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Evaluation of ancestral inbreeding coefficients: Ballou's formula versus gene dropping

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Abstract Estimation of the purging of detrimental effects through inbreeding and selection is an important issue in conservation genetics opening new perspectives for the management of small populations. In 1997 Ballou proposed the ancestral inbreeding coefficient, which is calculated recursively via pedigree inbreeding coefficients, as a tool for evaluating the purging of deleterious alleles in zoo populations. The formula of Ballou assumes independence of inbreeding and ancestral inbreeding coefficients at any stage of the recursion. This study investigates the consequences of this inaccuracy on the estimation of true ancestral inbreeding, i.e. the proportion of alleles within a genome that has undergone inbreeding in the past. As an alternative we propose the estimation of ancestral inbreeding by the method of gene dropping. The methods are compared by stochastic simulation for various models with respect to mode of inheritance (neutral, detrimental and lethal alleles) and different settings for population size and initial allele frequencies. In all scenarios the proportion of alleles within a genome that has undergone inbreeding in the past was overestimated by Ballou's formula. The overestimation was more pronounced in smaller populations but was not affected by genetic model or initial allele

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frequency. In contrast, the ancestral inbreeding coefficient calculated by gene dropping provided a robust estimate of ancestral inbreeding in most models and settings. A marginal overestimation was observed only in models with lethal alleles. Therefore, we recommend applying the gene dropping approach to estimate ancestral inbreeding coefficients.

Keywords Ancestral inbreeding \cdot Inbreeding depression \cdot Genetic load \cdot Purging \cdot Stochastic simulations

Introduction

Inbreeding depression, or the deterioration of traits closely related to fitness proportional to the increase in inbreeding, is a widely observed phenomenon in nearly all diploid species investigated (Wright 1977; Lynch and Walsh 1998; Hedrick and Kalinowski 2000). The magnitude of inbreeding depression effects is considerable and for small populations inbreeding is considered as a major risk factor (Frankham et al. 2001). Unfortunately, inbreeding is unavoidable in populations of small effective size due to mating of related individuals. Thus, purging of detrimental effects through inbreeding and selection is an important issue in conservation genetics opening new perspectives for the management of small populations.

The most referred experimental evidence showing the magnitude and effectiveness of purging for plants comes from the study of Byers and Waller (1999) and for animals from the studies of Ballou (1997) and Templeton and Read (1984). While the study of Templeton and Read (1983, 1984) has been a subject

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of continuous debate (Hedrick 1994: Willis and Wiese 1997; Templeton and Read 1998; Kalinowski et al. 2000), this was not the case for the method applied in Ballou (1997). To test the magnitude and effectiveness of purging of inbreeding depression, Ballou (1997) derived a coefficient (ancestral inbreeding coefficient) intended to estimate ancestral inbreeding as the extent to which individual's ancestors have been subjected to inbreeding. The basic idea behind his method was that an inbred individual with inbred ancestry should be less susceptible to inbreeding depression than an inbred individual with noninbred ancestors because surviving and reproducing inbred ancestors are less likely to be carriers of deleterious alleles. Further, in a regression model, Ballou (1997) tested the interaction between inbreeding and ancestral inbreeding effects on fitness traits as an evidence of purging. In the model applied, positive interaction is the evidence of purging effects.

In this study, we analysed the properties of the ancestral inbreeding coefficient as defined by Ballou (1997) to estimate ancestral inbreeding. The analysis was based on a computer simulation and considered various models with respect to mode of inheritance (neutral, detrimental and lethal alleles) and different settings for population size and initial allele frequencies. We also proposed calculation of ancestral inbreeding coefficient by the method of gene dropping as an estimator of ancestral inbreeding. The properties of this "new" ancestral inbreeding coefficient were tested and compared with Ballou's ancestral inbreeding coefficient over all models and settings previously analysed.

