

## Using genomic data to estimate genetic correlations between countries with different levels of connectedness

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### Abstract

Genetic correlations ( $r_g$ ) between countries are required for international evaluations. The estimation of those  $r_g$  is challenging or even unfeasible using only pedigree and phenotypes when poor connectedness between countries is structural in the data due to a limited number of bulls having recorded (grand-)offspring across countries. Genomic information could be used to estimate  $r_g$  between countries by capturing connectedness that is not traced by pedigree recordings. Indeed, populations that appear as (completely) disconnected through pedigree can, theoretically, be connected through genomic data. Thus, our study aimed to investigate if estimates of  $r_g$  between countries based on genomic information are more accurate compared to estimates based on pedigree data, considering different levels of genetic connectedness. A maternally affected trait mimicking weaning weight was simulated for two beef cattle populations of the same breed. Different levels of connectedness between populations were simulated by exchanging different proportions of top sires in the last five generations: 0% (completely disconnected), 2.5% (lowly connected), 5% (medium), and 20% (high). Genomic data in the form of individual SNP genotypes at medium density were stored in the last three generations and used only for the estimation process.  $r_g$  between populations were estimated using three different relationship matrices: i) a pedigree-based relationship matrix (**A**) including all phenotyped animals; ii) a genomic relationship matrix (**G**) including phenotyped and genotyped animals only from the last three generations; and iii) a combined pedigree and genomic relationship matrix (**H**) including all phenotyped and genotyped animals. With disconnected and lowly connected populations, estimates of direct and maternal  $r_g$  were, on average, close to the simulated values when using genomic data through **G** or **H**. With lowly connected populations, estimates of direct  $r_g$  were close to the simulated values when using **A**, but estimates of maternal  $r_g$  showed large variation. With more connected populations, estimates obtained with **A**, **G**, and **H** matrices were overall similar. For all scenarios, when using genomic data in the estimation process, estimates of  $r_g$  had smaller standard errors. Our results show that genomic data can help the estimation of  $r_g$  between countries and especially reduce their standard errors for populations that appear as completely disconnected or lowly connected through pedigree information, such as in beef and (small) dairy cattle populations.

**Key words:** genetic correlations between countries, international evaluations, genomic data, GREML, maternal traits, cattle.

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### Introduction

International genetic evaluations allow breeders to appropriately compare the genetic merits of domestic and foreign animals. Animals' estimated breeding values (EBVs) obtained from different national evaluations are

not directly comparable due to differences in scales and genetic bases, trait and model definitions, and environmental differences between countries (Philipsson, 1987; Zwald et al., 2003; Jakobsen et al., 2009; Nilforooshan and Jorjani, 2022). International evaluations, such as those performed by Interbeef (2006) for

beef cattle and Interbull (1983) for dairy cattle, combine data between countries into a single evaluation that takes into account such differences and computes animals' international EBVs. Through these international EBVs, foreign animals (mainly sires) can be compared with domestic ones, helping breeders to make their selection decisions. To account for differences between countries, international evaluations use multi-trait models that treat the same trait recorded in different countries as different correlated traits (Schaeffer, 1994; Phocas et al., 2005). A genetic correlation ( $r_g$ ) between countries below unity accounts for differences in trait and model definitions, scale and genetic bases, and for genotype-by-environment interactions (Falconer and Mackay, 1996; Mark, 2004; Nilforooshan and Jorjani, 2022). Moreover, the  $r_g$  between countries effectively models how much the information from one country contributes to the animals' international EBV in another country (Weigel et al., 2001). Thus,  $r_g$  between countries are crucial for international evaluations and directly impact the international EBVs.

Genetic connections are needed to estimate  $r_g$  between countries used in international evaluations. These genetic connections are usually provided by sires having recorded offspring in two or more countries, also called "common bulls" (CB). Moreover, for maternally affected traits, which are common in beef cattle, genetic connections established through common maternal grand-sires (CMGS) having recorded (grand-)offspring in two or more countries are needed to estimate maternal  $r_g$  between countries (Jorjani et al., 2005; Pabiou et al., 2014; Bonifazi et al., 2020). However, in beef cattle and small dairy cattle populations, there is often a low level of genetic connectedness, mostly due to the low usage of artificial insemination in the former (Berry et al., 2016) or the low past exchange of bulls' genetic material between countries in the latter (e.g., Jorjani, 2000; Mark et al., 2005a). The low genetic connectedness in beef and (small) dairy

cattle populations makes the estimation of  $r_g$  between countries challenging with current pedigree-based methods. Such challenges result in long computational times, uncertainty around the estimated  $r_g$  (i.e., large standard errors), and even in inestimable  $r_g$  in the extreme case of two completely disconnected populations (Jorjani et al., 2005; Mark et al., 2005a; Venot et al., 2009; Pabiou et al., 2014).

