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Potential bias in inbreeding depression estimates when using pedigree relationships to assess the degree of homozygosity for loci under selection

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Abstract A potential bias in estimation of inbreeding depression when using pedigree relationships to assess the degree of homozygosity for loci under selection is indicated. A comparison of inbreeding coefficients based on either pedigree or genotypic frequencies indicated that, as a result of selection, the inbreeding coefficient based on pedigree might not correspond with the random drift of allelic frequencies. Apparent differences in average levels of both inbreeding coefficients were obtained depending on the genetic model (additive versus dominance, initial allelic frequencies, heritability) and the selection system assumed (no versus mass selection). In the absence of selection, allelic frequencies within a small population change over generations due to random drift, and the pedigree-based inbreeding coefficient gives a proper assessment of the accompanying probability of increased homozygosity within a 'replicate' by indicating the variance of allelic frequencies over replicates. With selection, in addition to random drift, directional change in allelic frequencies is not accounted for by the pedigree-based inbreeding coefficient. This result implies that estimation of inbreeding depression for traits under either direct or indirect selection, estimated by a regression of performance on pedigree-based coefficients, should be carefully interpreted.

Key words Inbreeding · Finite-locus model · Selection

Introduction

Two individuals of common ancestry may each carry replicates of genes present in the ancestor and, when mated, they may pass to their offspring genes that are 'identical by descent'. Mating related individuals is called 'inbreeding'. The inbreeding coefficient of an individual is the average probability that two genes at any given locus are identical by descent (Falconer 1989). The average inbreeding coefficient of all individuals in a population expresses the amount of drift in allelic frequencies from a defined base population (Falconer 1989). As a result, inbreeding causes a change in the frequency of heterozygous animals and, therefore, a change (usually considered a reduction) in the mean for traits subject to positive dominance gene interactions: inbreeding depression. A broad survey of the effects of inbreeding on various performance traits in livestock is given by Pirchner (1985).

Models used to estimate inbreeding depression usually include inbreeding as a regression variable. For a model with *nl* unlinked, biallelic loci in gametic-phase equilibrium, the theoretical value of the regression coefficient for inbreeding (Kempthorne 1957; De Boer and Van Arendonk 1992) equals:

$$b = -2 \sum_{k=1}^{nl} p_k q_k d_k$$

where p and q are allelic frequencies and d is the genotypic value of the heterozygote at the kth locus. Early estimates of b were made on an intra-sire basis to account for some of the effects of both genetic and environmental time trends (e.g. Von Krosigk and Lush 1958; Allaire and Henderson 1965). More recently, mixed models have been applied, which correct for environmental trends by considering them as fixed effects (e.g. herd-year-season). Genetic trends are accounted for by random additive genetic effects, including additive genetic relationships (which account for in-

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breeding; Casanova et al. 1992; Miglior et al. 1992), dominance effects, and additive*additive interaction effects (without accounting for inbreeding in the dominance and additive*additive relationship matrices; Miglior et al. 1993). This latter model was shown to yield seemingly unbiased estimates of additive genetic effects (breeding values) in the presence of dominance and inbreeding for both selected and unselected populations (Uimari and Kennedy 1990; De Boer and Van Arendonk 1992; De Boer and Hoeschele 1993; Johansson et al. 1993). However, using stochastic simulation with a finite number of loci, Uimari and Kennedy (1990) and De Boer and Van Arendonk (1992) showed that for populations under selection these models might give estimates of inbreeding depression that do not correspond to theoretical values. This may be because theoretical values assume gametic-phase equilibrium (De Boer and Van Arendonk 1992). Ignoring inbreeding in the dominance-relationship matrix and ignoring covariance between additive and dominance effects also can lead to biased estimates of the dominance effects (Johansson et al. 1993). A third reason might be the inaccuracy of pedigree relationships for determining inbreeding coefficients in the case of loci with alleles under selection. To quote Falconer (1989; p. 85): "When the coefficient of inbreeding is deducted from the pedigrees of real populations, it does not necessarily describe the state of dispersion of the gene frequencies. It is essentially a statement about the pedigree relatiosnships, and its correspondence with the state of dispersion is dependent on the absence of the processes that counteract dispersion, in particular on selection being negligible."