Theoretical concept of ancestral inbreeding

Ballou's approach

According to Ballou (1997) the ancestral inbreeding coefficient (f_a) is calculated as follows:

$$f_{a} = [f_{a(s)} + (1 - f_{a(s)})f_{s} + f_{a(d)} + (1 - f_{a(d)})f_{d}]/2$$
(1)

where f_a is the ancestral inbreeding coefficient for an individual, f is the inbreeding coefficient. The subscripts s and d represent these values for the sire and dam, respectively. Ballou (1997) defined f_a as the cumulative proportion of an individual's genome that has been previously exposed to inbreeding in its ancestors. Ballou's coefficient for ancestral inbreeding can be interpreted as the probability that an individual inherits an allele which has undergone inbreeding in the past at least once.

Identity by descent (IBD) alleles in the parental generation and alleles having undergone IBD status in ancestral generations contribute to nonzero f_a values. Following this concept f_a can be derived as:

$$f_{a} = [(f_{a(s)} \cup f_{s}) + (f_{a(d)} \cup f_{d})]/2$$
(2)

where $(f_{a(s)} \cup f_s)$ and $(f_{a(d)} \cup f_d)$ are the probabilities of an allele in the sire's and dam's genome being either in IBD status or having undergone IBD in the sire's and dam's ancestors, respectively. When extended by a term for the joint probability of f_a and f in the parental generation, necessary to avoid double counting, the formula has to be written as follows:

$$f_{a} = [f_{a(s)} + f_{s} - (f_{a(s)} \cap f_{s}) + f_{a(d)} + f_{d} - (f_{a(d)} \cap f_{d})]/2$$
(3)

By rewriting Ballou's original formula (1) we see that f_a and f are assumed being independent:

$$f_{a} = [f_{a(s)} + f_{s} - f_{a(s)}f_{s} + f_{a(d)} + f_{d} - f_{a(d)}f_{d}]/2$$
(4)

Considering f_a and f as nonindependent the correct formula must be changed to:

$$f_{a} = [f_{a(s)} + f_{s} - (f_{a(s)}|f_{s})f_{s} + f_{a(d)} + f_{d} - (f_{a(d)}|f_{d})f_{d}]/2$$
(5)

Note that for two independent events E_1 and E_2 the joint probability, $Pr(E_1 \cap E_2)$, is calculated as $Pr(E_1)Pr(E_2)$ while in case of dependence the joint probability equals to $Pr(E_2)Pr(E_1|E_2)$ or $Pr(E_1)Pr(E_2|E_1)$.

Gene dropping approach

To overcome the pitfalls in Ballou's formula we propose a modified version of the gene dropping method developed by MacCluer et al. (1986). This method is based on the idea of gene flow through a pedigree introduced by Edwards (1968). Two unique alleles are assigned to each founder, and the genotypes of all descendants along the actual pedigree are generated following Mendelian segregation rules. To adapt the approach to the calculation of ancestral inbreeding coefficients, one needs to keep track of IBD events in the pedigree of an individual. This is done by flagging alleles once they are in IBD state for the first time. The gene dropping process is repeated 500 times.

This allows simulating for each animal a genome where the number of repetitions refers to the number of diallelic unlinked loci. The proportion of already flagged alleles out of all loci in an individual genome is

2 1 4 3
7 8 5 6
9 10
11 12
$$\cdots$$
 $f = 0.125$ $f_{a_{-}g} = 0.000$ $f_{a_{-}b} = 0.000$
13 14 \cdots $f = 0.313$ $f_{a_{-}g} = 0.125$ $f_{a_{-}b} = 0.125$
15 16 \cdots $f = 0.438$ $f_{a_{-}g} = 0.375$ $f_{a_{-}b} = 0.399$
17 19 18 20 \cdots $f = 0.547$ $f_{a_{-}g} = 0.585$ $f_{a_{-}b} = 0.662$
21 22 \cdots $f = 0.633$ $f_{a_{-}g} = 0.728$ $f_{a_{-}b} = 0.847$
23 \cdots $f = 0.633$ $f_{a_{-}g} = 0.822$ $f_{a_{-}b} = 0.944$

Fig. 1 Small pedigree illustrating the calculation of ancestral inbreeding coefficients according to gene dropping approach (f_{a_g} —1,000,000 repetitions) and Ballou's formula (f_{a_b}), and inbreeding coefficients (f)

considered as its ancestral inbreeding coefficient. Alleles which are identical by descent for the first time are flagged and contribute to ancestral inbreeding coefficient of offspring. A small example for ancestral inbreeding coefficients derived by gene dropping approach (1,000,000 repetitions) and Ballou's formula (1) for a small pedigree is shown in Fig. 1.

