A simple strategy for managing many recessive disorders in a dairy cattle breeding program

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Abstract

Background

High-density single nucleotide polymorphism genotypes have recently been used to identify a number of novel recessives that adversely affect fertility in dairy cattle, as well as to track other conditions such as red coat color and polled. Many current methods for mate allocation fail to consider that information, and it will be increasingly difficult to manage matings when a large number of recessives must be accounted for.

Methods

A simple, sequential mate allocation method that constrains inbreeding and accounts for the economic effects of Mendelian disorders was developed and compared with random mating, truncation selection, and Pryce's method of constraining genomic inbreeding for several different scenarios, including one group of 6 hypothetical alleles and a second group of 12 recessives currently segregating in the US Holstein population.

Results

Pryce's method and the modified Pryce's method showed similar ability to reduce allele frequency, particularly for loci with frequencies greater than 0.30. The modified Pryce's method may outperform Pryce's method for low-frequency alleles with small economic values. Cumulative genetic gain for the selection objective was slightly higher using Pryce's method, but rates of inbreeding were similar across methods.

Conclusions

The proposed method appears to reduce minor allele frequencies for recessives with low frequencies faster than other methods, and can be used to maintain or increase the frequency of desirable recessives. It can easily be implemented in software for mate

allocation, and the code used in this study is freely available as a reference implementation.

Keywords: dairy cattle, genetic selection, mating programs, recessive disorders

Background

Recessive disorders have been present in livestock populations since modern animal breeding programs began, and hundreds are known to exist [1]. While lethal recessives were present in livestock populations long before the dawn of modern animal breeding, increased levels of inbreeding and bottlenecks due to the differential use of parents have made it far more likely that offspring carrying two copies of rare alleles will result from those matings. In the past, test matings were used to identify recessive disorders [2], but most recessives were identified after the carrier bull sired many daughters and had sons in AI (e.g., bovine leukocyte adhesion deficiency [3], complex vertebral malformation [4], and deficiency of uridine monophosphate synthase [5]). It also is possible for novel recessives to be spread through a population by popular bulls before routine screening is possible because such defects were not directly observable, such as occurred with Jersey haplotype 1 [6].

Several authors have proposed methods for including QTL information in breeding programs. Many of those approaches focus on the calculation of the additive genetic value of a QTL which is then combined with other information using a selection index approach [7-10]. Shepherd and Kinghorn [11] have described how QTL information could be included in a look-ahead mate selection scheme, and they have suggested that it could be incorporated into a comprehensive mating service, such as Total Genetic Resource Management™ ([12]; http://www.xprime.com.au/products/tgrm/index.html) once efficient algorithms have

been developed. Li et al. [13,14] reported that the use of QTL genotypes provides more benefit when utilized in mate selection rather than index selection for a variety of modes of inheritance under several breeding structures. Recently, Van Eenennaam and Kinghorn [15] extended the MatSel program [16] to permit selection against the total number of lethal alleles and recessive lethal genotypes.

Genomic tools have enabled the detection of many new recessives which have deleterious effects on fertility [17], many of which have effects early in gestation and could not previously be distinguished from failed breedings. As the number of recessives continues to grow, new tools are needed to consider that information when making mating decisions. However, many mate allocation tools do not consider carrier status when bulls and cows are paired, and few make use of DNA marker or haplotype information that is increasingly available for bulls and cows. When there are only a few recessives in a population it is easy to monitor individuals to avoid carrier-to-carrier matings, but that is considerably more difficult, or even impossible, when there are many harmful defects segregating in a population.

Pryce et al. [18] recently proposed a simple method for controlling the rate of increase in genomic inbreeding by penalizing parent averages (PA) for matings that produce inbred offspring. After PA are adjusted, the bull that will produce the highest PA when mated to a cow is selected in a sequential manner, and the number of matings permitted for each bull is constrained to prevent one bull from being mated to all cows. This method is straightforward to program, and effectively constrains genomic inbreeding at reasonable levels. The objectives of this research were to extend Pryce's method to include information about recessives, and to examine its use in

simultaneously accounting for a large number of Mendelian disorders when allocating mates in dairy cattle breeding schemes by means of computer simulation. Managing genetic defects is a tradeoff between avoiding carrier matings in the short term and eliminating defects in the long run, so the simulation model will examine long-term changes in the population.

Methods

Base population

Base population cows had true breeding values (**TBV**) for lifetime net merit (**NM$**) that were randomly sampled from a normal distribution with a mean of $0 and a standard deviation of $200, which is similar to the genetic SD of lifetime net merit [19]. Bull TBV were sampled from a normal distribution with a mean of $300 (+1.5 genetic SD of NM$) and a standard deviation of $200. An animal's carrier status for each recessive was constructed by randomly sampling sire and dam alleles using the minor allele frequencies (**MAF**) shown in Table 1. Recessives were assumed to be independent of one another, as though each locus was located on a different chromosome. A sex ratio of 0.5 was used, and base population animals were assigned a birth year from -9 to 0 (bulls) or -4 to 0 (cows) by sampling from a uniform distribution.