The aim of the present study was to illustrate potential bias in inbreeding depression estimates when using pedigree relationships to assess the degree of homozygosity for loci under selection. The simulation study employed, using a finite-locus model, compared average inbreeding coefficients based on actual genotypic frequencies and those based on pedigree relationships.

Methods

Simulation model

The model simulated genotypic and phenotypic values for a single trait. An animal's genotypic value was the sum of its genetic values for 100 unlinked, biallelic loci. Allelic effects were $(1/2)a$ and $(-1/2)a$. The genotypic value of the heterozygote was d. Thus additive genetic variance is:

$$\sigma_A^2 = \sum_{l=1}^{100} 2pq[a+d(q-p)]^2 \tag{1}$$

where p and q are frequencies of favorable and unfavorable alleles, respectively, in the first generation. A normally distributed environmental effect with standard deviation σ_E was added to each genotypic value such that the narrow-sense heritability (h^2) was 0.30 in the first generation. Each simulation included nine generations. The first contained 75 males and 75 females whose genotypes were randomly generated assuming Hardy-Weinberg proportions and gametic-phase equilibrium, giving initial allelic frequencies (p and q). Genotypes of animals in later generations were simulated from parental genotypes. Selection, either randomly or on basis of own phenotype (mass selection), was both in males and females. The number of selected males (N_m), the number of selected females ($N_{f;m}$), with multiple females mated per male but only one male per female mated, and the number of progeny per mating (N_p), were to maintain a constant population size (150) over generations. The effect of inbreeding level was studied by varying the number of males and females selected. The probability of an offspring to be male or female was 50%.

Inbreeding coefficients

If inbreeding is the only source of disequilibrium, the inbreeding coefficient (f) in a population for a given locus can be estimated from the deviation between the expected ($\hat{x}$) and observed ($\hat{y}$) number of heterozygotes (Curie-Cohen 1982)

$$\hat{f} = (\hat{x} - \hat{y})/\hat{x}. \tag{2}$$

In a biallelic model, let the observed numbers of genotypes in a sample of n be a_{11}, $2a_{12}$ and a_{22} for the favorable homozygote, the heterozygote and the unfavorable homozygote, respectively, then

$$\hat{x} = 2\hat{p}\hat{q}n, \quad \hat{y} = 2a_{12} \tag{3}$$

where

$$\hat{p} = (a_{11} + a_{12})/n, \quad \hat{q} = (a_{12} + a_{22})/n. \tag{4}$$

Equations (2), (3) and (4) can be combined to obtain

$$\hat{f} = \frac{a_{11}a_{22} - a_{12}a_{12}}{(a_{11} + a_{12})(a_{12} + a_{22})}. \tag{5}$$

When information on genotypic frequencies is known for multiple unlinked loci, an averaged f over loci can be derived (e.g. Bumstead et al. 1987). When the expected number of heterozygotes, $\hat{x}$, is based on genotypic frequencies from the same generation for which f is estimated, equation (5) is expected to give non-zero inbreeding only when inbreeding is practiced as a mating system in the previous generation. With random mating in populations of finite size, inbreeding in terms of allelic dispersion can be assessed by using the allelic frequencies of the first generation to estimate expected genotypic frequencies in subsequent generations. In the present study, allelic frequencies in the first generation (for each alternative and replicate sample separately) were used to calculate the expected number of heterozygotes in subsequent generations.

Inbreeding coefficients on the basis of pedigree relationships were computed using the algorithm of Tier (1990). As a reference, a simple prediction of inbreeding trend was considered where N_e is the effective population size and f (averaged over animals) in generation t equals (Falconer 1989)

$$f_t = \frac{1}{2N_e} + \left(1 - \frac{1}{2N_e}\right) f_{t-1}. \tag{6}$$

Alternatives

First, estimated inbreeding coefficients on the basis of genotypic frequencies and pedigree, and the predicted inbreeding coefficient on the basis of effective population size, were compared for a situation with no selection and random mating (assuming $a = 20$, $d = 0$, $h^2 = 0.30$, initial frequency $p = 0.5$) for different effective population sizes N_e: 100 ($N_m = 50$; $N_{f;m} = 1$; $N_p = 6$), 40 (15; 2; 10), and 20 (6; 5; 10). (N.B. derivation of N_e from N_m, $N_{f;m}$, N_p is correct for situations without selection, but is used for situations with selection as well.)

