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Genomic Prediction of Individual Inbreeding Levels for the Management of Genetic Diversity in Populations With Small Effective Size

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ABSTRACT

In populations of small effective size (N_e), such as those in conservation programmes, companion animals or livestock species, inbreeding control is essential. Homozygosity-by-descent (HBD) segments provide relevant information in that context, as they allow accurate estimation of the inbreeding coefficient, provide locus-specific information and their length is informative about the "age" of inbreeding. Our objective was to evaluate tools for predicting HBD in future offspring based on parental genotypes, a problem equivalent to identifying segments identical-by-descent (IBD) among the four parental chromosomes. In total, we reviewed and evaluated 16 approaches using simulated and real data from populations with small N_e. The methods included model-based approaches as well as more computationally efficient rule-based approaches. The accuracy of the methods was then evaluated, including with low-density marker panels, genotyping-by-sequencing data and small groups of individuals, typical features of such populations. Two model-based approaches performed consistently well, while some rule-based approaches proved accurate for genome-wide predictions. The model-based approaches were particularly efficient when genomic information was sparse or degraded. Methods using phased data proved to be more accurate, while some approaches relying on unphased genotype data were sensitive to the assumed allele frequencies. In some settings, pedigree-based predictions ranked high for recent inbreeding levels. Finally, we showed that our evaluation is also informative about the accuracy of the methods for estimating relatedness and identifying IBD segments between pairs of present-day individuals. This study shows that future inbreeding can be accurately predicted, including at specific loci, but not all methods perform equally well.

1 | Introduction

In wildlife conservation, companion animals and livestock species, effective population sizes (N_e) are often small (e.g., below 250) and optimal management strategies are implemented to maintain genetic diversity and limit levels of inbreeding, often relying on reproducer selection and mating advice. The expected level of inbreeding of future offspring is an important criterion for such mating advice, as it allows the risk of inbreeding depression or genetic defects to be reduced.

The inbreeding coefficient (F) of an individual has been defined as the correlation between the uniting gametes (Wright 1922) and the probability that the two alleles present at a locus are identical-by-descent (IBD), i.e., inherited twice from a common ancestor (Malécot 1948). In that case, the neighbouring loci will also be IBD because a whole segment has been inherited IBD from the ancestor. In the absence of mutations, these segments are homozygous and are therefore called homozygous-by-descent (HBD) (Schäffer 1999). The length of these HBD segments depends on the number of generations to the common ancestor, with more generations providing more opportunities for the recombination process to cut the transmitted segment. With genotyping data, these HBD segments appear as long stretches of homozygous genotypes called runs-of-homozygosity (ROH), which can be used to identify HBD and to estimate F (Broman and Weber 1999; McQuillan et al. 2008). In rule-based approaches to detect such segments, markers are classified as HBD or non-HBD using a set of predefined rules, such as the minimum number of SNPs in a ROH, their minimum length and marker density, whereas model-based approaches rely on allele frequencies, the genetic map, genotyping error rates and a model to compute the probability that a position is HBD, identify HBD segments and estimate realised inbreeding levels (Leutenegger et al. 2003). Such model-based approaches have been shown to be more efficient than rule-based methods when information is degraded or marker density is low (Druet and Gautier 2017; Lavanchy and Goudet 2023).

Segment-based estimators of F present several advantages over other marker-based estimators. Indeed, studies from Nietlisbach et al. (2019) and Caballero, Villanueva, and Druet (2021) showed that they perform well in populations with low N_e. In agreement, Alemu et al. (2021) concluded that these methods are accurate in livestock species where deleterious alleles can reach high frequencies (e.g., Keller and Waller 2002; Bosse et al. 2019). In addition, these methods provide locus-specific estimates, which can be used to manage identified recessive alleles that cause genetic defects or have a large contribution to inbreeding depression. They are also informative about the age of HBD segments (Kirin et al. 2010; Pemberton et al. 2012), allowing the distinction between ancient and recent inbreeding, which is expected to be more deleterious (Hinrichs et al. 2007; Szpiech et al. 2013; Stoffel et al. 2021; Naji et al. 2024) and therefore more relevant for management strategies. They are also more robust to the used allele frequencies, which might introduce biases (Keller, Visscher, and Goddard 2011; Caballero et al. 2022; Naji et al. 2024). Finally, these estimators are interpretable as they range between 0 and 1 like the pedigree-based estimators, and allow us to define a base population comparable to the one from the pedigree (Solé et al. 2017). In summary, the use of measures based on HBD segments offers several advantages for managing diversity and inbreeding in populations with small N_e, as in conservation genetics, some wildlife species, companion animals and livestock populations. Actually, the benefits of using segment-based measures to maintain diversity and fitness have been demonstrated in similar populations (de Cara et al. 2013; Bosse et al. 2015; Gómez-Romano et al. 2016), for example by minimising the occurrence of long HBD segments in offspring (Bosse et al. 2015). Similarly, Meuwissen et al. (2020) concluded that the use of IBD-based approaches performed well in optimal contribution selection schemes.

In the present study, our objective was to evaluate different methods for predicting inbreeding levels in future offspring based on genotypes from their parents, as these are an important component in mating plans implemented to manage diversity and inbreeding in populations with small N_e. More specifically, our aim was to predict future HBD levels, as these metrics have been proven to be accurate and offer several advantages (see above). To that end, we first reviewed methods for identifying IBD segments between parental chromosomes and predicting HBD levels in offspring, and selected state-of-the-art model- and rule-based approaches to perform a comprehensive evaluation study. Importantly, this evaluation was carried out on real data sets from a large sequenced cattle pedigree and a population of Mexican wolves, populations representative of those typically found in conservation genetics, animal breeding or molecular ecology. It is indeed essential to measure the accuracy of the methods in such settings because the genomic structure of the population has been shown to affect their performance (e.g., Caballero, Villanueva, and Druet 2021), while most of the methods have only been evaluated on human datasets characterised by large N_e. Therefore, simulated data with similar population structures were also generated to consolidate our results. Accuracy was also assessed at lower marker density or with genotyping-by-sequencing (GBS) data, genotyping strategies that are also frequently used. We start by a description of the different evaluated methods.

2 | Material and Methods

2.1 | Overview of Approaches to Predict Homozygosity-By-Descent in Offspring

Our objective is to predict the level of inbreeding of an individual based on the genotypes of its parents (Figure 1A), i.e., to predict the overall proportion of HBD segments and to estimate the probability that a locus will be HBD. The expected inbreeding coefficient of an individual is equal to the kinship coefficient between its two parents (Malécot 1967; Lynch and Walsh 1998). Likewise, the prediction of HBD can be obtained from the probability that the haplotypes inherited from the parents are IBD. Each parent can transmit two haplotypes, so there are four possible combinations of pairs of parental haplotypes at a locus, and the HBD probability can be computed from the IBD probabilities of these four combinations (Figure 1). Note that due to recombination, the transmitted haplotypes might differ from the parental haplotypes. Nevertheless, the expected HBD level can still be obtained as the average IBD of the four parental combinations.

The methods we will evaluate are therefore based on the modelling of the IBD relationships between the four chromosomes of two individuals (here, the four parental homologues) that can take on 15 different configurations described in Figure 1B, called the identity states (Jacquard 1974). Basically, these identity states indicate which of the four parental haplotypes are IBD. If the parental origins of the haplotypes within the two individuals are unknown, we do not discriminate them and therefore the 15 identity states can be grouped into 9 condensed identity states (Jacquard 1974). The configurations can be further reduced to three states if the inbreeding of the individuals is ignored (Figure 1B). In this case, the three states simply

