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ORIGINAL ARTICLE

Restricting inbreeding while maintaining selection response for weight gain in *Mus musculus*

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Summary

An experiment with mice was designed to test the relative efficiency of three selection methods that help to minimize the rate of inbreeding during selection. A common house mice (*Mus musculus*) population was selected for 17 generations to increase the weight gain between 21 and 42 days. The population was split at random into three lines A, B and C where three selection methods were applied: individual selection and random mating, weighted selection with random mating and individual selection with minimum coancestry mating, respectively. There were three replicates for each line. Cumulated selection response was similar in the three lines, but there were differences in the level of inbreeding attained (in percentage): 31.24 (method A), 24.72 (method B) and 27.88 (method C). As consequence, lines B and C (weighted selection and minimum coancestry) showed a lower value of deterioration of fitness traits (the intrauterine mortality and the mortality at birth) than line A (random mating).

Introduction

Growth is an economically important trait in livestock species. Body weight at a given age and weight gain at a given period of time have an important economic impact on animal production. Given some genetic control of growth, it should be possible to change growth rate by artificial selection. Realized heritability for postweaning gain (ranging from 0.3 to 0.4) and realized genetic correlations for postweaning gain and body weight (ranging from 0.7 to 0.9) have been reported in the classic studies reviewed by Malik (1984).

Response to selection depends on the additive genetic variability (or on the heritability) of the traits under selection, which contributes to phenotypic variation, but also by changes in fitness that accompanies selection. Several studies relate the weight gain under selection to the deterioration of fertility and prolificacy (Ríos *et al.* 1986; Gaskins *et al.* 2005), being attributed partially to the effect of inbreeding depression. Thus, the combined effects of selection and inbreeding must be considered when analysing responses to selection experiments.

In fact, in a population under artificial selection, the effective population size will be lower than that expected under no selection because the parents with a higher breeding value will have a higher chance of contributing than those with a lower breeding value. Moreover, the probability of coselecting relatives as parents is higher than under no selection (Robertson 1961; Bijma *et al.* 2001). In addition, because the harmful effects of inbreeding on fitness are well known, it is desirable to maintain the rate of inbreeding as low as possible.

In recent years, considerable work has been carried out on the design of strategies that maintain genetic diversity in selection and conservation

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programmes. These strategies are aimed at simultaneously optimizing genetic gain and inbreeding, either by reducing the rates of inbreeding while keeping genetic gains at the same level or by increasing selection response under a restriction on inbreeding. Different methods are available (Toro & Nieto 1984; Toro & Pérez-Enciso 1990; Villanueva *et al.* 2004). One of the strategies is to act on the number of selected individuals and their contributions to the next generation (see Fernández & Toro 1999 and references therein). The idea of modifying the contribution of the selected individuals of one generation to the evaluated individuals of the next generation was first proposed by Toro & Nieto (1984) under the name of weighted selection. In a conventional selection process, the top N individuals of each sex are selected and each pair makes an identical contribution to the individuals scored in the next generation (w_i = constant). In the weighted selection method, a larger number of pairs (N') may be selected, with each pair making unequal offspring contributions, while maintaining the same selection differential. From all possible values of N' and w_i, we must choose those resulting in minimizing genetic drift (maximizing effective population size). Because this parameter is inversely proportional to Σw_i^2, the problem is reduced to minimize the last quantity, subject to the restriction of a fixed selection differential. Meuwissen (1997) presented the most sophisticated version of this idea that he called optimal contribution theory. Instead of minimizing genetic drift, the problem to be solved is the optimal contributions of the candidates to selection, which can be related or unrelated, so as to maximize genetic gain with restrictions on ΔF.

Another methodology was proposed by Wright (1921) for regular systems of mating under the name of maximum avoidance of inbreeding. Similarly, in a selected population of any size and structure, the strategy becomes the so-called minimum coancestry mating design (Nieto *et al.* 1986) that aims to find, through optimization techniques, for the scheme yielding the minimum global average pairwises coancestry coefficient between the sires and the dams that are going to be mated.

In a random mating population, average inbreeding and coancestry coefficients will increase with generations such that $f_t = F_{t+1}$. But with non-random mating, the two parameters, coancestry and inbreeding, are decoupled (recall that inbreeding coefficient in the offspring is just the coancestry coefficient of parents being mated). Thus, avoiding the mating between relatives will delay the rising of inbreeding but will increase the rate of coancestry and therefore will increase the long-term rate of both inbreeding and coancestry.