Individual genomic information in the form of single-nucleotide-polymorphisms (SNP) markers is increasingly becoming available at the national level for beef and (small) dairy cattle breeds (e.g., Van Eenennaam et al., 2014; Lourenco et al., 2015; Berry et al., 2016; Venot et al., 2016; Johnston et al., 2018; Bonifazi et al., 2022a; Adekale et al., 2023; Council on Dairy Cattle Breeding, 2023). In beef cattle, Bonifazi et al. (2022a) showed the feasibility and advantages of pooling national phenotypes and genotypes into an international single-step evaluation. In such settings, genomic data could also be used to estimate  $r_g$  between countries and possibly aid the estimation process, especially for lowly connected populations. In theory, populations that may appear as completely disconnected according to the pedigree can be connected through genomic information (Wientjes et al., 2015; Wientjes et al., 2018). Therefore, our study aimed to investigate if genomic data help to estimate  $r_g$  between countries more accurately than pedigree data, considering different levels of genetic connectedness between populations.

## Materials and Methods

Two beef cattle populations (POP1 and POP2) originating from the same breed were simulated, mimicking data from two different countries (Figure 1). Each population had data on a maternally affected trait simulating weaning weight as a representative trait in beef cattle international evaluations. Genetic parameters were simulated following those observed by Bonifazi et al. (2020) in real data. The trait heritability was 0.30 and 0.15 for

direct and maternal genetic effects, respectively, and the within-population direct-maternal  $r_g$  was  $-0.2$ . The  $r_g$  between populations was  $0.8$  and  $0.7$  for direct and maternal genetic effects, respectively, and the between-population direct-maternal  $r_g$  was  $0$ . About 2,000 QTLs were simulated to be randomly distributed across 30 chromosomes of 1 Morgan length each, and marker effects were sampled from a Gaussian distribution. Each population was independently selected for 20 generations (G; Figure 1). Selection was first at random (from G0 to G9), followed by selection on the total EBV, defined as the sum of direct and maternal EBVs with equal weights. Pedigree and phenotypic information were assumed to be recorded from G7 and G10, respectively. Genomic information in the form of individual genotypes at medium density ( $\sim 50,000$  SNPs) were assumed to be recorded for animals from G18 to G20 but not used for selection, similar to what has been observed in real data in Bonifazi et al. (2022a).