The base population in each scenario included 350 bulls and 35,000 cows distributed over 200 herds, and the population was permitted to grow to a maximum of 500 bulls and 100,000 cows over the 20 generations simulated. Bulls were permitted a maximum of 5,000 matings per year, and in the truncation selection scheme described later in this section only the top 10% of bulls based on TBV were retained for use as mates.

Descendants

The TBV for new calves were created by taking the parent average (**PA**) and adding a Mendelian sampling term:

$$TBV_{calf} = 0.5(TBV_{sire} + TBV_{dam}) + MS$$

where TBV_{calf}, TBV_{sire}, and TBV_{dam} are the TBV of the calf, its sire, and its dam, respectively. The Mendelian sampling term, MS, was drawn from a normal distribution with a mean of 0 and a variance of $\frac{1}{2}\left[1 - \frac{1}{2}(f_S + f_D)\right]\sigma_a^2$, where f_S and f_D are coefficients of sire and dam inbreeding, respectively, and σ_a^2 is the additive genetic variance of NM$ ($40,000). Sex was assigned randomly with a 50:50 sex ratio. For each recessive in the scenario, an allele was sampled at random from each parent and used to construct the progeny genotype. If the recessive was lethal, an affected (aa) calf was created and marked as dead. Calves were born in the same herd as their dams, and cows did not move between herds. Allele frequencies were updated each generation by counting alleles.

Mating schemes

Four systems of mating, referred to hereafter as schemes, were simulated: random mating, truncation selection, the scheme proposed by Pryce et al. [18], and a modified version of Pryce's scheme that accounts for recessive alleles. In the random mating scheme, bulls were mated randomly to cows, with a parameter in the simulation used to limit the maximum number of matings permitted for each bull (5,000). In the truncation selection scheme, the top 10% of the bulls, based on TBV, were randomly mated to the cow population. Both lethal (e.g., DUMPS) and non-lethal (e.g., red coat color) recessives were included in the simulations.

In the Pryce scheme, matings were assigned as follows. For each herd, 20% of the bulls were randomly selected from the list of live bulls to simulate different groups of

bulls available on different farms, and the top 50 bulls from that group were selected as herd sires based on TBV. This strategy is similar to that used by Pryce et al. [18] for cows and bulls, but only sires were selected in this manner because cows and their offspring were assigned to fixed herds where they remained until death. A matrix of parent averages, $\mathbf{B_0}$, was then constructed with rows corresponding to bulls and columns corresponding to cows. The elements of $\mathbf{B_0}$ were computed as:

$$\mathbf{B}_{ij} = 0.5(TBV_i + TBV_j) - \lambda F_{ij}$$

where TBV_i is the TBV for NM$ of bull *i*, TBV_j is the TBV for NM$ of cow *j*, λ is the inbreeding depression ($) associated with a 1% increase in inbreeding, and F_{ij} is the pedigree coefficient of inbreeding of the calf resulting from mating bull *i* to cow *j*. Recessive genotypes are simulated without error, and it was necessary only to simulate genotypes for recessives because pedigrees are free of errors. A value of $25 for λ was computed by weighting regressions for 1% inbreeding [20] with the 2014 lifetime net merit [19] weights; traits for which no inbreeding regressions were available were set to 0. This is similar to the $23.11 used by Weigel and Lin [21].

In the fourth scheme, recessives were accounted for by adjusting the elements of $\mathbf{B_0}$ to account for the recessives carried by the parents as:

$$B'_{ij} = B_{ij} - \sum_{r=1}^{n_r} P\,(aa)_r \times v_r$$

where n_r is the number of recessives in a scenario, $\mathbf{B}_{ij}'$ is the PA adjusted for all recessives in a scenario, $P(aa)_r$ is the probability of producing an affected calf for recessive *r*, and v_r is the economic value of recessive *r*. P(aa) will be either 0.25, for a mating of two carriers, 0.5, for a mating of an affected animal with a carrier, or 1, for a mating of two affected animals. Non-lethal recessives were entered into the

simulation with an economic value of either 0 or a negative number (which increases the PA). The recessives used in each scenario are described in Table 1, which includes the minor allele frequency and the economic value assigned to each. For each recessive there is a correlation of F_{ij} with P(aa) that will result in some double-counting of the economic impact of each locus, and this may produce suboptimal rates of genetic gain.