The relative efficiency of these methods has been evaluated using simulation (Nieto *et al.* 1986; Toro *et al.* 1988a; Toro & Pérez-Enciso 1990; Caballero *et al.* 1996; Meuwissen 1997; Grundy *et al.* 1998; Fernández & Toro 1999) and selection experiments with *Drosophila melanogaster* (Nieto *et al.* 1986; Sánchez *et al.* 1999) concluding that these methods contribute to the minimization of inbreeding in selection process. However, experiments using laboratory mammals are actually necessary. The mouse is a good mammalian model because results of genetic experiments carried out in mice can be more easily extrapolated to sheep, pigs and rabbits (Hill & Caballero 2000).

The objective of this work was to analyse the relative efficiency of three selection methods: method A (individual selection and random mating), method B (weighted selection and random mating) and method C (individual selection and minimum coancestry mating) for the trait weight gain between 21 and 42 days (WG) using a laboratory mouse population with high genetic variability.

Material and methods

Populations and data source

The common house mice (*Mus musculus*) population used in this study proceeds from a three-way cross of inbred lines (BALB/c, CBA and C57BL) and posterior panmixia for six generations to dilute heterosis effects, in which pedigrees were not recorded. At generation 00, 72 males were mated with two females each to obtain 144 litters. Two males from each litter constitute the generation 0 of selection experiment, and 32 of them were assigned randomly to each of the three methods of selection and the three replicates per method (32 × 3 × 3 = 288). All litters were standardized to eight pups at birth. Selection was carried out for 17 generations, which leads to 18 generations of records. The generations were discrete and the 3 lines × 3 replicates/line were contemporary. Within line and replicate, a total of 32 males (two per litter) were performance-tested for weight gain between 21 and 42 days (WG) and those with the largest WG were selected. Each selected male was mated with two females. Females were not evaluated but were chosen at random, one per litter. A more detailed explanation of the selection methodology follows:

Method A: Individual selection was carried out selecting eight males of 32 evaluated according to their performance. Mating was at random but avoiding brother–sister mating, and each selected male contributed equal number of offspring (4 ♂) to the next generation. The 16 females needed to be mated to the 8 males were taken one per litter. The predicted selection intensity in males for this method was 1.235, and the effective population size of the breeding population was $N_e = 19.8$.

Method B: In this case, 12 males were selected of 32 evaluated and their offspring contribution (w) were calculated such that Σw_i^2 was minimum maintaining the selection differential (Toro & Nieto 1984). The 12 selected males contribute to the next generations based on performance, $w_1 = 6$ ♂, $w_2 = w_3 = 4$ ♂, $w_4 = w_5 = w_6 = 3$ ♂, $w_7 = w_8 = w_9 = 2$ ♂ and $w_{10} = w_{11} = w_{12} = 1$ ♂, being the total contribution of 32 males from 24 litters. It can be calculated that the expected selection intensity on males was $\sum w_i s_i / 32$, where s_i is the ith order statistics of the standard normal distribution. This results in a value of 1.248, very similar to previous method, 1.235 based on order statistics in a population of size 32. The 24 females need to be mated to the 12 males were taken one per litter. The expected population sizes calculated following Nieto *et al.* (1986) were $N_e = 31.5$, greater than method A.

Method C: This is essentially analogous to A, but in the selected population (eight sires and 16 dams), matings occur among the least related animals. This was implemented using linear programming techniques (Toro *et al.* 1988a).The expected selection intensity and effective population size will be the same as in method A.

Throughout the experiment, the mice were maintained under laboratory conditions with temperature at 20–24°C and given pellet feed and water *ad libitum*. The whole data set finally consisted of 5273 records of WG in males and 9152 individuals in the whole pedigree file.