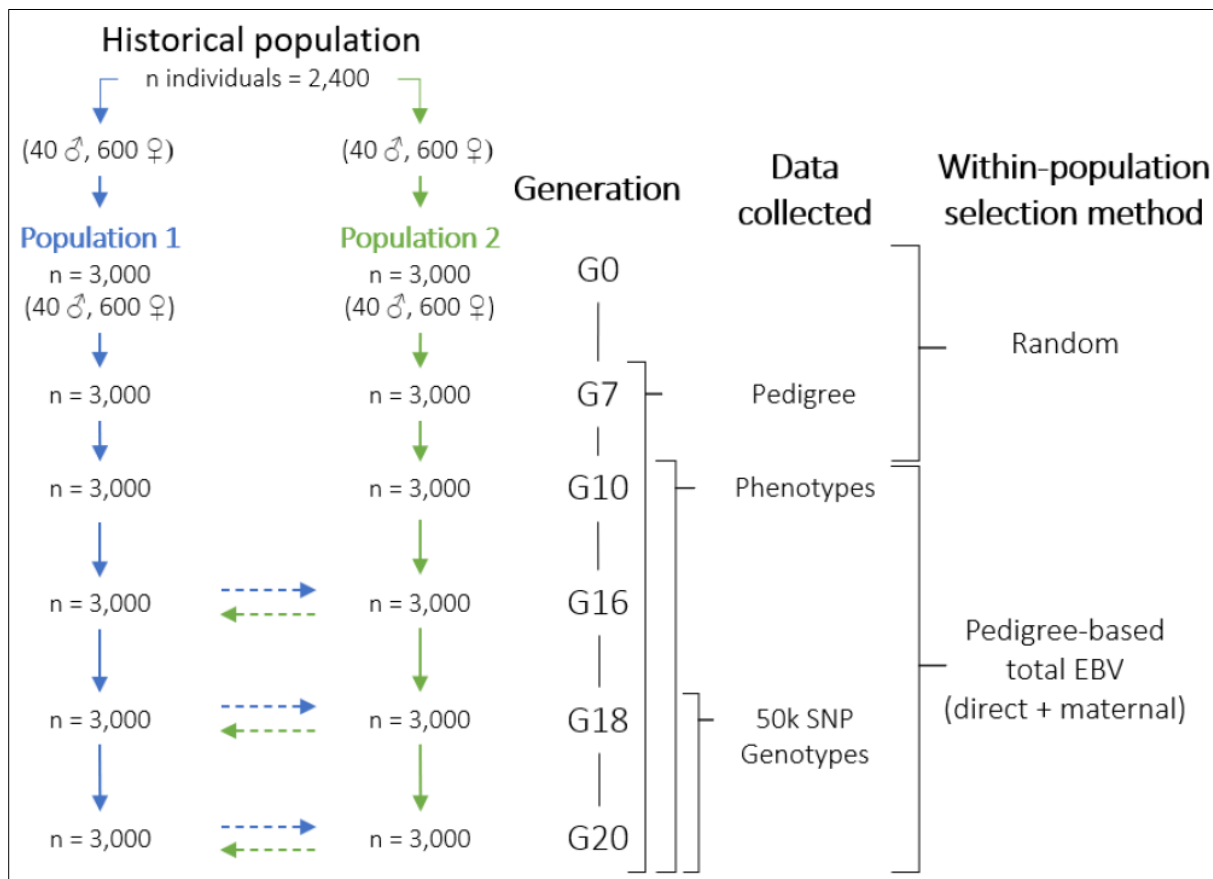
To simulate different levels of connectedness between the two populations, top sires from each population were exchanged throughout the last five generations (G16 to G20), called hereafter common bulls (CB). Four scenarios were simulated based on the exchanged proportions of top sires being: 0% (scenario 'disconnected'), 2.5% ('low'), 5% ('medium'), and 20% ('high'), corresponding to exchanging 0, 1, 2, and 8 sires, respectively, out of the 40 selected in each population and generation (Table 1). Each scenario was replicated 10 times. Following observations from Bonifazi et al. (2020), preferential treatment was simulated such that daughters of CB were used as dams in the next generation, ensuring the presence of common maternal grand-sires (CMGS) and, therefore, genetic connections to estimate maternal  $r_g$  between populations. The names of the scenarios are based on the level of genetic similarity (GS) coefficient for CB (Rekaya et al., 1999; Rekaya et al., 2003; Bonifazi et al., 2020) and follow the definition used in Bonifazi et al. (2020): low (GS < 0.05), medium (GS between 0.05 and 0.10) and high (GS > 0.10). The GS coefficients for CB and CMGS in each scenario are in Table 1.

$r_g$  between populations were estimated using a bi-variate model in which each population's trait is modelled as a different correlated trait with uncorrelated residuals. In each of the four simulated scenarios,  $r_g$  between populations were estimated using three different sources of information and relationship matrices:

- **A**: using phenotypes from G10 to G20, with a pedigree relationship matrix.
- **H**: using phenotypes from G10 to G20 and genotypes from G18 to G20, with a combined pedigree and genomic relationship matrix following Legarra et al. (2009).
- **G**: using phenotypes and genotypes from G18 to G20, with a genomic relationship matrix following VanRaden (2008) method 1.

The relationship matrices were built considering all 14 generations of pedigree information available (G7 to G20). Due to the presence of maternal genetic effects, one extra generation of pedigree information (i.e., G9 for **A** and **H**, and G17 for **G**, respectively) was included in the relationship matrix used for the estimation of  $r_g$  between populations to link the maternal genetic effect of the dam with the phenotype of the offspring in the first generation (i.e., G10 for **A** and **H**, and G18 for **G**, respectively). Therefore, the **G** matrix was effectively built as an **H** relationship matrix (Legarra et al., 2009).

The simulation was performed using the R-package MoBPS (Pook et al., 2020). The relationship matrices were built using `calc_grm` (Calus and Vandenplas, 2016). `mtg2` (Lee and van der Werf, 2016) was used to estimate EBV and  $r_g$  between populations, employing a CORE GREML approach (Zhou et al., 2020) to account for maternal effects and using a convergence criterion of  $1.0 \cdot 10^{-4}$ . Starting values were provided for within-population (co)variances, while between-population (co)variances starting values were set to 0, mimicking the procedure used in international evaluations (Bonifazi et al., 2021).