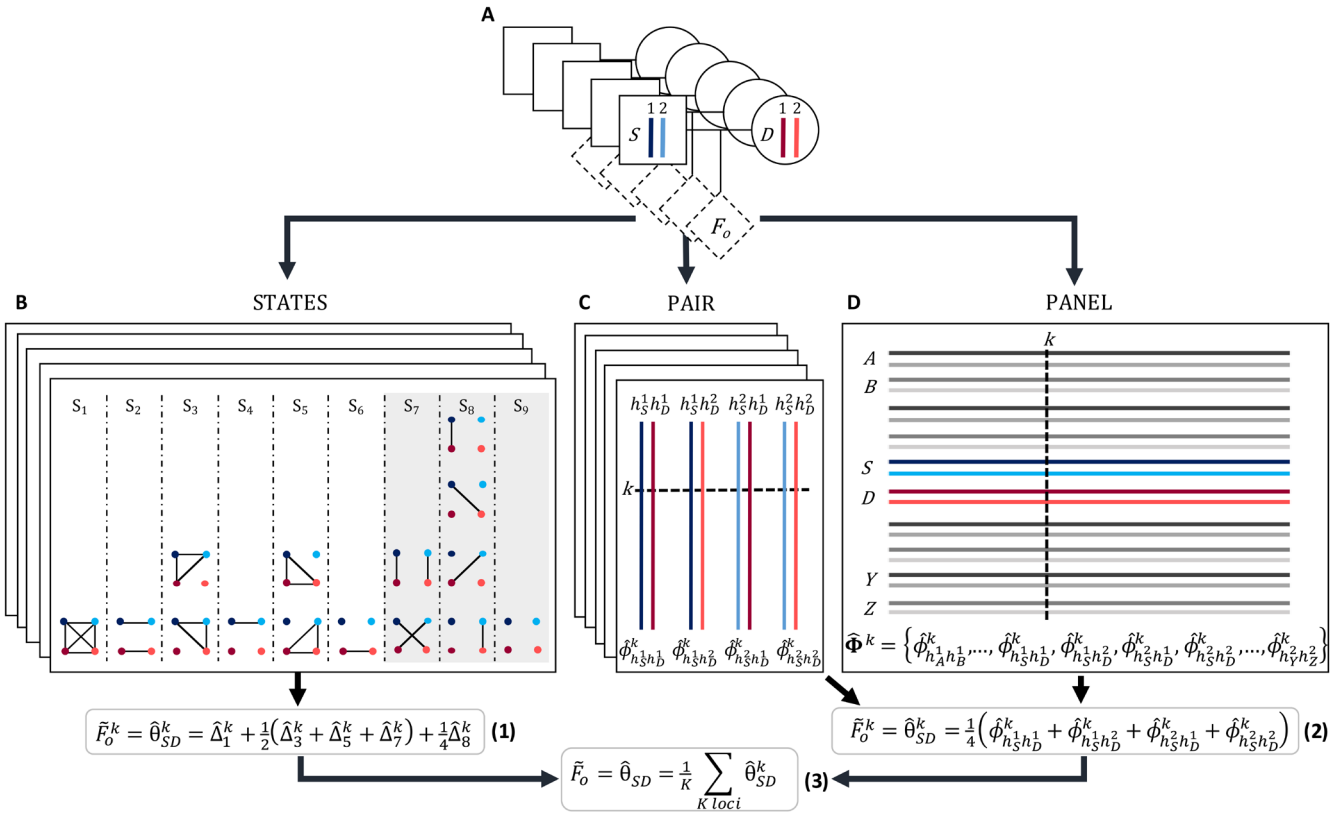

FIGURE 1 | Approaches used to predict the homozygous-by-descent (HBD) level of an individual (F_O) based on the genotypes of its parents. (A) Predictions were made in several trios, each including a sire (S) and a dam (D), having each a paternal and maternal haplotype (labelled 1 and 2, respectively), shown in blue for the sire and red for the dam, and the future offspring (dashed diamond). (B) STATES approach: For each pair of parents, the four parental haplotypes can take 15 possible identity-by-descent (IBD) configurations at a locus (Jacquard 1974). The four parental haplotypes are represented by dots using the same colours as in (A) while solid lines indicate IBD between linked haplotypes. Horizontal lines correspond to inbreeding within a parent, while vertical or diagonal lines indicate IBD between parents. The 15 IBD states can be grouped into 9 condensed IBD states $\{S_1, S_2, \ldots, S_9\}$ if the parental origins of the haplotypes within the two individuals are considered unknown. The number of states is reduced to three if the parents are assumed to be non-inbred (grey background). The STATES approaches model the observed genotypes or haplotypes conditional on these configurations. At locus k, the estimated probabilities of the 9 IBD modes $\{\hat{\Delta}_1^k, \hat{\Delta}_2^k, \ldots, \hat{\Delta}_9^k\}$ can be used to estimate the locus specific coancestry between the parents $\hat{\theta}_{SD}^k$ (see also Lynch and Walsh 1998), which corresponds to the predicted locus-specific HBD level in the offspring $\tilde{F}_O^k$ (Equation 1). (C) PAIR approach: IBD is modelled sequentially for each of the four possible combinations of parental haplotypes $(h_S^1 h_D^1, h_S^1 h_D^2, h_S^2 h_D^1, h_S^2 h_D^2)$, where h_I^1 and h_I^2 denote the paternal and maternal haplotypes of individual I, respectively. This analysis estimates the IBD probability $\hat{\phi}_{h_S^i h_D^j}^k$ between two haplotypes h_S^i and h_D^j at locus k for the four possible pairs. (D) PANEL approach: A large panel of haplotypes from a large number of individuals are analysed jointly to detect IBD segments. At locus k, a vector $\hat{\boldsymbol{\Phi}}^k$ containing the IBD probabilities for each pair of haplotypes is estimated (note that with rule-based approaches, IBD probabilities are either 0 or 1). In the PAIR and PANEL approaches, the locus specific coancestry between the parents is obtained as the average over the four possible pairs of parental haplotypes (Equation 2). Finally, the genome-wide HBD levels $\tilde{F}_O$ can then be predicted as the average locus-specific values at the K loci (Equation 3).

correspond to the sharing of 0, 1 and 2 IBD haplotypes between the two parents. For more details, see Lynch and Walsh (1998, 132-141). Accordingly, several methods model the observed genotypes or haplotypes conditionally on these possible configurations (referred to as 15, 9 or 3-STATES approaches). Another approach is to model chromosomes individually, ignoring which chromosomes belong to the same individual. In this case, methods can either model the IBD relationship between each of the four possible pairs of parental haplotypes sequentially (PAIR approach—Figure 1C), or jointly model the IBD sharing between all individual haplotypes in the analysed sample (PANEL approach—Figure 1D).

Prediction methods can be further classified according to whether they use genotypes or haplotypes. The use of genotypes is only possible in the 9 or 3-STATES approaches by modelling the genotype probabilities conditionally on the underlying state. Haplotypes require phasing of the data, a procedure that provides additional information, but that can also introduce errors.

Finally, we can also distinguish between rule-based and model-based approaches. Rule-based approaches use a set of rules to determine whether two individuals share IBD haplotypes based on their genotypes or whether two haplotypes are IBD. These rules are typically based on the number of identical-by-state (IBS) alleles or genotypes, the length of the segments compared or the number of mismatches. The optimal rules will vary for each data set, depending on marker density, genotyping technology and population structure, and should ideally be validated in new applications, although this is rarely done. For example,

the parameters used to identify ROH (number of SNPs, length, etc.) may need to be modified at lower marker densities. Model-based approaches compute the probability of different IBD configurations from the observed data under various assumptions. The possible configurations could, for example, correspond to the 9 identity states in a 9-STATES model, or to IBD versus non-IBD for a PAIR approach. Estimation of these probabilities may also rely on or capitalise on additional information such as population allele frequencies, the genotyping error rate, the genetic distance between successive markers, etc. Importantly, model-based approaches can also handle genotype probabilities to account for genotype uncertainty (e.g., when analysing low-fold sequencing data), and their underlying probabilistic framework can automatically account for varying marker densities and population structure, thereby requiring fewer parameter adjustments.

2.2 | Description of the Evaluated IBD Estimation Methods

2.2.1 | STATES Approaches

IBD_Haplo (Thompson 2008, 2009), GIBDLD (Han and Abney 2011, 2013) and LocalNgsRelate (Severson, Korneliussen, and Moltke 2022) model the IBD process along the four parental chromosomes based on continuous-time Markov chains that can be implemented as hidden Markov models (HMM). In these three methods, the probabilities of observing genotypes or haplotypes conditional on the IBD configurations between the four parental chromosomes, the so-called emission probabilities, are based on allele frequencies and genotype probabilities (including genotyping errors). The transition probabilities define the probability of changing from one IBD configuration to another between two markers and are a function of the genetic distances. Using these emission and transition probabilities, these methods estimate the posterior state probabilities, $P(X_i = k)$, at each locus i, where X_i is the unknown state at locus i and k is one of the modelled states. With genotyping data, these hidden states correspond to the 9 condensed identity states with IBD_Haplo and GIBDLD, and to sharing of 0, 1 or 2 IBD alleles with LocalNgsRelate (3-STATES model). With haplotype data, IBD_Haplo fits a model with 15 hidden states corresponding to the 15 identity states. At each locus, the offspring HBD can be predicted from the locus-specific state probabilities $P(X_i = k)$ using the rules shown in Figure 1. The three methods define the transition matrices, which are either predefined or estimated, and the emission probabilities differently. LocalNgsRelate is designed to work with low-coverage sequencing data, a feature made possible by using genotype likelihoods to define emission probabilities. Like LocalNgsRelate, TRUFFLE (Dimitromanolakis, Paterson, and Sun 2019) fits a 3-STATES model, but uses a rule-based approach.