Once the matrix of PA (**B** or **B'**, depending on the scenario) is constructed, a matrix of matings, **M**, is used to allocate bulls to cows. An element, $\mathbf{M}_{ij}$, is set to 1 if the corresponding value of $\mathbf{B}_{ij}$ is the greatest value in column *j* (that bull produces the largest PA of any bull available for mating to cow *j*), and all of the other elements of column *j* are set to 0. If the sum of the elements of row *i* is less than the maximum number of permitted matings for that bull then the mating can be allocated. Otherwise, the bull with the next-highest value of $\mathbf{B}_{ij}$ in the column is selected, and so-on, until each column has one and only one element in it with a value of 1. This approach overestimates genetic progress because it assumes that selection accuracy is perfect, but it should permit a reasonable comparison of the Pryce and modified Pryce algorithms. All animals are assumed to be genotyped so that recessive status is known and reliabilities are similar for most animals in the population, unlike a traditional progeny test scenario in which cows and bulls have substantially different reliabilities.

Each step in the simulation represents 1 year of calendar time. New animals are born at the beginning of each year, affected calves die, and surviving animals are culled on age, to maintain population size, and at random (when enabled) at the end of each round (year) of simulation. Generations overlapped, and bulls and cows could have

offspring in multiple years. Bulls were culled first for age, with a maximum age of 10 years, and then on TBV (lowest-ranking animals culled first) to maintain a maximum population size. Cows were first culled for age, with a maximum age of 5 years. After age-related culling, animals were culled involuntarily. Finally, cows were culled at random to maintain population size, if necessary. The time (generation) and reason for culling was added to each record, and records for dead bulls and cows were moved from live to dead animal lists. Animals were not culled based on carrier status, and cows were not culled due to abortions or stillbirths.

Recessive scenarios

Several scenarios were used to characterize the performance of the proposed method, where the term scenario is used to refer to one or more recessives studied together.

Economic values. Each recessive was assigned an economic value based on the occurrence of embryonic or foetal loss during pregnancy (for lethals), or literature values for non-lethal conditions such as red coat color and horned status. Holstein haplotypes 1 through 5 (**HH1**–**HH5**) occur early in pregnancy, as does deficiency of uridine monophosphate synthase (**DUMPS**), and they were assigned a value of $40 based on reproductive costs included in the 2014 revision of the NM$ index [19]. Brachyspina and mulefoot result in stillbirths or calves that do not survive to adulthood, and they were assigned relatively high costs of $150, although actual losses could be higher. Complex vertebral malformation (**CVM**) results in late-term abortions, so a value intermediate to that of the Holstein fertility haplotypes and brachyspina/mulefoot was used. Low- and high-cost scenarios used values of 0 and 3 times the assumed costs to assess the sensitivity of results to economic values. For the hypothetical recessives, values of either 0.10 ($20) or 1 ($200) genetic standard deviations of NM$ were used.

Holstein recessives. Twelve recessives currently segregating in the US Holstein population were grouped together in order to determine how the modified Pryce method will perform in a commercial livestock population: bovine leukocyte adhesion deficiency (**BLAD**), brachyspina, CVM, DUMPS, HH1–HH5, horned, mulefoot, and red coat color). Three scenarios that used the 12 Holstein recessives, but which differed in the economic value assigned to each locus, were used to determine the sensitivity of matings to different prices. In the normal scenario, prices were assigned based on the effect of the recessive and the timing of occurrence. For example, early embryonic lethals (e.g., HH1–HH5) were assumed to have smaller costs that those that result in late-term abortions or stillbirths (e.g., BLAD, brachyspina, mulefoot). In the zero-cost scenario all economic values were set to $0. In the high-cost scenario the prices used for the normal scenario were multiplied by 3. Allele frequencies for the 12 recessives were taken from [22].

Hypothetical recessives. The effect of initial allele frequency on response to selection under each strategy was examined using six scenarios, each of which included a single locus at low (0.01), medium (0.50), or high (0.90) frequency with either a low ($20) or high ($200) cost. In addition, a seventh scenario that included all of the hypothetical loci was examined.

Horned and other high-frequency non-lethal recessives. Not every recessive in a livestock population is lethal to homozygotes, one example being the horned locus in cattle. Because the horned condition in cattle is due to the action of a recessive allele [23], although it has a very high frequency, it was included in the simulation in place of polled with an allele frequency of 1 - 0.0071 = 0.9929. Based in part on the work of

Widmar et al. [24], who calculated average expected costs for dehorning and polled genetics of $11.79 and $10.73, respectively, a value of $40 was assumed for horned to also account for breeders' preferences and premium marketing opportunities. Recall that a positive value reduces the PA in the modified Pryce method, resulting in this case in a lower frequency of horned.