**Figure 1.** Schematic overview of the two simulated populations (POP1 and POP2), data collected, and selection method. n: number of individuals, G: generation, ♂: sires, ♀: dams. Horizontal arrows indicate the exchange of top sires between populations.

**Table 1.** Simulated scenarios and connectedness levels between populations <sup>1,2</sup>.

Scenario	n. of CB	n. off. from CB	GS <sub>CB</sub> <sup>3</sup>	Average n. CMGS	Average n. grand-off. from CMGS	Average GS <sub>CMGS</sub> <sup>3</sup>
Disconnected	0	0	0	0	0	0
Low	10	1,500	0.02	8	2,322	0.04
Medium	20	3,000	0.05	16	4,544	0.07
High	80	12,000	0.18	63	15,364	0.23

<sup>1</sup> Connectedness is computed from G10 to G20; results are averages of 10 replicates.

<sup>2</sup> n: number, CB: common bulls, GS: genetic similarity, CMGS: common maternal grand-sires.

<sup>3</sup> GS for CB (and CMGS) between two populations is defined as the proportion of recorded offspring (grand-offspring) born from CB (CMGS) over the total number of recorded offspring (grand-offspring) in the two populations.

## Results & Discussion

Figure 2 shows the estimated  $r_g$  between populations using different relationship matrices. As expected, in the disconnected scenario, using conventional sources of information (i.e., pedigree and phenotypes) through the **A** matrix did not allow to estimate  $r_g$ : estimates did not move from the provided starting values. However, using genomic data through **G** or **H** matrices resulted in estimated direct and maternal  $r_g$  close to the simulated underlying true values. With lowly connected populations, using the **A** matrix resulted in estimated direct  $r_g$  close to the simulated values, while there was a large variation for the estimated maternal  $r_g$  (Figure 2). For medium and highly connected populations, there were no large benefits of using genomic data compared to using conventional sources of information: overall, estimated  $r_g$  using **A**, **G**, and **H** were similar for medium and high scenarios.

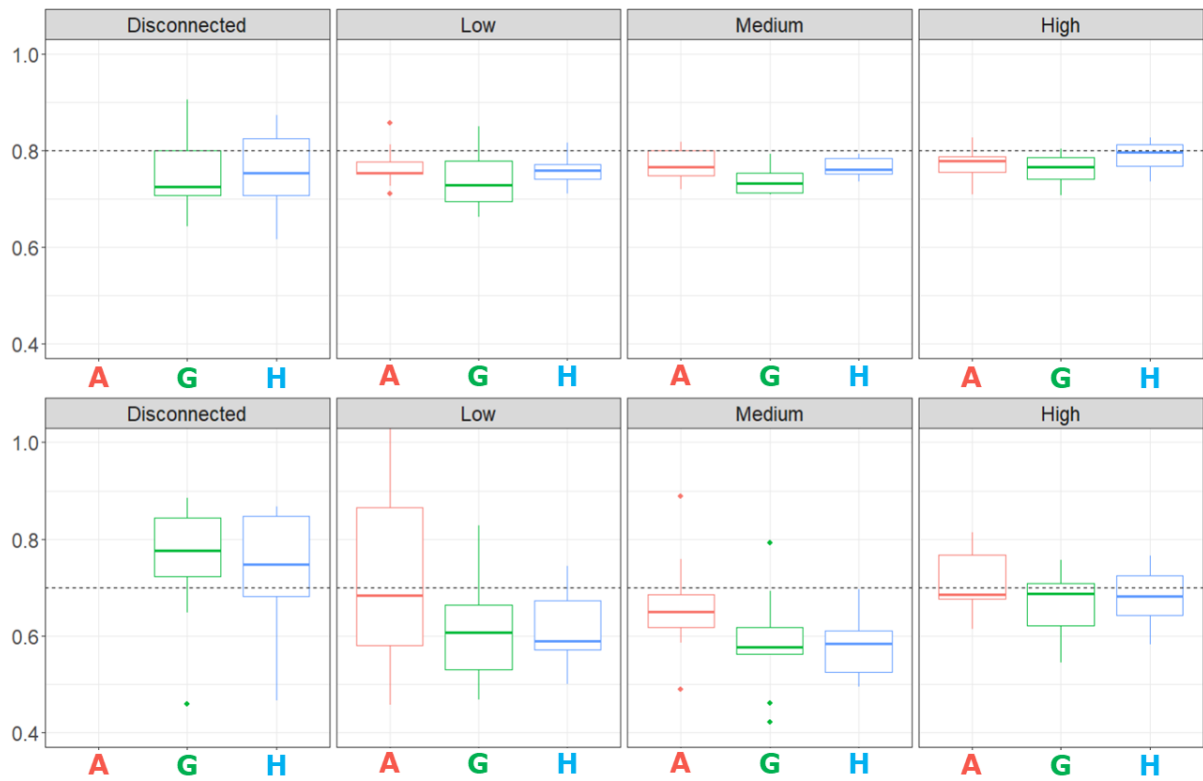
With increased connectedness between populations, the SE of direct and maternal  $r_g$  were smaller, regardless of the relationship matrix used (Figure 3). Furthermore, larger SE were observed for maternal  $r_g$  than for direct  $r_g$ . These results follow the findings of previous studies using real data where low levels of connectedness between populations were associated with large SE of the estimated  $r_g$  (e.g., Venot et al., 2009; Bonifazi et al., 2020). In all scenarios, the SE for direct and maternal  $r_g$  were smaller and showed less variation across replicates when using genomic information through **G** or **H** compared to **A**. Overall, using the **H** matrix resulted in the smallest SE of estimated  $r_g$ , while using the **G** matrix resulted in SE between those obtained with **A** and **H**. Thus, estimates of  $r_g$  between populations became more accurate, i.e., had smaller SE, when genomic information was included in the estimation process.