Statistical analysis

The model used to estimate genetic parameter$_{\text{s}}$ and predict genetic values of WG was the classical additive genetic model:

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{Wc} + \mathbf{e}$$

The sampling distribution of the data vector $\mathbf{y}$ given the unknown parameters is assumed to be the normal process

$$\mathbf{y}|\mathbf{b}, \mathbf{u}, \mathbf{c}, \sigma_e^2 \tilde{N}(\mathbf{Xb} + \mathbf{Zu} + \mathbf{Wc}, \mathbf{I}\sigma_e^2),$$

where $\mathbf{y}$ is a vector containing the WG of 5273 individuals; $\mathbf{b}$ is a vector that contains the mixed-method replicate-generation systematic effect with 163 levels (18 generations, three selection methods and three replicates by method = 18 × 3 × 3 and one level for founder population); $\mathbf{u}$ is the vector of direct additive genetic effects (9152 levels); $\mathbf{c}$ is the vector of litter effects (2649 levels); $\mathbf{e}$ is the vector of residual effects (5273 levels); $\sigma_e^2$the residual variance; $\mathbf{X}$, $\mathbf{Z}$ and $\mathbf{W}$ are known incidence matrices and $\mathbf{I}$ the identity matrix.

The distributions assumed *a priori* for the additive effects $\mathbf{u}$, litter effects $\mathbf{c}$ and residual effects $\mathbf{e}$ were independently normal distributions, i.e.: $\mathbf{u}|\mathbf{A}, \sigma_u^2 \sim N(\mathbf{0}, \mathbf{A}\sigma_u^2)$, $\mathbf{c}|\sigma_c^2 \sim N(\mathbf{0}, \mathbf{I_c}\sigma_c^2)$ and $\mathbf{e}|\sigma_e^2 \sim N(\mathbf{0}, \mathbf{I_e}\sigma_e^2)$, where $\mathbf{A}$ is the known additive relationship matrix and $\mathbf{I}$ the identity matrix. The vector $\mathbf{b}$ was assigned bounded uniform prior distribution and the variance components σ_u^2, σ_c^2 and σ_e^2 scaled inverted chi-squared distributions ($v = -2$ and $S = 0$).

Bayesian inference via Markov chain Monte Carlo (McMC) methods was used to analyse the data. The fully conditional distributions were normal for $\mathbf{b}$, $\mathbf{u}$ and $\mathbf{c}$ and inverted chi-square for the variances σ_u^2, σ_c^2 and σ_e^2. Marginal posterior distributions of all unknowns were estimated using the Gibbs sampling algorithm. After exploratory analyses, we used a single chain with a total of 500 000 samples, after a burn-in period of 50 000. Only one sample of 50 was saved to avoid the high correlation between consecutive samples. Convergence was tested separately for all dispersion parameters using the Raftery & Lewis (1992) algorithm and the Z criterion of Geweke (1992). Effective sample size was evaluated using the method of Geyer (1992), and Monte Carlo sampling errors were computed using the time-series procedures described by Geyer (1992). The Gibbs sampling process was adequate. Posterior distributions for all unknown parameters exhibited a Monte Carlo error of <0.001, and the Geweke test did not detect any lack of convergence.

A maternal genetic effect was not explicitly fitted in the model even though ignoring it might affect the estimation of the genetic variability of the direct effect if there was a genetic correlation between them. However, previous analysis on performances, fitting together both litter and maternal genetic effects, showed that the first one was carrying all the variability explained by the second one as the maternal genetic variance become null when litter effects were included. Thus, maternal influence cannot be considered as totally ignored in the model, but fitted to a large extent through the litter effect.

Selection responses per generation were obtained from regression of phenotypic means pooled across replicates on generations. Genetic trends were obtained from regression of genetic values on generation number in which the animal was born.

A genealogical analysis was carried out to calculate the inbreeding and coancestry coefficients. Inbreeding depression was evaluated at the end of experiment (generation 17) by evaluating the effect of inbreeding on the fitness traits intrauterine mortality and mortality at birth. Intrauterine mortality was evaluated by mating each male with an extra female, coming from the same lines and generation. Caesareans were practised on day 20 of pregnancy, and the percentage of foetus reabsorbed from total foetus implanted was calculated. The mortality at birth was simply the percentage of offspring born dead.

Program used for the analysis

The inbreeding analyses were performed using the endog program (current version v4.6), which can be freely downloaded from the World Wide Web at http://www.ucm.es/info/prodanim/html/JP_Web.htm. We have developed the software required to estimate the genetic parameters and the breeding values and the software to implement minimum coancestry matings using linear programming techniques.

Results

The variance component estimates for weight gain in the whole experiment are shown in Table 1 together with their 95% highest posterior density interval. All components can safely be assumed to be different from zero. The value of phenotypic variance was 3.74 and the variance of litter component (1.44) was twice as large as the additive genetic component (0.69), although it must be taken into account that the litter component also includes the maternal component.