2.2.2 | PAIR Approaches

Expected values of HBD-related measures of future offspring from two genotyped parents (with phased haplotypes) can be estimated using methods designed to identify HBD segments in individual genomes by analysing the four individuals (artificially) obtained by combining each pair of parental chromosomes (each parent contributing one chromosome to the pair). This strategy has been used, for example, with ROH in several studies (Pryce, Hayes, and Goddard 2012; Bosse et al. 2015; de Cara et al. 2013). The ZooRoH model (Druet and Gautier 2022) is an alternative to rule-based approaches to identify ROH. It is an HMM that describes the genome as a mosaic of HBD and non-HBD segments. A specific feature of ZooRoH is that it fits several HBD classes, each class c having its own rate parameter R_c that defines the expected length of HBD segments (equal to $1/R_c$ Morgans). Each class is therefore associated with a different set of ancestors present in different past generations. This makes it possible to estimate the level of inbreeding with respect to different base populations (Solé et al. 2017). Note that when a single HBD class is fitted, we refer to a ZooRoH-1R model. This model is identical to that of Leutenegger et al. (2003) and very similar to BCTtools/ROH (Narasimhan et al. 2016) and ngsF-hmm (Vieira, Albrechtsen, and Nielsen 2016).

2.2.3 | PANEL Approaches

GERMLINE (Gusev et al. 2009), hap-IBD (Zhou, Browning, and Browning 2020) and phasedibd (Freyman et al. 2021) belong to the PANEL approach and use rule-based methods to find long segments shared IBS between two haplotypes. These three methods avoid comparing each pair of haplotypes sequentially to improve computational efficiency. Although they share common principles, these methods differ in their implementation and their handling of genotyping and haplotyping errors. For example, hap-IBD and phasedibd can account for genotyping errors and even correct for some so-called switch errors resulting from the (statistical) phasing process. Finally, Refined-IBD (Browning and Browning 2013) first relies on GERMLINE to identify long segments shared IBS, and then uses a LOD score to determine whether the haplotypes are IBD or not.

2.2.4 | Pedigree-Based and Genomic Relationship Matrices

The genome-wide inbreeding coefficient can also be predicted as half the relationship between the parents obtained using either genealogical information or genotyping data, SNP-by-SNP. When the genomic relationship matrix (GRM) is calculated using the first rule described in VanRaden (2008), this is equivalent to predicting the inbreeding coefficient obtained from the diagonal elements of the GRM (F_{GRM}), also defined by VanRaden (2008). When the GRM is obtained using the second rule of VanRaden (2008), the relatedness between the parents corresponds to the prediction of the inbreeding coefficient defined as the correlation between the uniting gametes, F_{UNI} (Li and Horvitz 1953; Yang et al. 2010). See Text S4 of Alemu et al. (2021) for more details.

2.3 | Evaluation Design

The objective of the present study was to evaluate the accuracy of predicting HBD in future offspring based on parental genotypes in populations with small N_e. For this evaluation, we used

both simulated and real data sets. With simulations, the true HBD levels are known, whereas with real data, the methods were evaluated in more realistic data structures and conditions. Therefore, we used a design that can be applied to both datasets, taking advantage of the genotyped trios available for the real data. In this design, we used the parental genotypes to perform the predictions and the offspring genotypes to evaluate their accuracy (Figure S1). The genotypes of the offspring provide the possibility to estimate its realised inbreeding. In particular, with sequence data, genotypes are available for all variants, allowing accurate estimation of whole-genome heterozygosity (Kardos et al. 2016; Alemu et al. 2021).

The accuracy was then assessed using the correlations between the predicted and reference genome-wide levels of HBD (defined as the average locus-specific HBD levels). For locus-specific predictions, the correlations between predicted and reference locus-specific levels of HBD were computed, and ROC curves associated with these predictions were derived. We also compared reference and predicted HBD levels for both genome-wide and locus-specific predictions.

2.4 | Software and Parameters Used for Prediction of Homozygosity-By-Descent

For evaluation, offspring genotyping data were first removed from the analysis. Parental genotypes were then phased using Beagle 5.4 (Browning et al. 2021) and default parameters. The software used to predict global and locus-specific HBD levels in offspring based on parental genotypes or haplotypes are listed in Table 1 and Table S1. For all methods, we tried to use default and recommended parameters as much as possible, but when this resulted in detection of at best a few long IBD segments, we relaxed the parameters (Table S1). This was the case for TRUFFLE, ROH identified using PLINK (Purcell et al. 2007) and phasedibd. For the majority of rule-based methods, the minimum segment length was 2 Mb while the minimum number of SNPs per segment ranged from 40 to 128. IBD_Haplo (Thompson 2008) was run either with genotypes (IBD_Haplo9c), or with haplotypes (IBD_Haplo15c) and the transition matrix described in Brown et al. (2012). For RZooRoH (Bertrand et al. 2019), we used a 'layer' model (Druet and Gautier 2022) with 6 HBD classes with predefined rates $R_c = \{5; 25; 125; 625; 3125; 15{,}625\}$. We then estimated IBD between each pair of parental haplotypes using posterior probabilities from HBD classes with $R_c \leq 25$ (recent IBD—ZooRoH-25) or from HBD classes with $R_c \leq 125$ (total IBD or ZooRoH-125). The last HBD classes were not included as they are less reliable (only a few SNPs per segment) and more dependent on allele frequencies like maximum likelihood estimators (Alemu et al. 2021). In addition, we ran a model estimating the rate of a single HBD class (ZooRoH-1R).

By default, methods use allele frequencies estimated from the sample, although ideally those of the base population should be used. Therefore, we also tested methods that accept external frequencies as input (IBD_Haplo, ZooRoH, LocalNgsRelate, GRM and UNI) with founder allele frequencies estimated using the gene content approach of Gengler, Mayeres, and Szydlowski (2007). SNPs with a founder MAF ≤ 0.005 were discarded.

TABLE 1 | Main properties of the methods used to predict levels of homozygosity-by-descent in a future offspring of a genotyped pair of parents. The table also indicates whether the methods use genotype (GEN) or haplotype (HAP) data and the names of the corresponding software. The STATES, PAIR and PANEL approaches are described in the main text and in Figure 1. See Table S1 for further details on the options used for the different programmes.

Method name	Data	Approach		Software
IBD_Haplo15c	HAP	15-STATES	Model-based	IBD_Haplo
IBD_Haplo9c	GEN	9-STATES	Model-based	IBD_Haplo
GIBDLD	GEN	9-STATES	Model-based	IBDLD
LocalNgsRelate	GEN	3-STATES	Model-based	LocalNgsRelate
TRUFFLE	GEN	3-STATES	Rule-based	TRUFFLE
ZooRoH	HAP	PAIR	Model-based	RZooRoH
PLINK ROH	HAP	PAIR	Rule-based	PLINK
phasedibd	HAP	PANEL	Rule-based	phasedibd
hap-IBD	HAP	PANEL	Rule-based	hap-IBD
GERMLINE	HAP	PANEL	Rule-based	GERMLINE
Refined IBD	HAP	PANEL	Hybrid	Refined IBD
UNI	GEN	/	/	GCTA—algo0
GRM	GEN	/	/	GCTA—algo1
Pedigree	Pedigree	/	/	In-house script

2.5 | Data

2.5.1 | Simulation Study

We simulated two populations with small N_e in the most recent generations. These demographic histories, characterised by successive reductions in N_e, were chosen to obtain levels of inbreeding and genomic structure similar to those observed in the two real datasets (see below). The scenarios resulted in moderate and high levels of inbreeding, corresponding to the levels observed in a typical livestock population (dairy cattle) and an endangered wild population (the Mexican wolf).

Simulations were performed with SLiM 4.0.1 (Haller and Messer 2023) and msprime 1.2.0 (Baumdicker et al. 2022) using forward-time simulation and recapitation (Haller et al. 2018). For both populations, individual genomes consisted of 25 chromosome pairs of 100 cM each. Recombination and mutation rates were set to 10^{-8} per bp. The initial population consisted of 10,000 randomly mating diploid individuals with a balanced sex ratio. Subsequent evolution of demographic parameters is described in Figure 2. In total, 100 and 20 offspring were simulated in the last generation in the moderate and high inbreeding scenarios respectively. The simulated data consisted of the trios formed by these offspring and their parents. In each replicate, we selected a subset of 5000 or 25,000 evenly spaced bi-allelic markers with an MAF ≥ 0.01 to obtain a uniform MAF distribution as typically found on genotyping arrays (corresponding to low and medium-density arrays with 2 SNPs/cM and 10 SNPs/cM). In addition, we kept track of the pedigree for the last 15 generations. Each scenario was repeated 100 times.

We used the tree sequence recording feature available in SLiM to keep track of the true local ancestry at each marker position for each individual. At each position, HBD was then declared if the time to the most recent common ancestor was less than the age (in generations) of the defined base population. We used three different base populations to define the reference levels of inbreeding, corresponding respectively to recent inbreeding only (young base population set to 15 generations—F_{YOUNG}), to 50 generations of inbreeding (intermediate base population—F_{MID}) and to a large number of generations including ancient inbreeding (ancient base population set to 500 generations—F_{TOT}).

