sampling variances outlined in Table 1 as part of an iterative procedure, which involved two iterations. In the first iterations the asymptotic sampling variances were calculated using the PEV$_{GC1}$ and PEV$_{GC2}$ of the component formulations, in the second they used the PEV$_{GC3}$ approximated in the first iteration.

**Calculation of required variances and covariances**
It was not possible to store each of the 100,000 simulated values for each of the 50,435 animals in the main memory of the computer simultaneously meaning that textbook formulae to calculate the different variances and covariances required for the different formulations was not possible. Textbook updating algorithms to calculate the variance can be numerically unreliable [19]. Instead the required variances were calculated using a one pass updating algorithm based on Chan et al. [19] which updates the estimated sum of squares with a new record as it reads through the data and takes the form:

$$S_n = S_{n-1} + \left( n \right) \left( \frac{\left( T_{n-1} \right) - x_i \left( T_{n-1} \right) - y_i \left( T_{n-1} \right) - x_i \right)^2 }{n \left( T_{n-1} \right) - x_i \left( T_{n-1} \right) - y_i \left( T_{n-1} \right) - x_i} \right),$$

where $n$ are the number samples at any stage in the updating procedure and $T$ and $S$ are the sum and sum of squares of the data points 1 through $n$. It was modified to calculate the covariances between X and Y by changing $\left( \frac{T_{n-1} \left( T_{n-1} \right) - x_i \left( T_{n-1} \right) - y_i \left( T_{n-1} \right) - x_i} \right)$ to

$$\left( \frac{T_{n-1} \left( T_{n-1} \right) - x_i \left( T_{n-1} \right) - y_i \left( T_{n-1} \right) - x_i \times \left( T_{n-1} \right) - y_i \right).$$

Both of these algorithms were tested using one replication of 100,000 samples and found to be stable.

**Results**
As the $\sigma_g^2$ was taken to be 1.0, the PEV ranged between 0.00 and 1.0. For the purpose of categorizing the results PEV with values between 0.00 and 0.33 were regarded as low, values between 0.34 and 0.66 were regarded as medium, and values between 0.67 and 1.00 were regarded as high.

Henderson [20] showed that it is much easier to form $A^{-1}$ than $A$, where $A$ is the numerator relationship matrix among animals. This follows from the fact that, if the individuals are listed with ancestors above descendants, $A$ can be written as $TMT'$ where $M$ is a diagonal matrix and $T$ is a lower triangular matrix with non-zero diagonal ele-
ments and $i, j$ th elements that are non-zero if the $j$ th individual is an ancestor of the $i$ th [21]. The matrix $T$ has a simple inverse with both the diagonal elements and $i, j$ th elements being non-zero if the $j$ th individual is a parent of the $i$ th individual. Hence $A$ has a simple inverse. It is interesting to note that an animal effect can be written as an accumulation of independent terms from its ancestors

$$u_i = \frac{u_{si} + u_{di}}{2} + m_i,$$

where $u_{si}$ and $u_{di}$ are the additive genetic effects of the sire and dam of animal $i$ and $m_i$ is the Mendelian sampling effect with variance

$$A_{mi} = \frac{(1-F_i)}{2} \sigma_s^2,$$

where $F_i$ is the average inbreeding of the parents of animal $i$. Hence there is a simple recursive procedure for generation of the additive effects $u_i$ by generating independent Mendelian sampling terms $m_i$ with diagonal variance matrix $A_{mi}$.

**General trends of sampled PEV**

While all different formulations of the sampled PEV converged to the PEV\textsubscript{exact} and the sampling variance of the PEV reduced as the number of samples ($n$) increased, convergence rates differed between the formulations. For example, PEV\textsubscript{GC2} converged at a slower rate than all other formulations when the convergence rate was measured by the correlation between PEV\textsubscript{exact} and sampled PEV (Fig. 1). PEV\textsubscript{GC1}, PEV\textsubscript{AF3}, PEV\textsubscript{AF4}, and PEV\textsubscript{NF2}, all converged at a very similar rates and had the best convergence across all formulations.

As well as depending on the numbers of samples, the convergence rate also depended on the level of the PEV\textsubscript{exact}. The sampled PEV calculated using different formulations had different sampling variances and within each formulation the sampling variances differed depending on the level of the PEV\textsubscript{exact} (Fig. 2). Of the previously published formulations PEV\textsubscript{GC1} and PEV\textsubscript{FL} had low sampling variance at high PEV\textsubscript{exact}, with PEV\textsubscript{GC1} being better than PEV\textsubscript{FL}. PEV\textsubscript{GC2} had low sampling variance at low PEV\textsubscript{exact}. Accounting for the effects of sampling on the Var($u$) reduced the sampling variance in regions where the previously published formulations had high sampling variances but had little (or even slightly negative) effect where these formulations had low sampling variances. PEV\textsubscript{AF4}, which is the alternative version of PEV\textsubscript{FL} gave major improvements in terms of sampling variance low and intermediate PEV\textsubscript{exact}. Its performance was almost identical to PEV\textsubscript{NF2}, PEV\textsubscript{AF3}, and PEV\textsubscript{GC3}, which had low sam-

**Figure 1**

Correlations between exact prediction error variance and different formulations of sampled prediction error variance\textsuperscript{1} using $n$ samples ($n = 50, 100, \ldots, 950, 1000$), for 18,855 non-inbred animals. \textsuperscript{1}PEV\textsubscript{NF2}, PEV\textsubscript{AF3}, PEV\textsubscript{AF4} are not shown as they have trends, which match PEV\textsubscript{GC3}.
Sampling variance at both high and low PEV. No formulation had relatively low sampling variance for intermediate PEV.