Simulation

Mating scheme and procedure

A simulation study (Fortran90) was carried out for three different breeding population sizes (15, 30 or 60) with a sex ratio of 1:2 each. For the first parental generation potential parents were drawn randomly from a base population of unrelated animals. The size of this base population was 50, 100 or 200 for the different breeding population sizes. Each selected dam was mated randomly to one of the potential sires and gave birth to five offspring. From the produced offspring animals were chosen randomly as potential parents for the next generation and mated as described above. A 100 repetitions repeating the selection and mating procedure over 40 discrete generations were carried out.

Genetic model

We considered a genome including 500 fitness loci, each with two alleles, A and a. All loci were assumed to be unlinked and to segregate independently. One allele (a) was considered completely recessive (h = 0). Three genetic models were investigated: neutral (s = 0), detrimental (s = 0.15) and lethal (s = 1), where s is the coefficient of selective against aa and h is the level of dominance of a. Relative viability values of 1, 1 - hs, and 1 - s were assigned to the genotypes AA, Aa and aa, respectively. We assumed that selection occurs in the diploid stage of the life cycle and that different loci act multiplicatively in determining viability. Therefore, the viability of an individual is the product of its 500 relative viability values. The survival of an individual was determined by comparison of its viability with a randomly drawn number from a uniform distribution. The individual survived viability selection if the random number was smaller than its individual viability or died otherwise. In total, there were 18 scenarios with regard to breeding population size (15, 30 or 60), initial allele frequency (0.01 or 0.005 for allele a) and genetic model (s = 0, s = 0.15 or s = 1).

Validation of ancestral inbreeding coefficients

We calculated three different inbreeding coefficients. Ballou's ancestral inbreeding coefficient (f_{a_b}) was derived according to Eq. (1). The parental inbreeding coefficients required by the formula were calculated using the tabular method (Tier 1997).

In addition, ancestral inbreeding coefficients based on the gene dropping method were estimated as described above (f_{a_g}) . The true proportion of alleles of an individual, that has undergone IBD in the past at least once (f_{a_t}) serves as comparative value. Correlations between f_{a_t} and true inbreeding coefficients (f_t) defined as the true proportion of autozygous loci in an individual's genome (Baumung and Sölkner 2003) were used to show the relationship between ancestral inbreeding and inbreeding coefficients. To compare different estimators, the mean error (ME), mean deviation between estimated ancestral inbreeding coefficients and true ancestral inbreeding coefficient (also sometimes called bias) and the mean square error (MSE) were calculated within generation.

In all scenarios, the results presented refer to means and standard deviations across 100 repetitions.

Results

Ballou's ancestral inbreeding coefficient versus true ancestral inbreeding

 and initial allele frequencies (results for an initial allele frequency 0.005 are not shown), $f_{a_{-t}}$ evolved similarly over time. The comparison of $f_{a_{-t}}$ with ancestral inbreeding coefficients based on Ballou's formula $f_{a_{-b}}$ revealed an overestimation of the true proportion of the ancestral inbred part of the genome in all scenarios. Overestimation, e.g. the deviation of $f_{a_{-b}}$ from $f_{a_{-t}}$, occurred and disappeared earlier in smaller populations but reached a higher maximum (Fig. 2). Initial allele frequencies and genetic model did not influence duration and magnitude of the overestimation. Table 2 shows the positive mean error for $f_{a_{-b}}$.

Relationship between inbreeding and ancestral inbreeding coefficients

The correlation between f_t and f_{a_t} within each generation was calculated to show whether inbreeding and ancestral inbreeding coefficients are independent events. On average the correlation between f_{a_t} and f_t was positive and higher in smaller populations. Table 3 shows arithmetic mean, median and standard deviation for the mean correlation coefficients within generation over all 100 repetitions. Further, it could be shown that there is a nonlinear relationship between true inbreeding and ancestral inbreeding coefficients. In Fig. 3, true inbreeding coefficients and true ancestral inbreeding coefficient from 100 repetitions averaged within generations are plotted against each other. A nonlinear Richards function (Richards 1959) fitted the data well.