Second, random and phenotypic selection were compared at $N_e = 40$ (initial frequency $p = 0.5$ and $h^2 = 0.3$) under an additive model ($a = 20$ and $d = 0$), partial dominance model (20; 10), a complete dominance model (20; 20) and an overdominance model (20, 80).

The sensitivity of results was tested for alternative heritabilities ($h^2 = 0.5$), and alternative initial frequencies ($p = 0.3$ and $p = 0.7$). Results for each alternative are presented as averages of 30 replicates.

Results

With no selection and random mating, all three methods (genotypic frequencies, pedigree and prediction) showed similar trends in the inbreeding coefficient (Fig. 1). Differences in absolute levels were small. The inbreeding coefficient based on genotypic frequencies gave slightly lower estimates, even negative estimates in early generations. With low true inbreeding coefficients and small sample sizes, equation (5) will tend to slightly underestimate inbreeding coefficients (Curie-Cohen 1982). A decrease in effective population size, as expected, increased inbreeding over generations. In the absence of selection, all three effective population sizes gave average allelic frequencies which were very close to initial frequencies (Table 1). Variances of allelic frequencies increased with increasing generation number and with decreasing effective population size. Random dispersion of allelic frequencies (random drift) is assessed by the inbreeding coefficient. Assessment of random drift on the basis of genotypic frequencies and of pedigree gave similar results, i.e. the pedigree-based inbreeding coefficient can be used to assess the average change in homozygosity relative to a 'base population' associated with random drift.

Effects of mass selection (under an additive model) on inbreeding coefficients are in Fig. 2. Mass selection increased the pedigree-based inbreeding coefficient. Selection reduced effective population size because relatively more parents originated from the same (genetically superior) families (Wray and Thompson 1990). An appar-

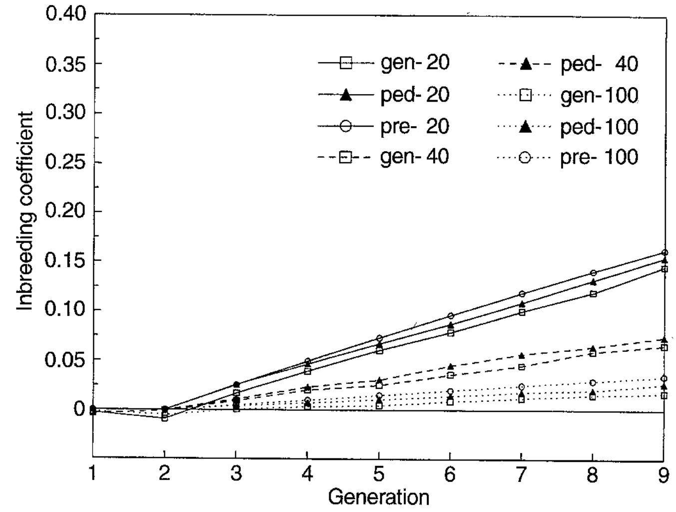

Fig. 1 Inbreeding coefficients per generation based on genotypic frequencies, pedigree and prediction for different effective population sizes (20, 40, 100), no selection, initial frequencies of $p = 0.5$, $h^2 = 0.30$, and an additive model ($a = 20$, $d = 0$)

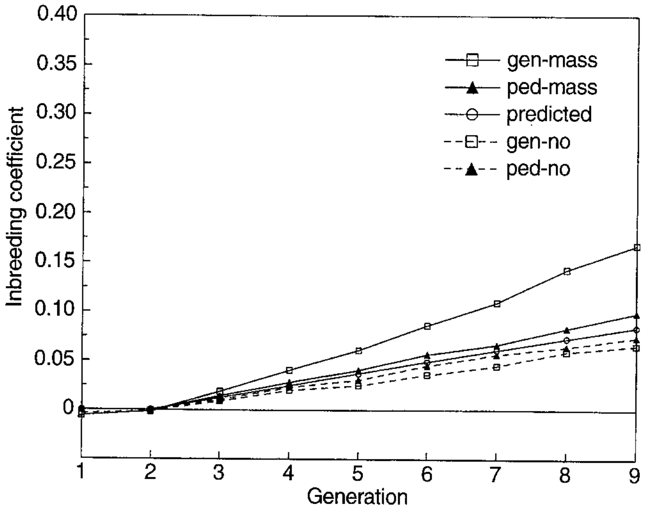

Fig. 2 Inbreeding coefficients per generation based on genotypic frequencies, pedigree and prediction for effective population size 40, mass selection, initial frequencies of $p = 0.5$, $h^2 = 0.30$ and an additive model ($a = 20, d = 0$)