Computational requirements can partly be explained by mtg2 using dense relationship matrices for the estimation process instead of

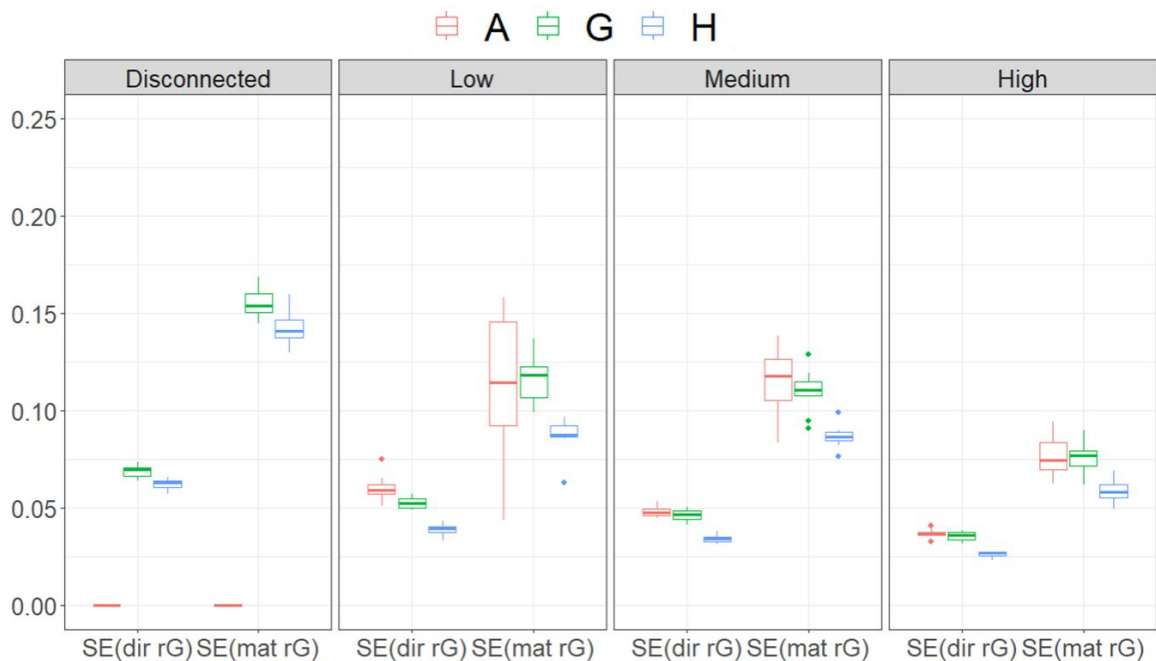
their inverses. As such, the estimation using **A** and **H** matrices showed similar computational resources (Table 2). The estimation using the **G** matrix required 12.5% of the memory of **A** and **H** matrices but required 2.43 times more computational time. Such computational requirements are likely due to the **G** matrix including only the last 4 generations of animals with 3 generations of phenotypes and genotypes, which, although resulted in a smaller matrix size, also led to an increased time to convergence (Table 2).