Many recessives. Scenarios including 100 and 1,000 recessives were run in order to examine the relationship of inbreeding and the sum of the P(aa) terms using the modified Pryce method. Minor allele frequencies were sampled from a uniform distribution on the interval [0.01, 0.10], and the economic values from a random uniform distribution on the interval [-$10, -$50]. Correlations of the two terms were calculated, and separate regressions were computed for matings selected from among the available choices and those not selected.

Analysis

Results were averaged over each of the 10 replicates for each scenario. Observed changes in allele frequency were compared against expectations, where the expected allele frequency in each generation for lethals was calculated using an equation derived from Van Doormaal and Kistemaker [25]:

$$p_t = \frac{p_{t-1}^2 + p_{t-1}q_{t-1}}{2p_{t-1}^2 + p_{t-1}q_{t-1}}$$

$$q_t = \frac{p_{t-1}q_{t-1}}{2p_{t-1}^2 + p_{t-1}q_{t-1}}$$

where p_t is the frequency of the major allele at time *t*, q_t is the frequency of the minor allele at time *t*, and *t* is the time in years (ranging from 1 to 20). The minor allele frequency at time 0 was the value used in each scenario for each recessive, and the major allele frequency was calculated by subtracting the minor allele frequency from

1 (Figure 1). Expected allele frequencies for non-lethals was calculated based on Hardy-Weinberg proportions [26] as:

$$p_t = p_{t-1}^2 + p_{t-1}q_{t-1}$$
$$q_t = q_{t-1}^2 + p_{t-1}q_{t-1}$$

For each recessive in each scenario, as well as for the expected frequencies, allele frequencies were regressed on generation using a linear model as implemented in the Python module Statsmodels version 0.5.0 ([27]; http://statsmodels.sourceforge.net/). For a given recessive, the slopes were extracted from the regression results and a two-sample *t*-test assuming unequal variances was used to compare the coefficients against each other, as well as against the expected frequencies. A Bonferroni adjustment was used to correct for multiple comparisons.

Computing environment

Simulations were carried out using programs written in Python 2.7.9 (http://www.python.org/) as packaged in the Anaconda 2.1.0 distribution (Continuum Analytics, Austin, TX). Results were analysed in IPython 2.2.0 notebooks (http://ipython.org/notebook.html) using pandas 0.15.2 [28] and visualized using matplotlib 1.4.0 [29]. The programs used to conduct the simulations, resulting data files, and notebooks used for data analysis are available in a GitHub repository (https://github.com/wintermind/multiple-recessives). All programs in the repository are in the public domain. INBUPGF90 version 1.27 [30] was used to compute coefficients of inbreeding for the Pryce scenario, and is available for download from the University of Georgia (http://nce.ads.uga.edu/wiki/doku.php?id=readme.inbupgf90).

All simulations were performed on a Pogo Linux Atlas 1205 (Pogo Linux, Inc., Redmond, WA) computer with an 8-core AMD Opteron 6328 processor with a clock

281 speed of 3.2 GHz, 64 GB of DDR3 1600 MHz RAM, and 64-bit CentOS Linux EL6
282 (Red Hat, Inc., Raleigh, NC), or a Thinkmate RAX QS6-4210 (Thinkmate, Inc.,
283 Waltham, MA) workstation with four 12-core AMD Opteron 6344 processors with a
284 clock speed of 2.6 GHz, 256 GB of DDR3 1600 MHz RAM, and CentOS Linux EL7.
285 Data analysis and visualization were performed on a MacBook Pro with two Intel
286 Core i7 processors running at 2.9 GHz, 8 GB of DDR3 1600 MHz RAM, and Mac OS
287 X 10.7.5 (Apple Inc., Cupertino, CA).
288
289 Computation time for the random mating scheme averaged 193 minutes per replicate
290 in a one-recessive scenario (high frequency, high cost) and 215 minutes in a 12-
291 recessive scenario (Holstein recessives). Considerably less time was required for the
292 truncation selection scheme, averaging 34 minutes in the one-recessive scenario and
293 38 minutes in the Holstein scenario. This may reflect the need to draw many more
294 random variates in the other scenarios than in the truncation selection scenario, which
295 does not impose a limit on the number of matings per bull and results in the rejection
296 of far fewer proposed matings. The time needed for the Pryce and modified Pryce
297 schemes averaged 206 minutes and 232 minutes in the one-recessive scenario, and
298 203 and 279 minutes in the Holstein scenario. Operations for the Pryce and modified
299 Pryce scenarios include allocation of large arrays, and the creation of large output
300 files that are not part of the random mating or truncation selection schemes. If matings
301 are done within herd, the memory used for 1 herd can be reused for the next to keep
302 memory requirements low. The time required for processing 1 generation rather than
303 20 should be very reasonable.