Table 1 Mean allelic frequencies for 3000 loci (100*30 replicates) and empirical variances (in brackets) per generation for varying effective population sizes (initial frequency $p = 0.5$, $h^2 = 0.30$, $a = 20$, $d = 0$)

Generation	No selection			Mass selection		
	Effective population size[a]			Effective population size[a]		
	20	40	100	20	40	100
1	0.500 (0.001)	0.501 (0.001)	0.500 (0.001)	0.499 (0.001)	0.500 (0.001)	0.499 (0.001)
2	0.500 (0.006)	0.500 (0.004)	0.500 (0.002)	0.527 (0.006)	0.520 (0.004)	0.510 (0.002)
3	0.499 (0.012)	0.500 (0.006)	0.500 (0.002)	0.551 (0.012)	0.541 (0.007)	0.519 (0.003)
4	0.501 (0.017)	0.501 (0.009)	0.500 (0.003)	0.572 (0.019)	0.560 (0.010)	0.529 (0.003)
5	0.501 (0.023)	0.502 (0.011)	0.500 (0.004)	0.592 (0.024)	0.579 (0.013)	0.539 (0.004)
6	0.499 (0.027)	0.501 (0.014)	0.500 (0.005)	0.612 (0.029)	0.598 (0.016)	0.548 (0.005)
7	0.500 (0.032)	0.502 (0.016)	0.501 (0.006)	0.633 (0.034)	0.614 (0.019)	0.558 (0.006)
8	0.500 (0.037)	0.503 (0.019)	0.502 (0.007)	0.652 (0.039)	0.631 (0.021)	0.567 (0.007)
9	0.503 (0.042)	0.504 (0.021)	0.502 (0.007)	0.671 (0.043)	0.647 (0.024)	0.575 (0.008)

[a] Derived as $1/N_e = 1/4N_m + 1/4(N_m^* N_{m;f})$, which in theory is only correct with no selection

ent difference between inbreeding coefficients based on genotypic frequencies and pedigree was observed, with the former being higher. An explanation can be found in the average allelic frequencies (Table 1). Variances of allelic frequencies were slightly higher with mass selection than with no selection which is related to the slightly higher pedigree-based inbreeding coefficient. However, with selection there is not only drift in allelic frequencies, there is also a directional change in allelic frequencies. Therefore, the inbreeding coefficient based on pedigree was no longer related to the change in number of homozygous loci.

Changes in allelic frequencies over generations with mass selection were not constant, but slowly decreased. Because σ_E^2 was constant in simulating phenotyic performance over generations and σ_A^2 gradually decreased with changing allelic frequencies [equation (1)], h^2 decreased over generations.

Genetic models with dominance effects should be considered when inbreeding depression is of interest (Fig. 3, Table 2). Pedigree-based inbreeding coefficients decreased slightly with increasing dominance values.

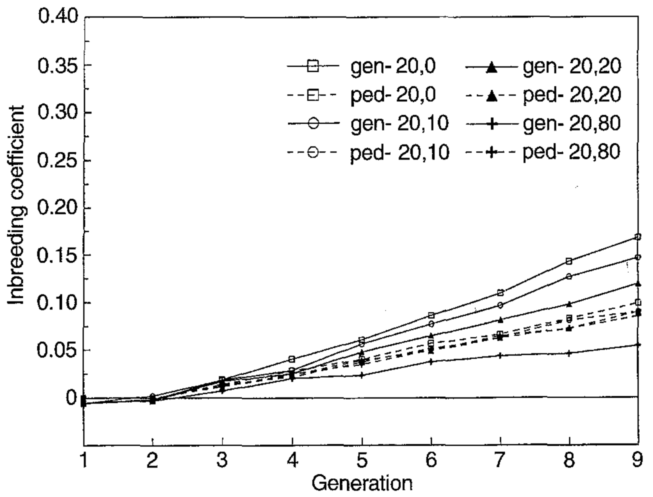

Fig. 3 Inbreeding coefficients per generation based on genotypic frequencies and pedigree for effective population size 40, mass selection, initial frequencies of $p = 0.5$, $h^2 = 0.30$ with an additive model ($a = 20, d = 0$), partial dominance ($a = 20, d = 10$), complete dominance ($a = d = 20$) or over dominance ($a = 20, d = 80$)