The mean weight gain between 21 and 42 days (WG) estimated from 328 males in generation 1 was 12.96 ± 0.13 g, which indicates the there was a significant response to selection. After 17 generations of selection, it was 18.36 ± 0.09 g. The phenotypic mean for weight gain within replicates and within selection lines across generations is summarized in the Figure 1, as well as the means pooled over replicates within methods. From generation 0 to generation 1, there was no selection and the mean decreased probably by drift or by some uncontrolled environmental effect. From generation 1 to generation 2, the phenotypic means also decrease but afterwards the mean increases steadily although the magnitude of the response decreased after the eighth generation. The patterns of response to selection were very similar for the three methods, and the differences between them were not relevant. Moreover, the responses under the three selection methods attain the same final values. For the first eight generations, the average phenotypic means increase by approximately 0.47 g per generation. After generation eight, the magnitude of selection response trend decreases to 0.13 g per generation although the management was the same throughout the experiment. The rate of weight gain for the

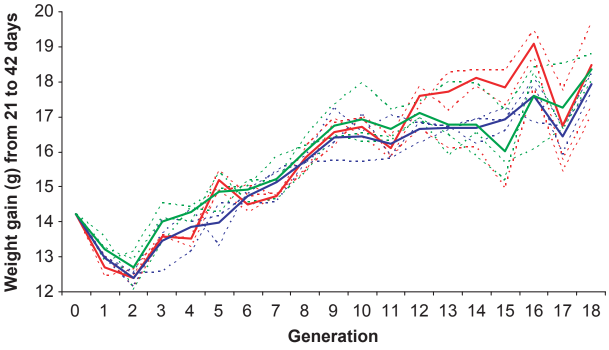

Figure 1 Trend in the phenotypic means of weight gain between 21 and 42 days (WG), plotted by generation of selection and averaged within methods A (red), B (blue) and C (green). Dotted lines are trends by replicates.

Table 1 Monte Carlo estimates of posterior means and 95% highest posterior density intervals (in square brackets) of variance components

σ^2_a	σ^2_c	σ^2_e	σ^2_p	h^2	c^2
0.69 [0.29–1.00]	1.44 [1.25–1.64]	1.61 [1.39–1.82]	3.74 [3.55–3.93]	0.18 [0.08–0.28]	0.38 [0.33–0.43]

σ^2_a, additive genetic variance; σ^2_c, litter variance; σ^2_e, residual variance; h^2, heritability; c^2, ratio between litter environmental variance (σ^2_c) and total phenotypic variance (σ^2_p).

whole experiment when averaged over all generations was approximately 0.34 g per generation.

Genetics trends are shown as the average of the BLUP values within selection method (Figure 2). Similar genetic progress results were obtained using the three selection methods. Although in most generations the method C ranks below A and B, the posterior distributions of the means indicate that the difference among them is not significant. In the last generation, for example, the differences in average genetic values among the three methods and their high posterior intervals were 0.37 (−0.48, 1.27), 0.63 (−0.36, −1.63) and 0.26 (−0.62, 1.17) for A–B, A–C and B–C, respectively. Regression coefficients of genetic trends on generations were 0.17, 0.16 and 0.15 for methods A, B and C, respectively, whereas the phenotypic trends were 0.29, 0.27 and 0.28, the differences between both trends being attributed to environmental trends. These results were expected because the same selection differential was applied in the three lines. Cumulated selection differential in males over generations was (in g) 34.41 ± 1.51 (method A), 33.97 ± 0.81 (method B) and 32.79 ± 1.48 (method C), respectively. Considering the two sexes, the values were around 17 g. There was a reasonable agreement between average selection differential per generation (17 g/17 generations), heritability (0.18) and average genetic response (0.16 g).

The trend of mean coancestry and mean inbreeding by generation is shown in Figure 3. The trend of mean coancestry that measures one minus the amount genetic diversity maintained shows that for all the selective process, method B maintains more genetic variability, the average rates of coancestry per generation being 2.0, 1.4 and 1.7% for methods A, B and C, respectively. The evolution of mean inbreeding that reflects the homozygosity by descent follows a similar trend. The average rates of inbreeding per generation were 1.9, 1.4 and 1.7% for methods A, B and C, respectively, almost identical to the rates of coancestry although there is a delay in the appearance of inbreeding, as expected. Overall, the introduction of minimum coancestry mating or the use of weighted selection resulted, at the end of the selection experiment, in a lower value of the inbreeding level than the practice of the random mating selection: 31.24 (Method A), 24.72 (Method B) and 27.88% (Method C).