Results and discussion

Holstein recessives

Normal costs. Observed allele frequency changes for 11 of the 12 recessives from the four mating schemes are shown in Figure 2. Horned is not shown because the allele frequency remained above 99% in all 4 schemes, and its inclusion in the plot obscured the changes in alleles at low frequency. The frequency of the 10 lethals generally decreased over time in all scenarios. The frequencies of HH1 and HH3 decreased significantly faster ($P < 0.05$ after a Bonferroni correction) under Pryce's method than under the modified Pryce's method. The rate of change in allele frequencies was similar under the Pryce's (Figure 3) and modified Pryce's (data not shown) schemes. An advantage of the modified Pryce approach is that it maintains the frequency of desirable recessives, such as red coat color, in the population. In the Pryce scheme, the frequency of red decreased over time because there is no mechanism in that scenario to balance undesirable economic effects of inbreeding against the desirable economic value of some recessives. In the modified Pryce scheme the positive economic value of red coat color offsets the inbreeding penalty and maintains a relatively constant gene frequency over time. Avoidance of genomic inbreeding limits homozygosity, but eventually the population should become homozygous for the favorable allele.

Average TBV for the total merit index under selection were similar among the schemes over time. The difference between cows in year 20 of the two schemes was $21, which was $2,966 versus $2,987 for Pryce and modified Pryce, respectively. Bulls in generation 20 differed by only $10 on average ($3,737 versus $3,747). These differences are relatively small when compared to the overall genetic gain in the

population, which averaged approximately $148 per year in cows and $186 per year in bulls.

Average coefficients of inbreeding by birth year were very similar for cows and bulls, increasing by approximately 0.35% per year in both populations. The same general pattern was observed across all scenarios and mate allocation schemes (data not shown). A value of λ of $25 was used, which is similar to the $23.11 calculated by [21], and higher than the $12 reported by Smith et al. [31] and the AUS$5.00 value used by Pryce et al. [18].

Zero costs. The scenario in which all recessives have an economic value of $0 is equivalent to assuming that all recessives have equivalent values and changes over time should be driven principally by allele frequencies, with similar trends expected for the Pryce and modified Pryce schemes. The observed allele frequency changes in this scenario were similar to those noted in the normal price scenario (Figure 2), with the lethals generally decreasing in frequency over time in all scenarios. Minor allele frequencies decreased faster in the Pryce and modified Pryce schemes than under random mating or truncation selection, and the rates were significantly faster than expectations for all traits but red coat color ($P < 0.05$). The frequencies of brachyspina, HH4, and BLAD decreased significantly faster in the modified Pryce scheme, while HH2, horned, and red decreased faster using Pryce's method. The rates of change of the other recessives did not differ. This may be due to the much lower initial allele frequencies for HH4 and BLAD, which results in much rarer instances of affected embryos. In both schemes, there was generally good correspondence between the observed and expected changes for each recessive for Pryce's method.

In generation 20, average TBV were $8 higher for bulls and $9 higher for cows under the Pryce scenario than the modified Pryce scenario. The difference was smaller for bulls than under normal pricing, and similar for cows. In generation 0, both populations had similar average TBV, so these differences represent the cumulative effect of a slightly higher genetic trend under the Pryce scenario, probably because matings of carrier cows to high genetic merit bulls were not penalized for the economic consequences of producing affected calves.

High costs. In this scheme, the economic value of each recessive was increased by a factor of 3 over the base Holstein scheme. Results were similar to the base Holstein scenario (Figure 4); this is probably due to the use of the same constant to scale values for all traits. The frequencies of HH5 and horned decreased faster under the modified Pryce scenario than the Pryce scenario ($P < 0.05$), while HH1 decreased more quickly under the Pryce scenario.

Hypothetical recessives

High frequency, lethal recessives. The rate of allele frequency change was similar for both the low ($20; Figure 5) and high ($200; data not shown) value scenarios. This suggests that at minor allele frequency the change from generation to generation is driven principally by genotype frequencies, not by economic value. The fit of the observed to expected allele frequency changes was very good in both scenarios (data not shown).