2.5.2 | Dutch Holstein Data Set

The first real data set represents a population typical of livestock species, with a small N_e and under intense selection. We used whole-genome sequence data (8,417,679 SNPs) available for 264 Dutch Holstein individuals from the cattle pedigree previously used by Oget-Ebrad et al. (2022). This pedigree can be divided into 127 parents, corresponding to 84 different pairs, and their 98 offspring. Offspring belonging to a sequenced trio that were also parents in another trio were excluded from the list of sequenced parents. The pedigree available for these individuals consisted of 12,238 individuals. The 127 parents had on average 99.8%, 67.6% and 5.7% known ancestors in their 5th, 10th and 15th pedigree generation, respectively.

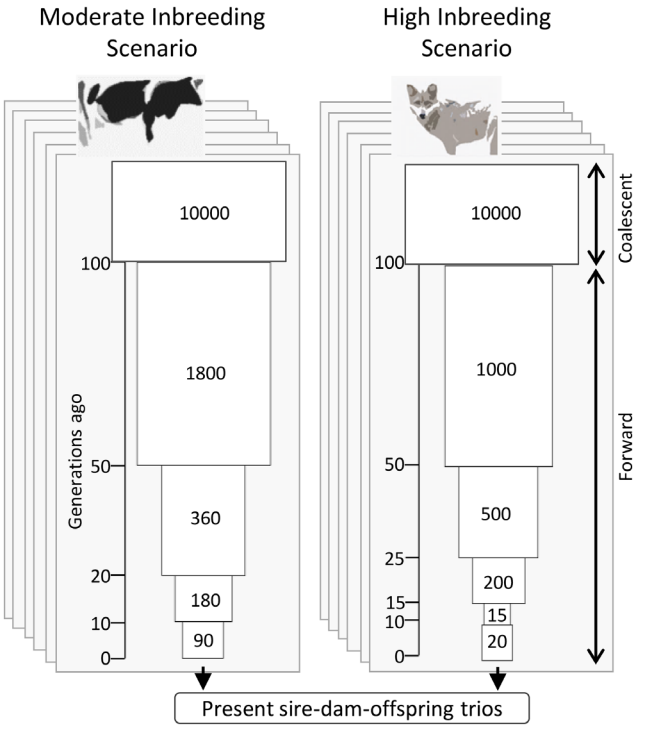

FIGURE 2 | Simulated demographic scenarios. We simulated a moderately inbred population corresponding to a typical livestock population (e.g., dairy cattle), and a highly inbred population corresponding to an endangered wild population under conservation (similar to the Mexican Wolf). In both scenarios, we run a forward-in-time simulation with an initial population of $N_e = 10{,}000$ and equal sex ratio. In the moderate and high inbreeding scenario, the proportion of males for the subsequent generations was set to 0.1 and 0.5, respectively. The figure represents the evolution of N_e across generations.

The reference inbreeding measures were computed using ZooRoH and the whole-genome sequence data because inbreeding estimation with ZooRoH proved highly accurate on the simulated data (Table S2). In addition, the model has been proven accurate and robust to genotyping errors in previous studies. We ran a 'layer' model (Druet and Gautier 2022) with 6 HBD classes with fixed rates $R_c = \{5; 25; 125; 625; 3125; 15{,}625\}$ on the sequence data from the offspring only. Recent inbreeding F_{YOUNG} was defined using only posterior HBD probabilities of classes with $R_c \leq 25$, while F_{MID} and F_{TOT} were obtained using HBD classes with $R_c \leq 125$ and $R_c \leq 3125$, respectively. These correspond approximately to base populations set at 12.5, 62.5 and 1500 generations in the past.

2.5.3 | Mexican Wolf Data Set

We also evaluated the accuracy of the methods in a population with higher levels of inbreeding and under a conservation programme. It consisted of 13 trios from the endangered Mexican Wolf (*Canis lupus baileyi*) population genotyped using the Illumina CanineHD BeadChip array (Illumina Inc., San Diego, CA). This population was reintroduced into the wild in the 1990s. It is derived from three unrelated captive lineages, called McBride, Aragón and Ghost Ranch, each descended from 2 or

3 founders. The trios were extracted from a data set including 88 wolves genotyped for 118,287 SNPs (Fitak, Rinkevich, and Culver 2018a). One individual was excluded for having more than 10% Mendelian inconsistencies with its parents. In addition to the original filtering, we kept only markers with call rate ≥ 0.90, MAF ≥ 0.01, without Mendelian conflicts and in Hardy–Weinberg equilibrium ($p \geq 0.05$). The final set included 87 individuals genotyped for 54,037 SNPs, of which we used 13 trios in our validation experiment. The reference inbreeding measures were computed using the 54,037 selected SNPs and the same approach as for the cattle data set.

2.6 | Impact of Marker Density and Genotyping Method

The methods were evaluated with different marker panels, such as low- and medium-density genotyping arrays. For the simulated data sets, these corresponded to densities of 2 and 10 SNPs per Mb. For the cattle data set, we selected markers in common with the Illumina BovineLD and BovineSNP50 commercial arrays. This resulted in a selection of 5388 and 29,375 SNPs respectively (approximately 2 and 10 SNPs per Mb). In addition, the sequence data allowed us to mimic genotyping-by-sequencing (GBS) data. To do this, we performed an in silico digestion of the bovine reference genome using the *PstI* restriction enzyme using the GBSX package (Herten et al. 2015). We selected 72,828 fragments out of 1,503,470 fragments with a length between 200 and 300 bp. The distance between fragments is shown in Figure S2. A total of 60,842 SNPs from the WGS data were located in the selected fragments. To account for allelic dropout (Gautier et al. 2013), when an SNP was located near the restriction site (±3 bp), heterozygous individuals were considered homozygous in the associated fragment for the haplotype carrying the reference alleles (the other haplotype was not amplified). If individuals were homozygous for the alternate alleles of the SNP in the restriction site, all genotypes in the associated fragment were set to missing. We then filtered out SNPs surrounding the restriction site (±3 bp), those with more than 5% missing genotypes or MAF < 0.01. This resulted in a GBS panel of 56,098 SNPs (GBS-50K). To further reduce the number of markers, we first selected fragments with a length ranging between 250 and 300 bp, resulting in a panel of 31,339 SNPs (GBS-30K). A smaller panel of 15,493 SNPs (GBS-15K) was obtained by randomly sampling half of these fragments. Finally, we used only one marker density for the wolves (54,037 SNPs, corresponding to about 20–25 SNPs per Mb). In addition to their variable marker densities, the different marker panels differ in the distribution of their MAF and of their marker spacing (Figure S3). These elements could also influence the properties of the prediction methods. Note that for the analysis of low-marker-density panels with rule-based methods, we had to reduce the minimum number of SNPs in a segment criterion to 25 (Table S1). In addition, for ROH identification with PLINK and the low-marker-density or GBS-15K panels, we set the maximum marker spacing to 1 Mb and the minimum marker density to 2 and 4 SNPs per Mb, respectively (Table S1). Such loose parameters are rarely used and have not been validated, but were necessary at these lower marker densities to identify some IBD segments.

3 | Results

The simulated data closely matched the inbreeding levels and partitioning of HBD observed in the corresponding real data (Figure S4). Comparisons also illustrate that dairy cattle and Mexican wolf populations, and the corresponding simulations, provide complementary scenarios.

3.1 | Accuracy of Predicted Genome-Wide HBD Levels

We first evaluated the predictions obtained using medium-marker density. The correlations between predicted and reference levels of HBD for the 16 methods compared and the four scenarios are shown in Figure 3 and Figure S5 (significance levels of pairwise comparisons are available in Table S3). The reference levels of HBD were defined with respect to different base populations, corresponding to approximately 15, 50 and 500 generations.

3.1.1 | Results of the Simulations

The correlations were high, ranging from 0.78 to 0.86 and from 0.74 to 0.83 in the moderate and high inbreeding scenarios, respectively (Figure 3A,C). The ranking of the methods was comparable in the two simulation scenarios and for the different base populations. Several methods, including IBD_Haplo15c, ZooRoH, phasedibd, PLINK ROH and hap-IBD, were consistently among the best methods. Using unphased data with IBD_Haplo (IBD_Haplo9c) also performed well, but was generally less accurate than using phased data (IBD_Haplo15c). For ZooRoH, only minor differences were observed between the three models tested. Among the three best rule-based approaches, the correlations obtained with hap-IBD (minimum 100 SNPs) were generally slightly lower than those obtained with phasedibd or PLINK-ROH (minimum 40–50 SNPs). Other methods achieved lower correlations or presented variable performances. Finally, the vast majority of genotype-based predictors outperformed the pedigree-based predictions.

In the simulations, we could also compare the true and predicted inbreeding levels (Figure S6). The best model-based approaches and phasedibd predicted higher inbreeding levels, slightly below the true levels when the base population was intermediate (50 generations ago). Considering a more recent base population resulted in an overestimation of future inbreeding levels in the moderate inbreeding scenarios, but predictions remained unbiased in the high inbreeding scenario (see Figure S6 for performance of other methods).