With a complete dominance model, as opposed to an additive model, the negative bias in the pedigree-based inbreeding coefficient decreased relative to the in breeding coefficient based on genotypic frequencies. However, there was a positive bias with an overdominance model. The decrease in the pedigree-based inbreeding coefficient was related to a decrease in variance of allelic frequencies with increasing dominance values (Table 2). With an overdominance model and selection, variance in allelic frequencies and inbreeding are lower relative to no selection alternatives. The decrease in inbreeding coefficient based on genotypic frequencies with increasing dominance values might be explained by a smaller effect of selection on the frequency for the beneficial allele from selection (Table 2). However, comparison of these alternatives with the no selection alternative is not obvious. For example, the assumed d-value in the overdominance model did not result in a complete stabilization of allelic frequencies. However, it did result in a reduction in variance of allelic frequencies when compared to the situation without selection (Table 2), and a lower inbreeding coefficient based on genotypic frequencies (0.0542 versus 0.0659 in generation 9). It should be noted, that the additive genetic variance in the first generation was not influenced by d. However, as p changed over generations, the amount of additive genetic variance depended, in addition to other factors, on the magnitude of d [equation (1)].

Changes in inbreeding coefficients with different heritabilities (0.3 versus 0.5) are given in Fig. 4. Higher heritability increased the accuracy of mass selection and, therefore, under a finite-locus model, resulted in greater changes in allelic frequencies. As a result, the difference between inbreeding values based on pedigree and genotypic frequencies increased with increasing heritability.

Figure 5 gives inbreeding coefficients with different initial frequencies ($p = 0.3$, $p = 0.5$, or $p = 0.7$). The pedigree-based inbreeding coefficient was not influenced by initial frequency. With an initial frequency of the beneficial allele of less than 0.5, selection resulted in increasing frequencies of the heterozygote (at generation 9, p was 0.447). Therefore, in this situation the inbreeding coefficient of genotypic frequencies was found to be negative.

Table 2 Mean allelic frequencies for 3000 loci (100*30 replicates) and empirical variances (in brackets) per generation for varying genetic models ($N_e = 40^a$, initial frequency $p = 0.5$, mass selection, $h^2 = 0.30$)

Generation	No selection	Mass selection			
	Additive $a = 20; d = 0$	Additive $a = 20; d = 0$	Partial dom. $a = 20; d = 10$	Compl.dom. $a = 20; d = 20$	Over dom. $a = 20; d = 80$
1	0.501 (0.001)	0.500 (0.001)	0.500 (0.001)	0.500 (0.001)	0.500 (0.001)
2	0.500 (0.004)	0.520 (0.004)	0.522 (0.004)	0.520 (0.003)	0.512 (0.003)
3	0.500 (0.006)	0.541 (0.007)	0.542 (0.006)	0.538 (0.006)	0.522 (0.006)
4	0.501 (0.009)	0.560 (0.010)	0.560 (0.009)	0.554 (0.009)	0.531 (0.007)
5	0.502 (0.011)	0.579 (0.013)	0.579 (0.011)	0.571 (0.011)	0.539 (0.009)
6	0.501 (0.014)	0.598 (0.016)	0.596 (0.014)	0.586 (0.012)	0.547 (0.011)
7	0.502 (0.016)	0.614 (0.019)	0.611 (0.016)	0.599 (0.014)	0.555 (0.012)
8	0.503 (0.019)	0.631 (0.021)	0.627 (0.018)	0.614 (0.016)	0.559 (0.013)
9	0.504 (0.021)	0.647 (0.024)	0.643 (0.020)	0.627 (0.017)	0.565 (0.013)

[a] Derived as $1/N_e = 1/4N_m + 1/4(N_m^* N_{m;f})$, which in theory is only correct with no selection