Medium frequency, lethal recessives. Results for a minor allele with an initial frequency of 0.50 and an economic value of either $20 or $200 were very similar to

379 those for the previous section. The economic values were again dwarfed by the allele
380 frequency, and a different mate allocation strategy will be needed to decrease the
381 allele frequency more quickly.
382
383 ***Low frequency, lethal recessives.*** The two low-frequency scenarios discussed in this
384 section are perhaps the most representative of the deleterious recessives seen most
385 commonly in livestock populations [22], that is, harmful alleles with low frequencies
386 (< 0.05). Both the Pryce and modified Pryce methods are successful at decreasing the
387 allele frequency over time when the value of the recessive is high, and they do so
388 more quickly than expected. However, the modified Pryce's method appears to be
389 more effective than random mating, truncation selection, or Pryce's method schemes
390 at lowering the allele frequency when the economic value of the recessive is low. It is
391 not clear why the modified Pryce's method performed so much better than Pryce's
392 method in the latter scenario because, at low allele frequency, the only way to
393 increase the frequency of the minor allele is either through inbreeding, or the spread
394 of a *de novo* mutation by a popular sire. While mutation is included in the simulation,
395 each replicate uses a different seed for the random number generator, so new
396 mutations are not expected to arise at the same time across different runs of the
397 program.
398
399 ***Six hypothetical, lethal recessives.*** All four systems of mate allocation produced
400 similar changes in allele frequencies over time. Pryce's method and the modified
401 Pryce's method do produce slightly lower frequencies for some of the alleles that had
402 high or medium initial frequencies, but there was no apparent pattern based on the
403 economic value of each locus. Observed allele frequencies showed much better fits to

404 the predicted values than in the scenarios based on the actual Holstein recessives, but
405 that is expected when alleles have initial frequencies greater than 0.20.
406
407 There was no apparent difference between the change in allele frequencies over time
408 even though there was a tenfold difference between the high- ($200) and low-valued
409 ($20) recessives. When the minor allele frequency is high, many of the potential mate
410 pairs in the population will have their parent averages reduced, but the loci with large
411 values will be decreased more than those with low values, which should result in few
412 carrier-to-carrier matings.

413 **Horned and other high-frequency non-lethal recessives**
414 The horned allele is present at a frequency greater than 99% in the US Holstein
415 population, and there is increasing interest in reducing its frequency to improve
416 animal welfare. Spurlock et al. [32] recently studied three breeding schemes for
417 increasing the frequency of polled animals, concluding that it is possible to
418 substantially increase the number of polled animals in the population over a
419 reasonable time horizon. One of the key challenges is that there are few polled bulls,
420 but a haplotype test for polled added to the US genomic evaluation program in 2013
421 now makes it easier to identify heterozygous and homozygous polled animals for
422 mating. A scenario including only the horned recessive was simulated to determine if
423 the modified Pryce's scheme is an effective tool for increasing the frequency of polled
424 animals in the population.
425
426 Including horned with a value of $40 was not effective in reducing the minor allele
427 frequency, which remained essentially unchanged over 20 years of selection. This is
428 probably because the frequency of the polled allele is so low that carriers were

unlikely to be one of the top-ranked bulls by TBV, and even if one was, the simulation included a limit of 5,000 matings per bull per generation. That limited a single bull to only being mated to 5% of the cow population in a generation. A second horned scenario in which the economic value was increased from $40 to $400 was run to determine if a higher cost would increase the rate of change. The second scenario was also unsuccessful in changing the frequency of horned. These results are consistent with the results from scenarios that included 12 Holstein recessives described above, in which there was not appreciable change in the frequency of horned. A more sophisticated approach for selecting mate pairs that will either produce polled offspring or heterozygotes, such as a scheme described by Li et al. [13,14] or Spurlock et al. [32] or the use of tools for non-meiotic allele introgression [33], will be needed to effectively increase the frequency of polled (decrease the frequency of horned) cows in the national dairy herd.

Mating schemes

As expected, there was negligible genetic trend under the random mating scheme except in scenarios in which lethals had initial minor allele frequencies greater than 20%, which suggests that the simulation was performing reasonably. The results from the truncation selection scheme were generally similar to the Pryce's and modified Pryce's schemes for lethals, and to random mating for non-lethal recessives. This is reasonable because the allele frequency of the lethals is expected to decrease over time even if no additional selection pressure is imposed, and the threshold that retains the top 10% of bulls for breeding ensures that genetic trend is positive. The truncation selection scheme loosely resembles current mating strategies used on large commercial dairies in North America.

More affected calves were observed in the Pryce's and modified Pryce's schemes than in the random mating and truncation selection schemes. Figure 6 shows the proportion of simulated calves that are culled due to recessive genotypes averaged over replicates of the Holstein scenario; results were similar for the high value, high frequency and low value, low frequency scenarios (data not shown). This is expected because a bull can have genetic superiority over his contemporaries that exceeds the economic value assigned to the recessive alleles that he may carry. Selection for reduced allele number rather than reduced frequency of recessive genotypes could result in fewer embryonic losses [15]. There also is conflict between the goal of eliminating recessives from the population, which involves fixing associated haplotypes in a homozygous state, and minimizing inbreeding, which seeks to avoid such increases in homozygosity.