3.1.2 | Evaluation With Real Data

Compared to the simulations, the correlations between predicted and reference HBD levels were lower in the cattle data set (Figure 3B), which contains about 100 trios for evaluation, and higher in the wolf population, where we have only 13 trios (Figure 3D). Regarding the relative performance of the evaluated methods, some trends observed in these two real data sets were similar to those highlighted with simulated

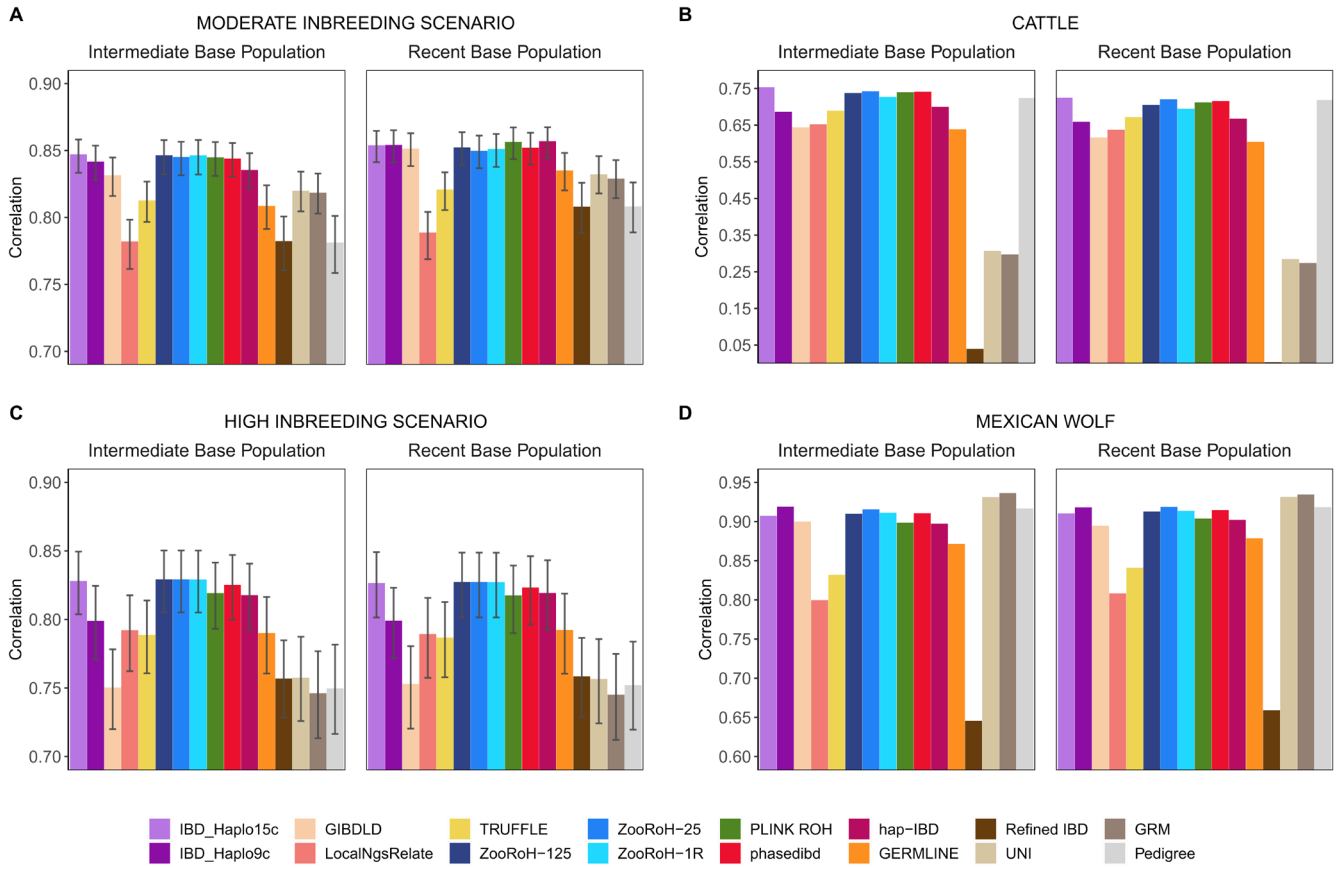

FIGURE 3 | Correlations between predicted and reference genome-wide levels of HBD for the 16 methods compared and the four scenarios, using a medium-density array. Methods and their abbreviation are described in Table 1. (A) moderately inbred simulated population; (B) cattle data set; (C) highly inbred simulated population; (D) Mexican Wolf data set. The reference levels were defined for either a recent or an intermediate base population (approximately 15 or 50 generations ago, respectively). Mean and 99% confidence intervals are shown for the simulated scenarios.

data. IBD_Haplo15c, ZooRoH, PLINK ROH and phasedibd performed well, closely followed by hap-IBD. As in the simulated data set, IBD_Haplo performed better with haplotypes (IBD_Haplo15c) than with genotypes (IBD_Haplo9c) in the cattle data, while the performances of different ZooRoH models were close. The SNP-by-SNP approaches still had variable performances, achieving the highest correlations in the wolf population but almost the worst prediction in the cattle data set. Interestingly, the correlations obtained with the pedigree-based approach were quite high, among the best methods, especially for recent HBD levels.

3.2 | Results for Locus-Specific HBD Levels

3.2.1 | Accuracy Comparison

We then evaluated the methods in terms of the accuracy of locus-specific correlations (Figure 4, Figures S7 and S8). The SNP-by-SNP-based and pedigree-based methods were not included in these comparisons because they only provide genome-wide predictions. As expected, prediction accuracies decreased compared to genome-wide predictions averaged over many more loci. Overall, the best methods were almost the same as for genome-wide predictions (Figure 4A,C). However, the best model-based approaches (IBD_Haplo15c and ZooRoH models) now outperformed the best rule-based methods (phasedibd and PLINK ROH). With regard to the model-based approaches, the disadvantage of using unphased data (IBD_Haplo9c vs. IBD_Haplo15c) was more pronounced, while the three ZooRoH models still had similar performances. Interestingly, the prediction of recent HBD (ZooRoH-25) was more accurate at predicting HBD levels defined with respect to a recent base population, which was not clearly observed with genome-wide predictions. The other evaluated methods achieved lower accuracies or showed variable performances. These observations were consistent across all evaluated scenarios with both simulated (Figure 4A,C, Figure S7) and real data sets (Figure S8), with a few rare exceptions.

3.2.2 | Additional Evaluation Metrics

When the locus-specific accuracy was assessed using ROC curves (Figure 4B,D, Figure S9) and the associated AUC (Figures S10 and S11), these trends were confirmed. The advantages of the best model-based approaches were even clearer. ZooRoH and IBD_Haplo15c were indeed associated with the highest AUC across all scenarios. Most often, ZooRoH models were the best, especially when the base population was more ancient. For more recent reference HBD levels, predictions using ZooRoH-25 (recent HBD only) were better than those using ZooRoH-125.