Table 1 True ancestral inbreeding coefficient $(f_{a.t})$, mean ancestral inbreeding coefficient according to Ballou $(f_{a.b})$ and derived via gene dropping method $(f_{a.b})$ shown as mean over 100

Ancestral inbreeding coefficient estimated by gene dropping versus true ancestral inbreeding

The ancestral inbreeding coefficient derived by the gene dropping method (f_{a_g}) was identical to the true ancestral inbreeding coefficient (f_{a_t}) in the neutral model and almost equal to detrimental models for all population sizes and initial allele frequencies. However, in the case of lethal allele models, f_{a_g} overestimated the true level of ancestral inbreeding marginally (Table 1).

Mean error (ME) and mean square error (MSE) within generation are shown in Table 2. The mean square error for f_{a_g} is almost zero. A higher number of repetitions of the gene dropping procedure (10,000 instead of 500) lead to a further reduction of MSE.

Discussion

The genetic models assumed in our study are comparable to models used for investigation of purging effects. The number of lethal equivalents considered here were 2.5 and 5 for lethal cases (s = 1) and 2.125 and 4.25 for detrimental cases (s = 0.15) for the initial allele frequencies of 0.005 and 0.01, respectively. The number of lethal equivalents is agreement with literature (e.g. Hedrick 1994; Fu et al. 1998).

Interestingly, Ballou's paper (1997) has been cited about 50 times, but ancestral inbreeding coefficients were rarely calculated. In Ballou's formula ancestral inbreeding and inbreeding are considered being independent events. Our results show that this assumption does not hold. The positive correlation found between

repetitions (*standard deviation in italic*) for neutral, detrimental and lethal allele model with an initial allele frequency of 0.01

Generation	Neutral		Detrimental			Lethal		
	f _{a_t}	fa_b	$f_{\mathrm{a_t}}$	$f_{\mathrm{a_b}}$	$f_{\mathrm{a_g}}$	fa_t	$f_{\mathrm{a_b}}$	$f_{\mathrm{a_g}}$
Population size	50							
5	0.270	0.288	0.257	0.276	0.262	0.221	0.239	0.229
	0.058	0.066	0.054	0.060	0.055	0.046	0.049	0.044
10	0.642	0.724	0.632	0.720	0.639	0.625	0.719	0.636
	0.045	0.057	0.043	0.052	0.042	0.049	0.053	0.043
20	0.941	0.993	0.939	0.993	0.941	0.942	0.995	0.945
	0.010	0.003	0.011	0.003	0.010	0.011	0.002	0.009
Population size	200							
5	0.078	0.079	0.073	0.076	0.074	0.057	0.060	0.059
	0.018	0.018	0.016	0.017	0.017	0.011	0.011	0.011
10	0.261	0.277	0.256	0.272	0.257	0.233	0.251	0.239
	0.027	0.029	0.023	0.025	0.023	0.020	0.021	0.019
20	0.643	0.720	0.641	0.718	0.643	0.630	0.714	0.637
	0.021	0.024	0.018	0.020	0.017	0.017	0.020	0.017



Fig. 2 Mean error for ancestral inbreeding coefficients according to Ballou $(f_{a,b})$ and true ancestral inbreeding coefficients $(f_{a,l})$ for the lethal allele model with an initial allele frequency of 0.01

 $f_{a_{-t}}$ and f_t can be explained by the decreasing variability of allele origin per locus and generation. Due to the increasing proportion of alleles fixed via IBD over time the joint probability for f_a and f increases as well. In addition, the error in Ballou's formula accumulates over generations because of the recursive calculation method. Interestingly, population size has not only an influence on the temporal occurrence of overestimation but also on its magnitude. This is corresponding with higher positive correlations between inbreeding and ancestral inbreeding coefficients in smaller populations. All population sizes investigated were quite

Table 2 Mean error (ME) and mean square error (MSE) for ancestral inbreeding coefficients according to Ballou (f_{a_b}) and derived via gene dropping method (f_{a_g}) based 500 or 10,000

small, which might be justified by the fact that ancestral inbreeding and its possible effect on purging is of specific interest in small endangered populations.