Relationships of inbreeding with recessive load

The relationship of inbreeding with the number of recessives carried by parents was examined by computing the correlation of f_{ij} with the sum of P(aa) for each possible mating in each generation ($\Sigma P(aa)$) for scenarios including 12 (the Holstein scenario discussed above), 100, or 1,000 recessives. Contrary to expectations, the correlation of f_{ij} with $\Sigma P(aa)$ was near 0 in the Holstein scenario, and negative in the 100- and 1,000-recessive scenarios. The correlation was stronger for matings made than those not made, suggesting that the modified Pryce's method was successful in identifying matings that reduced the accumulation of recessives. Figure 7 shows the regressions for the matings evaluated in birth year 20 of replicate 1 of each scenario by mating category (0: mating not made, 1: mating made); results were similar across replicates. The final birth year in each scenario was chosen for plotting because they provided

the most opportunity to generate correlations among inbreeding and the number of recessives carried by individuals.

The lack of large correlations may be due in part to the low allele frequencies used in most scenarios. With deleterious recessives having very low frequencies the probability that an individual mating will be affected by more than one recessive, and that such a mating will have a DGV extreme enough overcome the penalty, is extremely low. If the frequencies of the recessives were high a stronger relationship would probably be observed, but it is difficult to consider a situation in which several recessives would be at a high frequency in the population, although individual recessives have been observed at relatively high frequency in a population, such as the JH1 haplotype in Jerseys [6]. It also is possible that there were too few recessives segregating in the population to see the expected relationship. However, the results from the 100- and 1,000- recessives scenarios suggest that this is not the case.

While inbreeding is inevitable in finite populations under selection [e.g., 34], the deleterious effects of inbreeding can be managed if harmful alleles are removed from the population. This typically happens when homozygotes have very low fitness, such as when recessives are lethal, or when individuals are culled on some performance metric. There is evidence that such purging of genetic load has occurred in livestock populations, such as the Irish Holstein-Friesian [35] and US Jersey populations [36]. In the 100- and 1000-recessive cases all of the defects were lethal, so that affected animals were eliminated from the population quickly. This may be one reason that the observed correlations were not in accordance with initial expectations. As the number of recessives increases, it is more likely that affected matings will occur, which will

result in the purging of those copies of the allele, which is consistent with the trend observed in Figures 7a and 7b. In the 1000-recessive case, there were so many harmful alleles in the population that the population size gradually decreased over time, and only 152 live animals were born in the final year of the simulation.

Mate allocation

Mate allocation, the process of selecting mating pairs from a population of female and some portfolio of males, has a long history in animal breeding programs in both general [16,37,38,39] and trait-specific [40] applications. Many artificial insemination firms provide recommended mate allocations to their customers as part of their services, but the algorithms used are usually very simple. In 2012, Pryce et al. [18] proposed the use of a simple sequential method that maximizes the parent average of a mating after adjusting for any inbreeding of the offspring, subject to constraints on the number of matings per bull per generation, and showed that their method effectively constrains inbreeding when genomic relationships are used. Sun et al. [41] recently showed that rates of genetic gain can be further increased when genomic relationships are used and matings are allocated using linear programming to simultaneously account for all desired constraints. The modified Pryce's method proposed in this paper uses a sequential allocation method that also accounts for the economic effect of recessives in the population. This may be a more practical approach to account for recessives than to include them in selection indices because of the difficulty of obtaining the marginal cost of a recessive independent of all other costs already accounted for by the other traits in the index, although the possibility of double-counting costs remains.

An advantage of the modified Pryce method over Pryce's original method is that the former can be used to maintain the frequency of desirable recessives, such as red coat color, in the population. There are other recessives, such as slick hair coat [42], that are segregating in some lines of Holstein that are desirable to producers in sub-tropical regions, and the modified Pryce's method could be used to increase the frequency of that allele in the general population.

Pryce's method and the modified Pryce's method described in this paper also suffer from order-dependence, that is, if the cows are reordered before bulls are allocated the mate pairs change. This is probably not a serious problem if the elite bulls in the population have similar breeding values, but could be important if there is a small group of, for example, elite young genomic bulls that have much higher breeding values than other active bulls. The use of linear programming (**LP**) rather than sequential allocation of mate pairs could eliminate this problem, at the cost of some added complexity in the implementation phase. Sun et al. [41] found in simulation that expected progeny differences were slightly higher for Holsteins ($494 versus $474) when using LP compared to Pryce's method, and the Pryce strategy gave only 72% of the LP benefit over random mating. Progeny inbreeding also was slightly lower (5.17 versus 6.03) using LP. This is similar in magnitude to the gains using LP reported by Weigel and Lin [21].