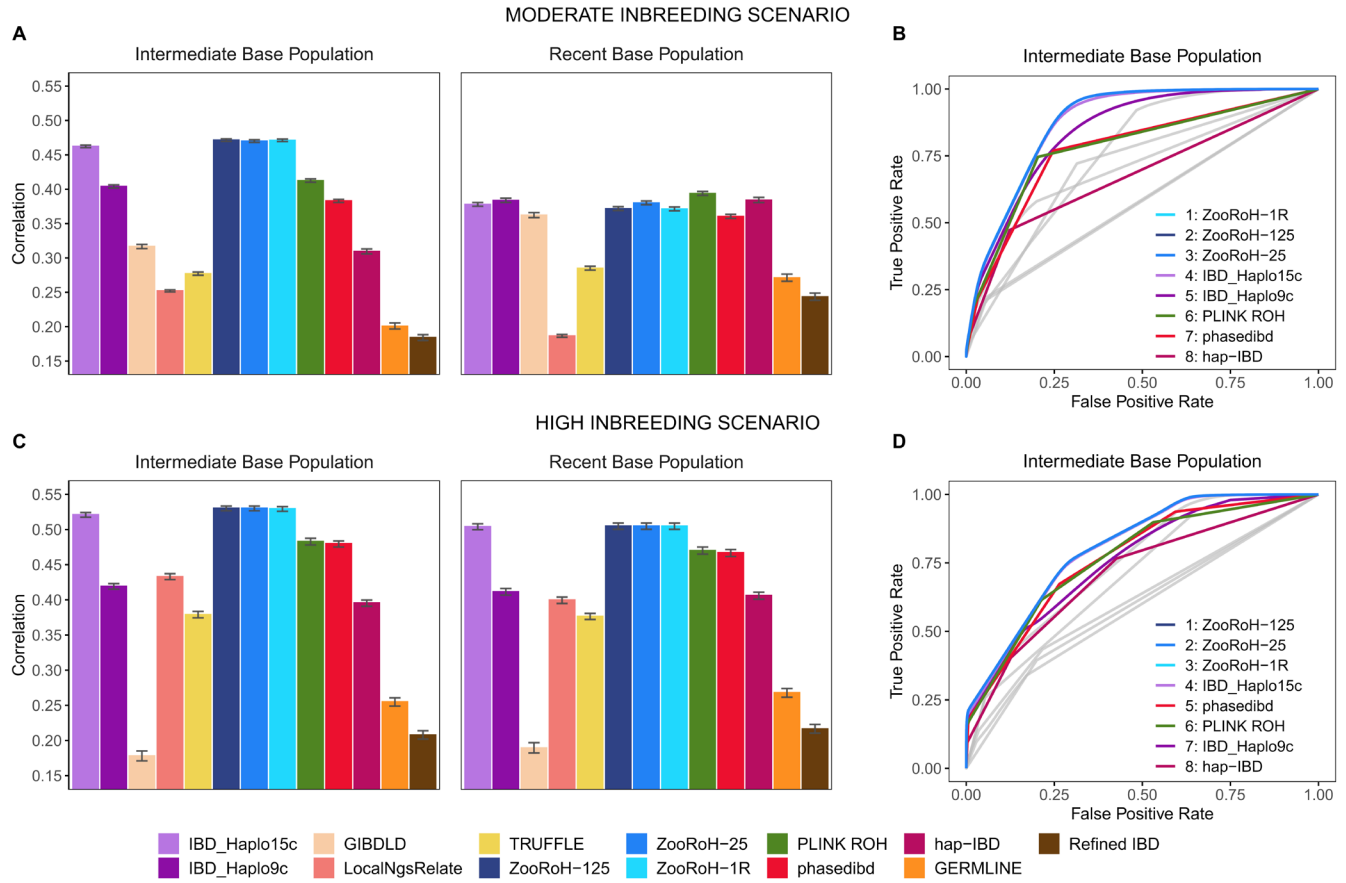

FIGURE 4 | Locus-specific accuracy of 13 HBD prediction methods in the simulated data sets using a medium-density array. Methods and their abbreviation are described in Table 1. Accuracy was assessed in the moderate (A and B) and high (C and D) inbreeding scenario using correlations (mean and 99% confidence intervals) between predicted and reference locus-specific HBD levels (A and C). The reference levels are the true HBD status at every marker position and defined using either a recent (15 generations ago—F_{YOUNG}) or an intermediate (50 generations—F_{MID}) base population. The Receiver operating characteristic (ROC) curve for each method were also computed (B and D), with coloured curves for the eight best methods. Their relative ranking in terms of AUC is also specified.

Finally, we also compared predicted and true locus-specific HBD levels in simulations (Table S4). For an intermediate reference population, the ZooRoH models and IBD_Haplo15c were relatively well calibrated (i.e., the predicted HBD levels matched the true levels), suggesting that HBD is neither under- nor overestimated. For example, when no IBD segments were detected among the parents (locus-specific predictions of 0), the offspring were not HBD at that position (low false-negative rate). Other methods had higher rates of false negative predictions (e.g., offspring were HBD at some genomic position although the predicted values were zero). As with genome-wide predictions, the two model-based approaches overpredicted future inbreeding levels in the moderate inbreeding scenarios when considering a recent base population.

3.3 | Impact of Marker Density and Genotyping Method on Accuracy of HBD Predictions

To reduce genotyping costs, low-marker-density panels or GBS data are commonly used in genomic studies of wild populations, conservation genetics or livestock species. To evaluate HBD predictions in such data, we relied mainly on the cattle data, for which low-marker-density panels are available (Boichard et al. 2012) and for which we could use the reference genome to generate in silico GBS panels. In addition, we also defined a low-marker-density panel in the simulations. Below, the prediction accuracies obtained with these "reduced" marker panels are expressed relative to those achieved with medium-density genotyping arrays.

3.3.1 | Genome-Wide Predictions of Inbreeding

With the cattle data, the methods that achieved the highest correlations using low-marker density (Figure 5A) or GBS data (Figure 5B–D) were generally the same as those that performed well at medium-marker density. Indeed, although the correlation decreased for some methods, the best model-based approaches (IBD_Haplo15c, ZooRoH) were relatively robust, while some rule-based approaches such as phaseibd or hap-IBD were sometimes even more accurate, allowing them to frequently reach the top of the ranking (e.g., with GBS-30K and GBS-50K). With GBS data, the correlations were generally lower than those obtained with genotyping arrays with a similar number of markers (Figure 5A–D, Figure S12). Interestingly, the rank of the pedigree-based predictor increased, especially when fewer markers were available (low-density, GBS-15K or GBS-30K) or when predicting recent HBD levels (Figure S13). Similar trends were observed for low-density marker analyses in the

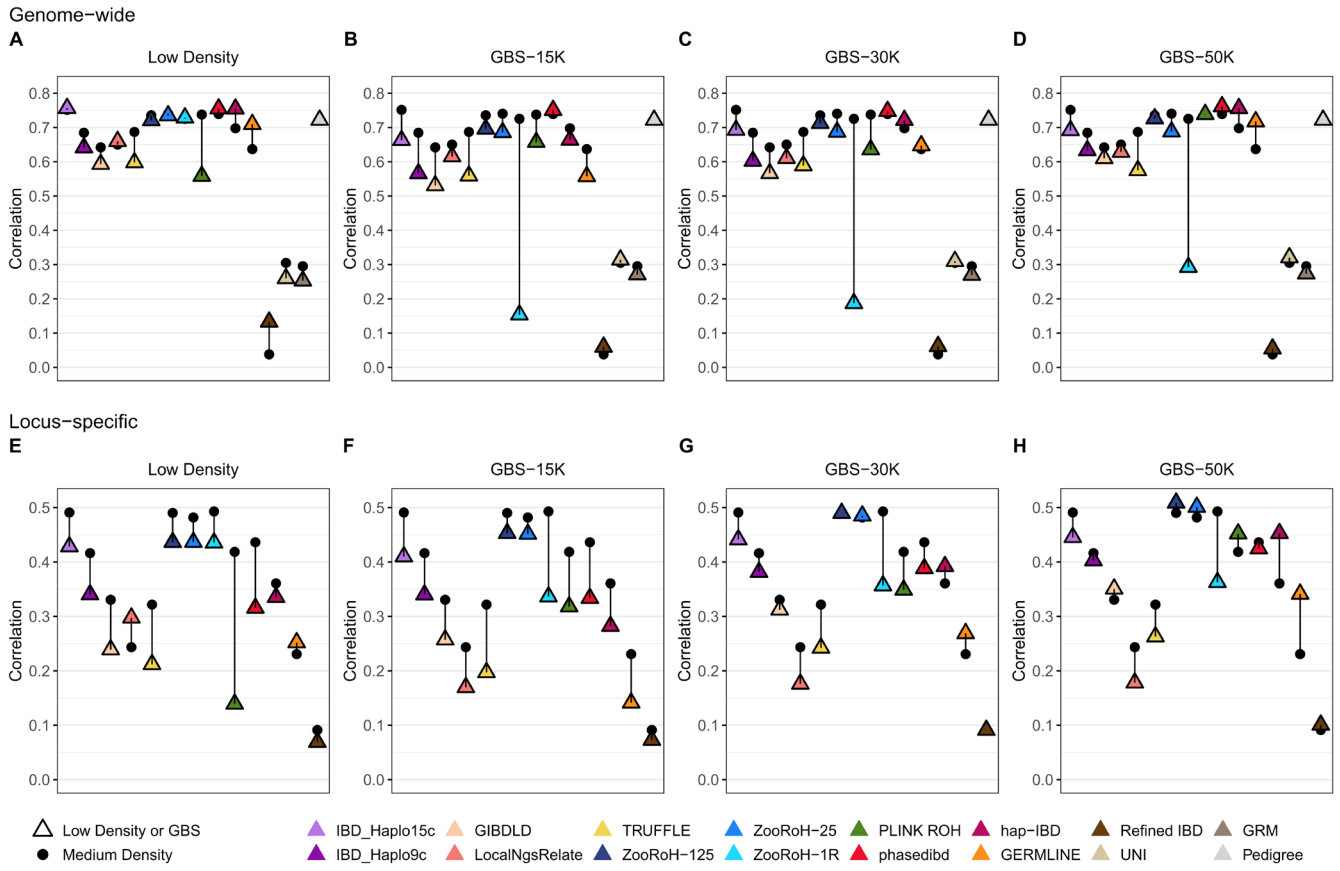

FIGURE 5 | Correlations between predicted and reference genome-wide (A–D) or locus-specific (E–H) HBD levels for the 16 evaluated methods in the cattle data set using reduced genotyping arrays. Methods and their abbreviation are described in Table 1. Correlations obtained with low-density (A and E) or genotype-by-sequencing (GBS) (B–D and F–H) data were compared to those achieved with the medium-density array (triangles vs. dots). Reference inbreeding was estimated using the intermediate base population $\hat{F}_{MID}$.

simulations (Figure S14), although the accuracy of phasedibd decreased in one scenario. Overall, the best methods were still accurate with these different panels, resulting in correlations close to those obtained at medium marker densities. However, the predicted HBD levels with low-marker-density panels were generally lower (Figure S6), even for rule-based methods for which parameters have been relaxed. This suggests that fewer IBD segments are captured at lower marker densities. We also observed that the impact of reduced genotyping information was slightly less for the prediction of recent inbreeding in the simulations (Figure S14). PLINK-ROH and ZooRoH-1R were among the methods that showed a greater reduction in accuracy, with degraded performance at low-marker density and GBS data, respectively (Figure 5A–D).