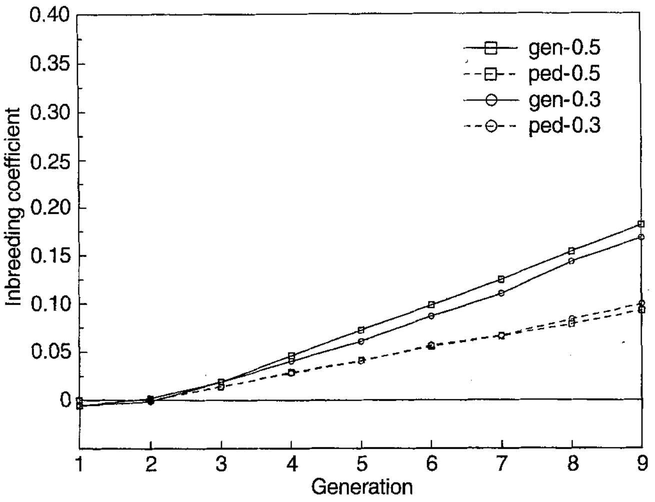

Fig. 4 Inbreeding coefficients per generation based on genotypic frequencies and pedigree for effective population size 40, mass selection, initial frequency $p = 0.5$ with a partial dominance model ($a = 20, d = 10$), and with different heritabilities (0.3 versus 0.5)

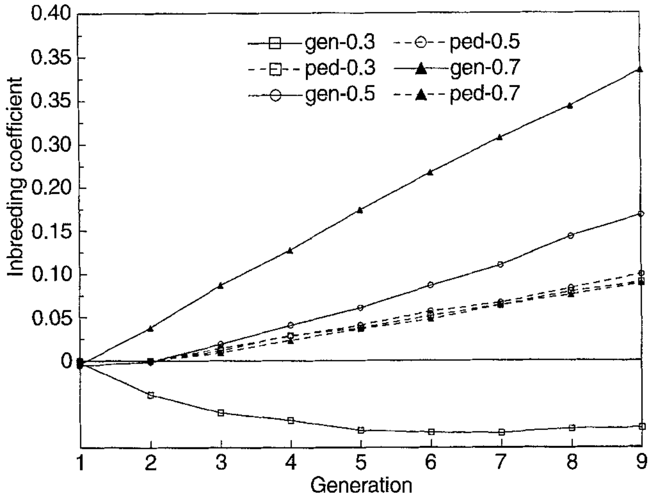

Fig. 5 Inbreeding coefficients per generation based on genotypic frequencies, pedigree and prediction for effective population size 40, mass selection, and a partial dominance model ($a = 20, d = 10$) with different intial frequencies ($p = 0.5, 0.3$, or 0.7)

A high initial frequency of the beneficial allele considerably increased inbreeding based on genotypic frequencies.

The distribution of inbreeding coefficients over loci is illustrated in Fig. 6. In the base generation, the average inbreeding coefficient is zero, where non-zero values originate from the sampling of animals. Figure 6 indicates that the inbreeding coefficients based on genotypic frequencies tend to be normally distributed, with the variance increasing with increasing mean. The distribution of inbreeding coefficients over animals based on pedigree is illustrated in Fig. 7. In the base generation, by definition all animals have zero inbreeding coefficient. With an increasing mean-inbreeding coefficient over generations, the variance of the distribution increases, but the distribution is very skewed.