This lower rate of inbreeding when using methods B and C was accompanied by a lower deterioration of fitness traits at the end of experiment (generation 18). The evaluation of fitness traits is presented in Table 2. Both B and C methods of selection were accompanied by lower fitness deterioration than A: intrauterine mortality was significantly lower in line B ($p < 0.05$) and C ($p < 0.01$) and mortality at birth

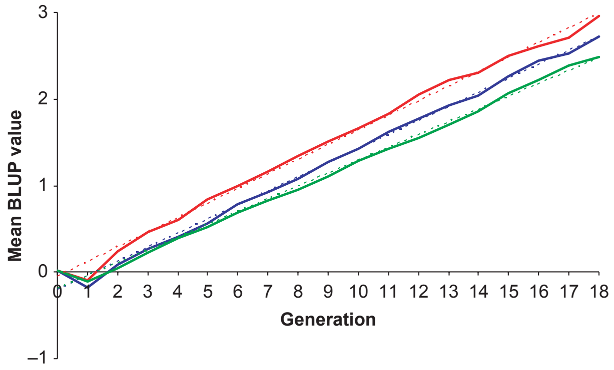

Figure 2 Average genetic trends across three replicates of weight gain between 21 and 42 days (WG) in lines A (red), B (blue) and C (green), plotted by generation of selection. Dotted lines are linear trends.

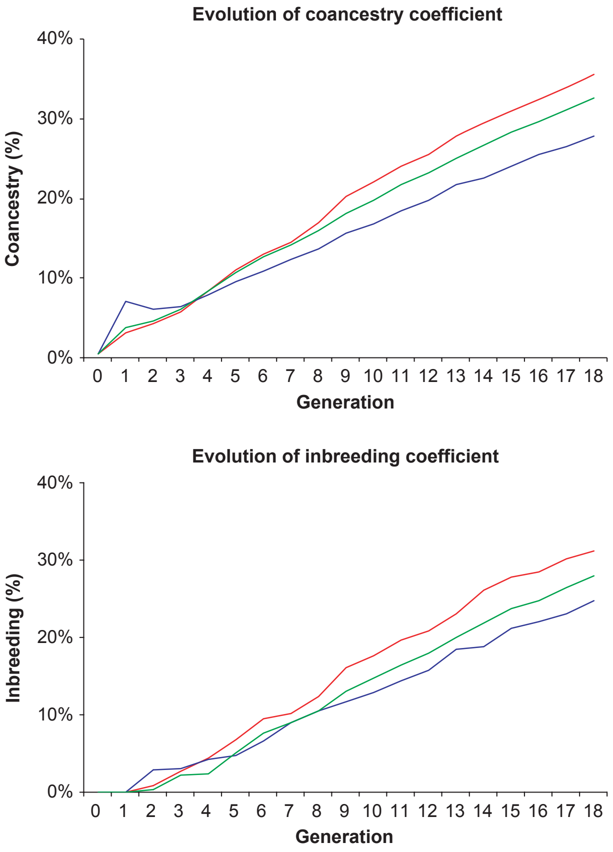

Figure 3 Trends of inbreeding and coancestry coefficients throughout generations in the three methods of selection in lines A (red), B (blue) and C (green).

Table 2 Values of fitness traits at the end of selection process

Fitness traits	Random mating	Weighted selection	Minimum coancestry mating
Intrauterine mortality	19.16	12.27	6.18
Birth mortality rate (in %)	9.05	4.85	4.46

A, random Mating; B, weighted Selection, C, minimum coancestry mating; IMR, intrauterine mortality; BMR, birth mortality rate (in percentage).

was also significantly lower in line B ($p < 0.01$) and C ($p < 0.01$).

Discussion

For the trait studied in this paper, weight gain between 21 and 42 days, approximately 18% of the phenotypic variance can be attributed to additive genetic effects and 38% to litter effects, although the latter could also include maternal effects. These genetic parameter estimates showed that heritability was lower than those reviewed by Malik (1984), reported by Eisen & Prasetyo (1988) and in a classical paper by Falconer (1953). This lower heritability might be explained with the current model if maternal and direct effects are negatively correlated.