3.3.2 | Locus-Specific Predictions

The performance reduction was more pronounced for locus-specific predictions, especially when fewer markers were used, such as with the low-marker-density (Figure 5E) or GBS-15K (Figure 5F) panels. The accuracy of some rule-based methods increased with GBS-30K and GBS-50K (Figure 5G,H). However, it is important to note that locus-specific accuracy was evaluated at the marker positions, and with GBS data, this corresponds to small fragments with high marker density. Nevertheless, the ZooRoH models (with multiple HBD classes) were relatively stable and achieved the highest correlations for locus-specific predictions, followed by IBD_Haplo15c, both with the cattle data (Figure 5E–H) and in simulations (Figure S14). The impact of reduced genotyping information was clearly less for the prediction of the most recent inbreeding levels (Figure S14). These locus-specific trends were confirmed by ROC curves and AUC values (Figures S10 and S11). As could be expected with lower marker density, locus-specific HBD levels were underestimated more often than with medium-density genotypes (Table S5).

In summary, the best model-based approaches (IBD_Haplo15c and ZooRoH with multiple HBD classes) were among or close to the best for genome-wide predictions and outperformed other methods for locus-specific predictions. With GBS data, some rule-based methods performed better than model-based approaches for genome-wide predictions, especially for GBS-30K and GBS-50K.

3.4 | Accuracy of Predictions When Founder Allele Frequencies Are Used

Ideally, methods that use allele frequencies in their model should work with founder allele frequencies, but these are rarely available. The cattle data set provides an opportunity to estimate

these founder allele frequencies and to assess the impact of using founder versus sample allele frequencies in these methods. For genome-wide prediction of HBD levels (Figure 6A), the use of founder allele frequencies dramatically increased the correlations obtained with SNP-by-SNP approaches. Significant improvements were also observed for IBD_Haplo9c (using unphased data), which achieved similar accuracy to IBD_Haplo15c (using phased data). When using commercial genotyping arrays, the performance of the other methods was unaffected or slightly affected at low-marker density (e.g., ZooRoH). With GBS data, large and modest improvements were observed for ZooRoH-1R and IBD_Haplo15c, respectively. Nevertheless, ZooRoH-1R was still less accurate than the other ZooRoH models. For locus-specific predictions, the allele frequencies used had little effect, and we did not observe any changes in performance (Figure 6B).

3.5 | Direct Estimation of Relatedness Between the Parents

The expected inbreeding coefficient of an individual is equal to the relatedness coefficient between its parents. Similarly, the prediction of HBD segments in the offspring is closely related to the identification of IBD segments between the parents. Thus, our evaluation procedure also provides indirect information on the accuracy of estimation of IBD segments and relatedness between parents. In simulated data, it is possible to directly assess the efficiency of the same methods for estimating relatedness. We therefore took advantage of our simulations to compare the accuracy of relatedness measures (see Figure S15). The ranking of the methods was the same as for the prediction of HBD levels, but with higher levels of accuracy and smaller differences between methods. The higher accuracy may be due to the fact that there is unpredictable random variation associated with Mendelian sampling in predicting HBD levels, a feature not present in kinship estimation. Interestingly, the pedigree-based approach was also less accurate for kinship because it can only estimate expected relatedness, whereas molecular-based estimators estimate realised relatedness.

4 | Discussion

4.1 | Benefits of Real and Simulated Data for Evaluation

We herein used simulations and empirical comparisons with two real data sets, corresponding to a typical livestock species and a wild population in a conservation programme, to evaluate the accuracy of different approaches used to predict HBD levels in future offspring of a pair of genotyped parents, important information for the management of these populations. The two types of data set we used are complementary. The

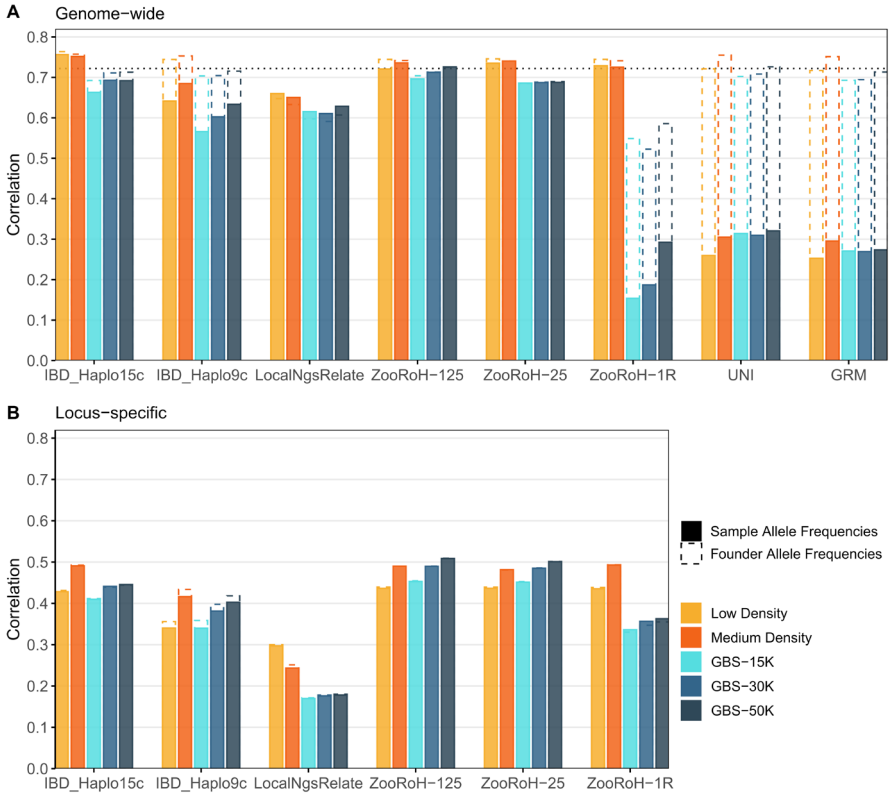

FIGURE 6 | Impact of using founder versus sample allele frequencies on correlations between predicted and reference genome-wide (A) and locus-specific (B) HBD levels in the cattle data set, for the methods described in Table 1 that accept external allele frequencies as input. Reference inbreeding was estimated using the intermediate base population $\hat{F}_{MID}$. Correlations are shown for different marker panels including low-density, medium-density, and GBS panels with different number of markers. Correlations are compared for predictions computed using founder versus sample allele frequencies. The horizontal dashed line is the correlation obtained with the pedigree.

true HBD levels are known in the simulations, whereas more realistic conditions are obtained with real data sets. These include levels of relatedness in the sample, past demographic history, genome and LD structure, distribution of MAF, effects of past and ongoing selection, levels of genotyping and phasing errors. Evaluations of prediction methods on both types of data showed the same trends in terms of ranking the methods, indicating that the empirical analysis of real data was informative. The two real data sets had different structures. Mexican Wolves had higher inbreeding levels and a smaller sample size, which could affect, for example, the accuracy of phasing and allele frequency estimation. These would be the typical field conditions in conservation genetics or studies of wild fauna. The use of small samples might also increase the impact of random variation in method comparisons. The cattle population had the advantage of containing more whole-genome sequenced individuals, providing more information on the true inbreeding levels. In general, valuable information is available in livestock populations, including deep and accurate pedigrees, a good reference genome and genetic maps, that are important to identify IBD segments (see also Bosse et al. 2015). Genotyping marker arrays are also available at different densities and the reference genome allowed us to simulate GBS data, although these were probably cleaner than real GBS data. This illustrates that data available from livestock populations might be useful to study techniques that will be applied in molecular ecology. Here, we had access to a relatively large sequenced pedigree including many trios, as needed for our study.

4.2 | Relative Performance of Evaluated Methods

Using these data sets, we evaluated 16 methods for predicting HBD levels in the offspring of genotyped parents (see Figure S16 for a condensed comparison across all scenarios). Importantly, we showed that this evaluation is also informative about the accuracy of the methods for estimating relatedness and identifying IBD segments. Such estimators are useful in more applications than the prediction of HBD levels, including, for example, diversity management, selection or control for population structure.