**Comparison of formulations**

Different formulations were compared in greater detail using \( n = 300 \) samples (Table 2), which is a practical number of samples. PEV\(_{GC1}\), PEV\(_{AF3}\), PEV\(_{AF4}\), and PEV\(_{NF2}\) were the best formulations across all of the ten formulations. The slopes and \( R^2 \) of their regressions were always among the best where PEV\(_{exact}\) was low, intermediate, or high (Table 2). These formulations gave good approximations at both high and low PEV\(_{exact}\), their performance was less good at intermediate PEV, measured by each of the summary statistics (Table 2).

PEV\(_{GC1}\) and PEV\(_{FL}\) gave good approximations for high PEV\(_{exact}\) and poor approximations for low PEV\(_{exact}\). PEV\(_{GC2}\) gave good approximations for low PEV\(_{exact}\) and poor approximations for high PEV\(_{exact}\). Improving the published formulations by correcting for the effects of sampling resulted in better approximations in areas where the published formulations were weak. Slight (dis)improvements were observed where the previously published formulations were strong. Of the new formulations PEV\(_{NF1}\) gave poor approximations and PEV\(_{NF2}\) gave good approximations.

Using the three alternative weighting strategies to combine the component formulations for PEV\(_{GC3}\) and PEV\(_{AF3}\) gave almost identical results (Table 3).

**Required number of samples**

The formulations PEV\(_{GC3}\), PEV\(_{AF3}\), PEV\(_{AF4}\), and PEV\(_{NF2}\) gave similar approximations and had the lowest sampling variance. Even when a few samples (\( n = 50 \)) were used,
low and high PEV were well approximated and intermediate PEV exact were poorly approximated. Correlations between PEVNF2 and PEVexact were 0.88 for low, 0.96 for high PEV exact and 0.51 for intermediate PEV exact. To increase the correlation for intermediate PEVexact to at least 0.90 at least 550 samples was needed. At this number of samples the correlations for low and high PEV exact were ≥ 0.99. To obtain a satisfactory level of convergence 300 samples were sufficient.

**Discussion**

**Differences between formulations**

Ten different formulations of the PEV approximated using sampling were compared and these were each shown to converge to the PEV exact at different rates. Within each of these formulations differences in convergence were observed at different levels of PEV exact. PEVGC1 and its corresponding alternative formulation PEV AF1 make use of information on the \( \text{Var}(\hat{u}) \). PEV GC2 and its corresponding alternative formulation PEV AF2 make use of information on the \( \text{Var}(\hat{u} - \hat{\mu}) \). The sampling variance of the \( \text{Var}(\hat{u}) \) is lower at high PEV exact than it is at low PEV exact (Fig. 3), therefore the formulations using information on the Var(\( \hat{u} \)) are more suited to approximating high PEV exact than to low PEV exact. The opposite is the case for formulations which use information on the \( \text{Var}(\hat{u} - \hat{\mu}) \), they perform better at low PEV exact. Formulations PEV GC3, PEV AF3, and PEV NF2 use information on both the \( \text{Var}(\hat{u}) \) and the \( \text{Var}(\hat{u} - \hat{\mu}) \) and result in curves for their sampling variance which are symmetric about the mean PEV exact. They either explicitly or implicitly weight this information by the inverse of its sampling variance. PEV FL and PEV AF4 make use of information on the Cov(\( u, \hat{\mu} \)).

With infinite samples the Var(\( u \)) is equal to the \( \sigma_g^2 \), but due to sampling error resulting from using a limited number of samples this not likely to be true in practice. Therefore each of the alternative formulations makes use of information on the Var(\( u \)) in addition to making use of information on either/or/both of the Var(\( \hat{u} \)) and the Var(\( u - \hat{\mu} \)) or the Cov(\( u, \hat{\mu} \)). The Var(\( \hat{u} \)) = Cov(\( u, \hat{\mu} \)) when the Cov((\( u - \hat{\mu} \)), \( \hat{u} \)) = 0. The Var(\( \hat{u} \)) ≠ Cov(\( u, \hat{\mu} \)) when the Cov((\( u - \hat{\mu} \)), \( \hat{u} \)) ≠ 0.

**Competitive formulations**

Of the ten different approaches four competitive formulations, PEV GC3, PEV AF3, PEV AF4, and PEV NF2, were identi-
fied. These gave similar approximations. Of the four, two, $\text{PEV}_{CC3}$ and $\text{PEV}_{AF3}$, were weighted averages of component formulations. The weighting was based on the sampling variances of their component formulations. These sampling variances can be calculated using a number of independent replicates, using Jackknife procedures, or asymptotically. Each of these approaches gave almost identical results but the Jackknife and asymptotic

Conclusion

PEV approximations using Monte Carlo estimation were affected by the formulation used to calculate the PEV. The difference between the formulations was small when the number of samples increased, but differed depending on the level of the exact PEV and the number of samples. Rescaling from the scale of $\text{Var}(u)$ to the scale of $\sigma_g^2$ improved the approximation of the PEV and four of the 10 formulations gave the best approximations of $\text{PEV}_{exact}$ thereby improving the efficiency of the Monte Carlo sampling procedure for calculating the PEV. The fewer sam-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/figure3.png}
\caption{\label{fig:3} X-Y plot of the exact prediction error variance and the $\text{Var}(\hat{u})$ and $\text{Var}(u - \hat{u})$.}
\end{figure}
ples that are required the less the computational time will be.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
RT derived most of the mathematical equations. JH derived the remaining equations, carried out the simulations and wrote the first draft of the paper. RV supervised the research and mentored JH. MC and HM took part in useful discussions and advised on the simulations. All authors read and approved the final manuscript.

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