The three selection methods show similar selection response although there are some statistical problems in disentangling the environmental and genetic trends with the design used where maternal and litter effects are partially confounded. However, the important point is that methods B and C were able to restrict inbreeding in a more effective way.

The influence of a limited population size on the selection response has been extensively studied (Hill 1986). In particular, the inclusion of information from relatives in selection decisions has some undesirable consequences (Toro *et al.* 1988b) because the probability of coselecting related individuals, and therefore, the rate of inbreeding will be higher. In recent years, considerable work has been done on the design of strategies to maintain genetic diversity in selection programmes. These strategies are aimed at optimizing both genetic gain and inbreeding, either by reducing the rates of inbreeding while keeping genetic gains at the same level or by increasing selection response under a restriction on inbreeding. Following Toro & Pérez-Enciso (1990), these strategies can be classified into three groups depending on the selection criterion used, the number of selected individuals and their contribution to the next generation and the mating system imposed. Here, we have tested the latter two.

Because the idea of managing genetic contributions of the selected individuals to the evaluated individuals of the next generation was proposed under the name of weighted selection (Toro & Nieto 1984), there have been important theoretical developments. The most efficient way of managing genetic contributions is what it has been called selection with optimal contributions (Meuwissen 1997). The strategy looks by looking for the set of contributions that maximize genetic gain but with a restriction in the global coancestry of the candidates weighted by those particular contributions.

On the other hand, avoiding mating between relatives will delay the rise of inbreeding. This is the rationale of the so-called minimum coancestry mating design (Nieto *et al.* 1986) that searches, through optimization techniques, for the scheme yielding the minimum global coancestry between couples. In the short term, it is obvious that forcing mating between relatives will increase the average inbreeding in the population, and the opposite will occur if matings between relatives are avoided. However, in the long term, the effects can be the same or the opposite depending on the variance in family size. If, for example, there is no variance in family sizes, inbreeding will be larger in the short term but smaller in the long term (Caballero & Toro 2000). In animal breeding, because short-term inbreeding may have negative consequences in terms of inbreeding depression, avoidance of matings between relatives may be more appropriate. In our results, the level of inbreeding attained was lower in C than in A as expected in a context where there is variance in family size and where there is not a long-term perspective.

The potential usefulness of all these methods has been shown mainly by computer simulation (Toro *et al.* 1988a,b; Meuwissen 1997; Grundy *et al.* 1998; Fernández & Toro 1999). The weighted selection method has also been compared with classical truncation selection in an experiment using *Drosophila* (Nieto *et al.* 1986). After 13 generations, the two methods achieve the same selection response, but fitness deterioration was lower in the line selected with the weighted method (less percentage of matings without offspring and less replicates lost). The present experiment differs from the previous one in several aspects: in the species utilized, in the trait measured, in the selection pressure applied and in the inclusion of a new method of minimum coancestry mating.

There is currently some discussion about the value of selection experiments (see Hill 2011) when simulations can be performed easily. Experiments with mice could be seen in an intermediate position between simulation work and livestock practice. In simulations, we assume oversimplified genetic models for the studied characters, with additive and homogeneous gene effects, and simple mechanisms of inbreeding depression. On the other hand, with livestock populations, it is not possible to compare methods (only the best one should be used) and it is not possible, in general, to take a medium- or long-term perspective. In our case, if we made the same comparison among methods using computer simulation, we would have conclude that all the three methods attain a similar genetic response but that methods B and C maintain less inbreeding. Here, besides confirming the theoretical predictions, we have presented an experiment with a mammal that indicates that both the introduction of unequal contribution (weighted selection) and the minimum coancestry matings can contribute to the minimization of inbreeding and to attain less deterioration of fitness. In our study, the intrauterine mortality was 36 and 68% and birth mortality 46 and 48% lowered when methods B and C were applied.

Combining both methodologies is possible and should be recommended. Some of these ideas are now being applied in practical breeding programmes that are being implemented using these methodologies (Avendaño *et al.* 2003; Kearney *et al.* 2004; Colleau & Tribout 2008). Finally, in the context of genomic selection, it seems that these methods are valuable, although the concepts of inbreeding and genetic diversity should be re-considered (Sonesson *et al.* 2010).

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