Overall, the more accurate estimation of  $r_g$  between populations with increasing numbers of CB and CMGS, agrees with Mark et al. (2005a). This relationship highlights the importance of establishing genetic links across countries by exchanging frozen semen to accurately estimate  $r_g$  between populations, especially when only conventional data is available. However, creating such genetic links is time-consuming since sires need recorded offspring in both populations.

The results of this study indicate that genomic data can be helpful to estimate  $r_g$  more accurately for disconnected and lowly connected populations and to reduce the associated SE compared to only using pedigree and phenotypic data. This was especially the case for maternal  $r_g$  between populations, which are reportedly challenging to estimate with low connectedness levels (Pabiou et al., 2014; Bonifazi et al., 2020; Bonifazi et al., 2021). In international evaluations, GS is usually reported to estimate connectedness between countries. The GS levels of the simulated scenarios are close to the values reported in beef and dairy cattle international evaluations. In particular, low to medium levels of connectedness are common in beef cattle. In Limousin, GS between countries was equal to 0.04 in Phocas et al. (2005) and ranged between 0.02 and 0.15 in Bonifazi et al. (2023; 2022b; 2020). Venot et al. (2009) reported values of GS between countries as low as 0.01 for both Limousin and Charolais. Therefore, using genomic data could



**Figure 2.** Boxplots of direct (top row) and maternal (bottom row) estimated  $r_g$  between populations across four connectedness scenarios (panels). **A**, **G**, and **H** indicate the different sources of information and relationship matrices used in the estimation process. Horizontal dotted lines indicate the simulated values of 0.8 for direct  $r_g$  and 0.7 for maternal  $r_g$ . Boxplots report estimated values of 10 replicates. One estimated maternal  $r_g$  in scenario “low” using **A** was out of parameter space ( $r_g > 1$ ).



**Figure 3.** Boxplots of direct (left-side) and maternal (right-side) standard errors (SE) of estimated  $r_g$  between populations across four connectedness scenarios (panels). **A**, **G**, and **H** indicate the different sources of information and relationship matrices used in the estimation process.

help the estimation of  $r_g$  between beef cattle populations with a low exchange of bulls and low levels of GS and could reduce the uncertainty of the estimated  $r_g$ , i.e., the associated SE (Figure 2 and Figure 3). Similar to beef cattle, including genomic data in the estimation process could be beneficial for small and weakly linked dairy cattle populations such as Ayrshire, Guernsey, and Jersey (Jorjani, 1999; Jorjani, 2000; Mark et al., 2005b). On the other hand, for large dairy cattle international evaluations in which connectedness levels between populations are high, such as those of Holstein-Friesian (2000), it is unlikely that including genomic data would improve the estimation of  $r_g$  between countries (Figure 2).

Genomic information is increasingly becoming available at the national level for beef and small dairy cattle populations. Therefore, the proposed approach could be applied to estimate  $r_g$  between countries in (small-breed) international beef and dairy cattle evaluations. The **G** matrix used 3 generations of data and gave estimated  $r_g$  between populations similar to those obtained with **A** and **H** matrices, in which 10 generations of data were used. These results suggest that three complete generations of phenotypes and genotypes could be sufficient to estimate  $r_g$  between countries. However, in real data, additional challenges may be expected due to an unbalanced number of genotyped and phenotyped animals, missing records and incomplete pedigrees, and, depending on the population, a low number of offspring per dam. Finally, the genomic REML estimation approach used (Lee and van der Werf, 2016; Zhou et al., 2020) assumes that raw genomic data is available at the international level to calculate the relationship matrices. When sharing data is not possible due to privacy or political constraints, an approach based on summary statistics such as LDSC (linkage disequilibrium score regression analysis; Bulik-Sullivan et al., 2015; van Rheezen et al., 2019) could be investigated, albeit it is expected to

**Table 2.** Computational requirements.

	A	G	H
Animals in matrix (number)	66,000	24,000	66,000
Elapsed time (hours)	3.1	7.3	2.9
RAM peak usage (GBytes)	106	13	102

Averages across scenarios and replicates.

require a larger amount of data and to be less accurate (Ni et al., 2018; van Rheezen et al., 2019).

## Conclusions

Our simulation results showed that genomic data may help to obtain more accurate estimates of  $r_g$  between countries and especially reduce their associated standard errors compared to current methods using only pedigree and phenotypes. Larger advantages were observed for estimates of maternal  $r_g$  and for populations that appear completely disconnected or lowly connected through pedigree information, such as in beef and (small) dairy cattle populations.

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