Instead of deriving a new deterministic formula gene dropping method was adopted to derive reliable ancestral inbreeding coefficients. Due to the nonlinear relationship between ancestral inbreeding coefficients and inbreeding coefficients, a simple formula for calculation of ancestral inbreeding coefficients with universal validity for different mating and selection systems cannot be derived. However, the stochastic method of gene dropping provides a good and applicable estimator of ancestral inbreeding.

Gene dropping has been applied to analyse allele survival in animal populations (MacCluer et al. 1986; Princee 1988; Haig et al. 1990; Toro et al. 2000; Honda et al. 2002) and to estimate the probability for the occurrence of homozygous lethal genotypes (*LL*) at any locus (Ballou 1997). However, only one study was found where gene dropping was used to estimate ancestral inbreeding (Kalinowski et al. 2000), but f_a was not defined in the sense of Ballou (1997) as a cumulative proportion. The authors used the simulated gene transmission to estimate the proportion of an animals' genome that is currently in IBD status and had been IBD in an ancestor of the animal. They split the standard inbreeding coefficient into two parts, alleles which had undergone inbreeding in the past and

gene drops. Errors	are shown as mean	over 100 repetitions
(standard deviation	in italic) for populat	tion size of 100 and
detrimental allele m	odel with an initial allo	ele frequency of 0.005

Generation	Mean error	(ME)		Mean squared error (MSE)			
	fa_b	$f_{a_{-g}}(500)$	$f_{a_g}(10^4)$	f _{a_b}	$f_{a_{g}}(500)$	$f_{a_{g}}(10^{4})$	
5	0.0053	0.0020	0.0014	0.0007	0.0088	0.0006	
	0.0084	0.0088	0.0081	0.0001	0.0001	0.0004	
10	0.0396	0.0011	0.0004	0.0024	0.0010	0.0008	
	0.0130	0.0124	0.0115	0.0017	0.0001	0.0004	
20	0.0920	0.0019	0.0013	0.0087	0.0004	0.0003	
	0.0081	0.0089	0.0073	0.0018	0.0001	0.0002	

Table 3 Arithmetic mean, median and standard deviation over 100 repetitions for correlation coefficients between true ancestral inbreeding coefficients ($f_{a.t}$) and true inbreeding coefficients (f_t)

within single generations for the neutral allele model with an initial allele frequency of 0.01

Generation	Population size								
	50			100			200		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
5	0.082	0.091	0.388	0.058	0.060	0.276	0.049	0.006	0.184
10 20	0.125	0.130	0.344	$0.110 \\ 0.107$	0.109	0.236	0.068	0.054	0.146



Fig. 3 Non linear relationship between true ancestral inbreeding coefficients $(f_{a,t})$ and true inbreeding coefficients (f_t) for the detrimental allele model with initial allele frequency of 0.005 and population size of 100. Full line presents Richards curve of the relationship while dots represent average values within generations

alleles identical by descent for the first time. This definition of f_a seems to be useful especially for completely recessive deleterious or lethal alleles. For genetic models assuming other levels of dominance Ballou's approach is more suitable, because heterozygous loci might influence an individual's fitness as well. Therefore we propose to use gene dropping to derive ancestral inbreeding according to the definition of Ballou (1997).

Our study revealed a marginal overestimation of ancestral inbreeding for the lethal models. This can be explained by the fact that alleles are assumed being neutral to selection in the gene dropping procedure. Therefore, homozygosity in surviving animals is overestimated. However, the average levels of true ancestral inbreeding and estimated ancestral inbreeding are almost the same in detrimental and neutral models for initial allele frequencies and population sizes investigated. Mean squared errors are 20 to 30 times higher for ancestral inbreeding coefficients calculated with Ballou's formula compared to gene dropping. These results indicate that gene dropping provides robust estimates for ancestral inbreeding if the genetic basis of inbreeding depression is caused by a combination of large and small effect alleles, as supported by literature (Charlesworth and Charlesworth 1987; Hedrick 1994; Wang et al. 1999).

The extent of potential bias as illustrated by a small example (Fig. 1) is quite likely to appear in experimental studies based on full-sib matings (e.g. mice and Drosophila). Thus, when ancestral inbreeding coefficients are used to estimate purging inbreeding depression we recommend the application of the gene dropping approach presented in this study.

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