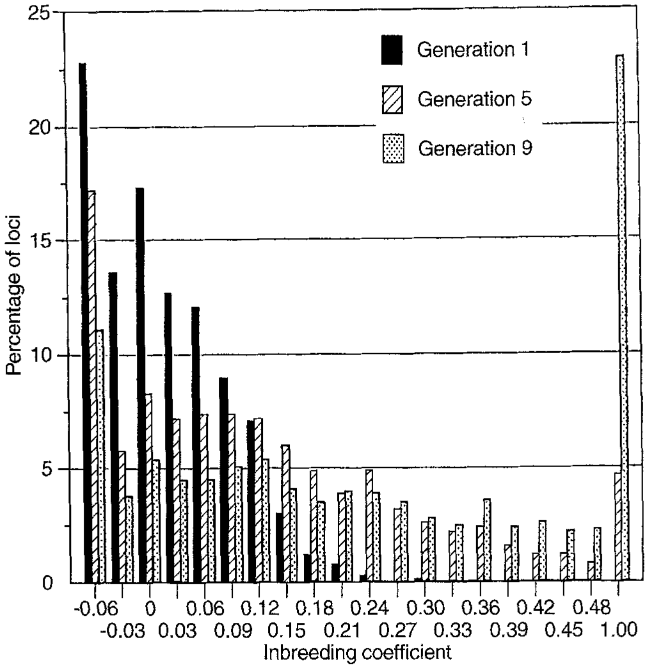

Fig. 6 Distribution of inbreeding coefficients per locus based on genotypic frequencies, in first, fifth and ninth generations with effective population size of 20, mass selection, initial frequencies of $p = 0.5$, $h^2 = 0.3$ and an additive model ($a = 20, d = 0$)

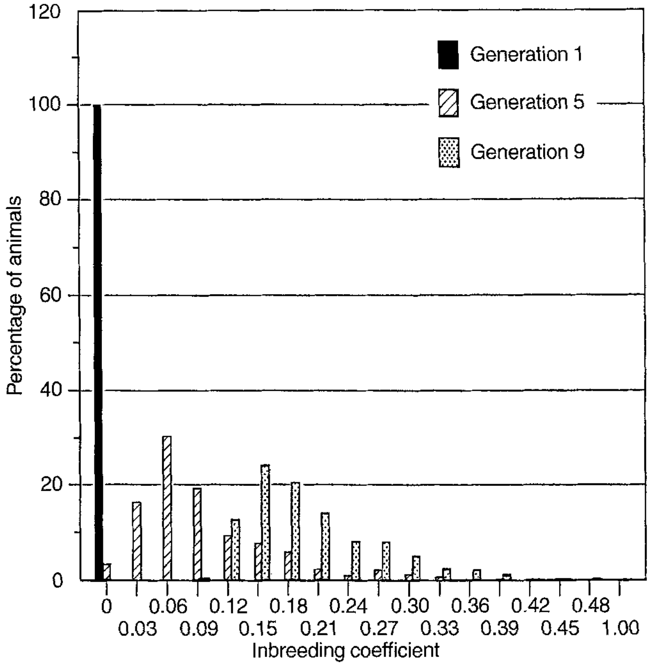

Fig. 7 Distribution of inbreeding coefficients per animal based on pedigree in first, fifth and ninth generation with effective population size of 20, mass selection, initial frequencies of $p = 0.5$, $h^2 = 0.3$ and an additive model ($a = 20, d = 0$)

Discussion

The aim of this study was to illustrate potential bias in estimation of inbreeding depression when using pedigree relationships to assess the degree of homozygosity for loci under selection. The statement by Falconer (1989; p. 85), that the inbreeding coefficient based on pedigree as a result of selection might not correspond to a random drift of allelic frequencies, was illustrated by comparing inbreeding coefficients based on pedigree and on genotypic frequencies. Apparent differences in average levels of both inbreeding coefficients were obtained depending on the genetic model (additive versus dominance, initial allelic frequencies, heritability) and the selection system assumed (no versus mass selection). In the absence of selection, allelic frequencies within a small closed population change over generations due to random drift. The pedigree-based inbreeding coefficient gives a proper assessment of the accompanying probability of increased homozygosity within a 'replicate' by indicating the variance of allelic frequencies over replicates. With selection, however, there is a directional change in allelic frequencies, in addition to random drift, which is not accounted for by the pedigree-based inbreeding coefficient. This result implies, that estimates of inbreeding depression for traits under either direct or indirect selection should be carefully interpreted. It is not possible to quantify the actual degree of bias, as both the genetic model and the selection history cannot be quantified. Pedigree-based inbreeding coefficients, of course, can be used for traits not under selection in a given population.

In this study (Tables 1 and 2), empirical variances of allelic frequencies [$V(q)$] were determined. Theoretically, with no selection $V_t(q) = p_0 q_0 F_t$ (Falconer 1989). This equation was used with both pedigree- and genotype frequency based inbreeding coefficients. With no selection, $p_0 = 0.5$ and $N_e = 40$, the use of both inbreeding coefficients slightly underestimated observed variances (-0.002 to -0.004). The predictive value of this equation for situations with selection is worse, as expected from the increase in F with selection (Fig. 2): biases up to $+0.018$.