4.2.1 | Performance of Best Model-Based Approaches

In terms of accuracy, IBD_Haplo15c and multiple HBD class ZooRoH models (ZooRoH-MixKL) were consistently among the most accurate. IBD_Haplo15c is the most complex model-based approach as it models the 15 identity states, while ZooRoH-MixKL, designed to estimate HBD levels within individuals, conceptually has two main states (HBD and non-HBD) but adds an additional layer of complexity by partitioning HBD into different length-based classes. Both methods outperformed the best rule-based methods when information was reduced, at lower marker density and for locus-specific predictions. This behaviour has previously been described for reduced marker panels in Lavanchy and Goudet (2023), at lower marker densities (Solé et al. (2017); Druet et al. (2020)) and for locus-specific estimation of HBD levels (Alemu et al. 2021). Such locus-specific predictions could be useful for managing identified recessive deleterious alleles that cause genetic defects, loci that are major contributors to inbreeding depression, predicted harmful mutations, or for maintaining heterozygosity at specific loci that should have high diversity, such as the major histocompatibility complex. This could be particularly valuable in managing populations derived from a few founders with fully characterised genomes, including at deleterious loci. This information could also be used to reduce future HBD levels more specifically for regions predicted to contribute to genetic load (Bertorelle et al. 2022), as neutral diversity may not always be representative of extinction risk (Teixeira and Huber 2021). Locus-specific HBD predictions could also be used to manage inbreeding and diversity at all loci simultaneously, using algorithms that optimise all loci together. Finally, deviations between predicted and observed locus-specific HBD levels may also reveal segregation biases, due for example to a recessive lethal variant.

4.2.2 | Behaviour of Best Rule-Based Approaches

For genome-wide HBD predictions and with our parameter settings, phasedibd (minimum 50 SNPs), PLINK-ROH (minimum 40 SNPs) and, to a lesser extent, hap-IBD (minimum 100 SNPs) were also very accurate. Nevertheless, the performance of PLINK-ROH and hap-IBD decreased in some configurations, for example at low-marker density for PLINK-ROH which may be even less accurate in the presence of genotyping errors. Phasedibd performed well in most scenarios and thus represents an excellent option for genome-wide predictions, combining accuracy and computational efficiency. Here we have focused on small samples of interest in conservation genetics and wildlife, where model-based approaches are still applicable, but this may not be the case for larger data sets or at higher marker densities (biobanks and large livestock populations). However, these rule-based approaches were less accurate for locus-specific predictions, especially with the genotyping arrays.

4.2.3 | Ranking of Other Methods

The other methods evaluated were less accurate in most scenarios, although they could perform well in some rare exceptions. In addition, many of them had high variability and therefore performed particularly poorly in some configurations. The SNP-by-SNP approaches did not perform well in all configurations, especially with sample allele frequencies, and only provide genome-wide predictions, but they have the advantage of being applicable with sub-optimal genome assemblies or without a genetic map.

4.3 | Method Features Affecting Predictions Accuracy

4.3.1 | Use of Phased Data and Estimation of Allele Frequencies

The use of phased data achieved higher accuracy than the use of genotypes, despite possible errors introduced during the phasing process, consistent with the findings of Gómez-Romano

et al. (2016). This was also the case for (real) small data sets, where phasing errors are expected to be more common. Interestingly, we observed no differences in accuracy using true versus estimated haplotypes at the genome-wide level, and only minor differences for locus-specific predictions (Figure S17). However, accurate statistical phasing is not always possible, e.g., when physical or genetic marker maps are not available or with low-fold sequencing data (genotypes are not unambiguously known). Among the methods evaluated, LocalNgsRelate was the only one to handle low-fold sequencing data. This feature could also be added to other model-based methods using unphased data (e.g., IBD_Haplo9c).

Several methods, including the SNP-by-SNP approaches, were sensitive to the allele frequencies used. In agreement with theoretical expectations and the study by Caballero et al. (2022), better estimators were obtained with founder allele frequencies. Interestingly, the performance of IBD_Haplo9c (using unphased data) increased close to that of IBD_Haplo15c (using phased data). This suggests that when phasing accuracy is compromised, such as with smaller datasets or low-fold sequencing data, methods that work with unphased data may be a good option if founder allele frequencies are available, but this is unfortunately rarely the case. Here we used the gene content approach, which requires a relatively large genotyped sample and a deep pedigree, which are rarely available in conservation genetics or wildlife. Conversely, it also shows that when founder allele frequencies are not known, it is better to rely on a method using phased data. Overall, several methods were robust to the allele frequencies used, including obviously the rule-based approaches, but also IBD_Haplo15c and ZooRoH-MixKL. It should be noted that the allele frequencies used had only a marginal impact on the accuracy of locus-specific HBD predictions, which depend more on the homozygosity of the markers around the target position.

4.3.2 | Rule-Based Methods Parameters

We observed that better results were obtained with the rule-based methods for which we reduced the minimum number of SNPs required per IBD segment. Setting this threshold to 50 allowed shorter IBD segments (e.g., 5 Mb) to be captured, whereas only long segments (> 10 Mb) could be captured with the default settings (> 100 SNPs) due to our moderate marker densities, which were lower than those typically used in human studies. We subsequently compared the performance of several rule-based methods with default or adjusted parameters (Table S6) and found that methods were better with adjusted parameters. For example, hap-IBD performed as well as phasedibd when using at least 50 SNPs per IBD segment. This shows that adjustment of parameters is essential in similar populations. Overall, it confirms that the accuracy of rule-based methods depends on the selection of optimal parameters, which ideally should be modified and validated for each new dataset. Here, we used default parameters as much as possible, but in some cases, we had to use less stringent parameters. However, we do not recommend the use of such loose parameters without careful prior validation (e.g., on simulated data mimicking the characteristics of the sample being analysed). This also means that when interpreting the relative performance of methods, we should not exclude the possibility that some methods may perform better with different parameters, although finding the optimal parameters is not always trivial and ultimately depends on the ability of the users to select good values. Conversely, the model-based approaches require less parameter definition and adapt better to different data sets. For instance, the parameters were not modified at low-marker density.

4.3.3 | Features of Model-Based Approaches

Different characteristics of model-based approaches may also impact their efficiency. First, we observed that the 3-STATES models were not among the best methods. This suggests that the assumption that the parents were non-inbred is not optimal in populations with small N_e. Locus-specific coancestry and predicted HBD levels are indeed reduced if we ignore that the haplotypes from one or both parents are IBD (e.g., the maximum value drops from 1 to 0.5), and this can have a significant impact in inbred populations. Second, using fixed parameters defining the frequency of IBD (as in IBD_Haplo) or the length of IBD segments (as in IBD_Haplo or ZooRoH-MixKL) did not result in worse performance than estimating these parameters (as in GIBDLD or LocalNgsRelate). Finally, for the ZooRoH models, we observed that multiple HBD class models were more robust to variable marker density or assumed allele frequencies than single-class models. This is consistent with the observation that pruning strategies are recommended with single HBD-class HMMs (Leutenegger et al. 2003; Narasimhan et al. 2016; Vieira, Albrechtsen, and Nielsen 2016), whereas this is not required with a ZooRoH-MixKL model (Druet and Gautier 2017). Nevertheless, the ZooRoH-1R performed well with the LD and MD genotyping arrays.

4.4 | Performance of Pedigree-Based Predictions

We observed that in some configurations, pedigree-based predictions of HBD levels performed well compared to methods using molecular data. This is different from estimating individual levels of inbreeding, where genomic estimators proved superior (Keller, Visscher, and Goddard 2011; Wang 2016). In this situation, molecular data allow estimation of realised HBD levels, whereas the pedigree-based approach is limited to expected levels because it cannot predict Mendelian sampling. In the prediction context, both pedigree- and marker-based approaches are unable to predict Mendelian sampling and therefore achieve more similar accuracies. The pedigree-based approach thus becomes more competitive for predicting recent HBD levels (since pedigrees only capture recent generations), especially when the accuracy of molecular-based approaches decreases, such as with LD marker arrays, some GBS panels, unavailable founder allele frequencies (for some methods) and inaccurate phasing. These results are in agreement with Woolliams and Meuwissen (2022), who suggested that the pedigree-based approaches could be a good option for genetic diversity management. However, the pedigree-based estimators require that the genealogy is accurately and deeply recorded, which is not always possible, particularly in wild populations. This argues for recording pedigrees as well as possible for population management, even when molecular data are available (Galla et al. 2022).

Author Contributions

Tom Druet, Natalia Soledad Forneris and Mathieu Gautier conceived the research and designed the experiments. Natalia Soledad Forneris performed the analyses. Tom Druet and Natalia Soledad Forneris drafted the manuscript. All authors interpreted the results and contributed to the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The real data sets used in this study were previously generated and made publicly available by other contributors. The raw sequence from the DAMONA pedigree was submitted by Lee et al. (2023) to the European Nucleotide Archive (ENA; https://www.ebi.ac.uk/ena/browser/home) under accession number PRJEB53518/ERA15565221. The list of filtered variants we used is available as Supporting Information in Oget-Ebrad et al. (2022). The Mexican Wolf data set from Fitak, Rinkevich, and Culver (2018a) is available in Dryad: https://doi.org/10.5061/dryad.g68k008 (Fitak, Rinkevich, and Culver 2018b). Scripts used in the present study are available on Github: https://github.com/nsforneris/predHBD.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.