The model used in this study had a finite number of loci, as did the model used by Uimari and Kennedy (1990) and De Boer and Van Arendonk (1992). Using pedigree-based inbreeding coefficients with selection, both Uimari and Kennedy (1990) and De Boer and Van Arendonk (1992) reported an over-estimation of inbreeding depression with an initial frequency $p < 0.5$, no apparent bias with $p = 0.5$ and under-estimation with $p > 0.5$. These results correspond with results from this study as presented in Fig. 5. With $p = 0.3$, the genotype-based inbreeding coefficient is lower than the pedigree-based inbreeding coefficient. Now, with the 'true' (genotype) F lower than the assumed (pedigree) F, the regression coefficient b is over-estimated in the analysis. The empirically measured bias in inbreeding depression shown with selection under finite-locus models can be explained by the inappropriate use of pedigree-based inbreeding coefficients to assess relative changes in homozygosity. Under an infinitesimal model, selection is assumed not to influence allelic frequencies. In that case the results of this study will not be applicable. The question of whether or not an infinitesimal model is a correct starting point when assuming non-additive genetic effects was recently discussed by Smith and Mäki-Tanila (1992).

The present study focussed on differences in average levels of inbreeding coefficients over generations and on the distribution of inbreeding coefficients (over loci or over animals) within a generation. This study illustrated a potential bias in estimated inbreeding depression due to a bias in the average inbreeding level within a population, assuming that differences in inbreeding coefficients between generations are reflected properly in differences in inbreeding coefficients between individuals within a generation. Our study did not consider the relation between the pedigree-based inbreeding coefficient (probability of increased homozygosity) and the true level of homozygosity on an individual basis. With random mating this relation might be close to 1, but selection might disturb this relation depending on the true genetic model. Natural or artificial selection might give rise to increased fitness (e.g. relatively within full-sib groups) of animals with lower true levels of homozygosity. Thus, in practice the probability of increased homozygosity on the basis of pedigree information might be systematically over-estimated for those animals that have a high probability. This point requires further research.

In this study simulated distributions are given. Comparison with experimentally observed distributions (e.g., Allarie and Henderson 1965; Miglior et al. 1992) is difficult because in practice overlapping generations exist. It is important to recognize that the pedigree-based inbreeding coefficient will not be normally distributed and, at low levels of inbreeding, a majority of animals will not be inbred.

The pedigree-based inbreeding coefficient is used in breeding value estimation. Studies by Uimari and Kennedy (1990) and De Boer and Van Arendonk (1992) have shown that mixed models, using dominance effects (without accounting for inbreeding in the relationship matrix) and a regression on inbreeding, yield seemingly unbiased estimates of breeding values for selected and unselected populations. The inbreeding coefficient is also used to optimize breeding programmes with regard to the expected level of additive genetic response and its variance (i.e. risk) considering population size (Meuwissen 1991; Meuwissen and Woolliams 1994), selection system (Goddard and Smith 1990; Woolliams and Meuwissen 1993), or mating system (Toro and Perez-Enciso 1990). These studies used pedigree-based inbreeding coefficients. The most stringent restriction on the rate of inbreeding in practical breeding programmes may be imposed by inbreeding depression on fitness traits (Meuwissen and Woolliams 1994). In many practical situations fitness traits are not under artificial selection, so that the use of the pedigree-based inbreeding coefficient in optimization studies following the principle of limiting inbreeding depression on fitness might be justified. Optimizing breeding programmes by adjustment of the economic value of the additive response for the effect of inbreeding depression on traits under selection (Goddard and Smith, 1990) might be inappropriate if a pedigree-based inbreeding coefficient is used.

Conclusion

For (simulation) models assuming a finite number of loci, thereby allowing allelic frequency changes due to selection, the pedigree-based inbreeding coefficient does not give an appropriate assessment of the average change in homozygosity for loci under selection relative to a base population. Therefore, the use of pedigree-based inbreeding coefficients to estimate inbreeding depression for traits under selection is potentially biased. The practical value of these findings depends on the true underlying genomic model. As this model is seldom known, caution should be used in interpreting estimated inbreeding depression for traits under selection.

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