Unlike an evolutionary algorithm-based approach, sequential allocation as used in the Pryce and modified Pryce algorithms cannot account for a situation in which the value of one mating is affected by other matings. This situation is common, for example, when matings on multiple farms are considered simultaneously or when management

552 of parental coancestry is desired. Van Eenennaam and Kinghorn [15] recently
553 extended the MatSel program [16], which is based on an evolutionary algorithm, to
554 permit selection against the number of lethal alleles and recessive lethal genotypes
555 considering either 6 or 100 lethal loci in high and low SNP frequency situations. Their
556 results show that the amount of genetic progress foregone in order to decrease the
557 incidence of lethal homozygous progeny is dependent upon allele frequencies, the
558 number of lethal loci, and the emphasis that is placed on avoiding embryonic deaths.
559 The approach they propose is theoretically more desirable than the modified Pryce
560 algorithm presented in this paper, but there is often considerable reluctance by
561 breeding organizations in the US to modify their software. Because of this, ease-of-
562 implementation is often accorded more importance than theoretically optimal
563 properties, and it is better to have an imperfect mate allocation tool used than no tool
564 at all.

565 **Integration with on-farm systems**

566 As of 27 July 2015 there were 1,059,438 genotypes in the National Dairy Database
567 maintained by the Council on Dairy Cattle Breeding (Reynoldsburg, OH, USA), of
568 which 854,766 were from females (https://www.cdcb.us/Genotype/cur_freq.html).
569 There is considerable interest from the farmers who have invested in those data in
570 using them to make optimal management and breeding decisions. Initial research
571 focused on increased genetic gains from the use of genomic information for early
572 culling decisions [43], but there also is interest in using those data with integrated on-
573 farm decision support systems. Gaddis et al. [44] showed that genotype information
574 may have value in predicting changes in health status, and it is reasonable to assume
575 that similar approaches can be used to make decisions about what animals to breed
576 based on fertility status, or what animals to dry-off or cull based on predicted future

performance. The modified Pryce's method described in this paper can easily be integrated into existing herd management and mate planning software, where it could be used to better inform culling decisions or identify matings that should be avoided. In the case of some haplotypes, such as A2 beta-casein and polled, this may be a useful tool for increasing allele frequencies without sacrificing substantial cumulative genetic gain. It has been suggested that selecting for the number of alleles rather than the frequency of homozygous genotypes might provide greater power for changing allele frequencies.

Tradeoffs and limitations

Van Eenennaam and Kinghorn [15] found that the compromise between genetic gain and the incidence of lethal homozygotes depends upon allele frequencies, the number of deleterious loci, and the relative weighting that is placed on avoiding embryonic mortalities. Selection against low-frequency alleles at 6 loci had little effect on genetic gain, but gain decreased to 94% when selecting against lethal genotypes (their closest scenario to the modified Pryce method). Genetic gain increased as the number of loci increased, as did parental coancestry, and in their 100-locus situation it was not possible to reduce embryo mortality to 0. Under the modified Pryce scenario it was possible to reduce but not eliminate embryonic mortality. As the relative weighting (economic value) of loci increases the foregone genetic progress also will increase. MacArthur et al. [45] recently estimated that human genomes contain approximately 100 loss-of-function mutations, and about 20 genes that are completely inactivated. While not all of those mutations are lethal, it suggests that the 100-locus scenario of Van Eenennaam and Kinghorn [15] represents a plausible limit to the selection problem. Segelke et al. [46] suggested that a genetic index including haplotypes of interest should be used when selecting females for mating, and breeding values should

be used to select bulls in order to balance selection for specific alleles with genetic gain. As the number of known recessives continues to increase it will be increasingly difficult to assign proper weights to each of them because individuals will be more likely to be carriers of multiple lethals, and the marginal value of each recessive will be difficult to calculate without double-counting.

Conclusions

A modified version of Pryce's method [18] that accounts for the economic effects of recessive conditions was developed and compared with random mating, truncation selection, and Pryce's method for several different scenarios, including hypothetical alleles as well as 12 recessives currently segregating in the US Holstein population. The new method appears capable both of reducing the frequency of undesirable recessives with low frequencies and maintaining or increasing the frequency of desirable recessives. The method can easily be implemented in software used for mate allocation, and the code used in this study is freely available for use as a reference implementation.

Competing interests

The author declares that he has no competing interests.

Authors' contributions

JBC designed the study, wrote the simulations, analyzed the data, and prepared the manuscript.

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Figures

Figure 1 - Expected allele frequencies

The expected decrease in minor allele frequency for lethal recessives with initial frequencies of 0.01, 0.05, 0.10, 0.25, 0.75, and 0.99.

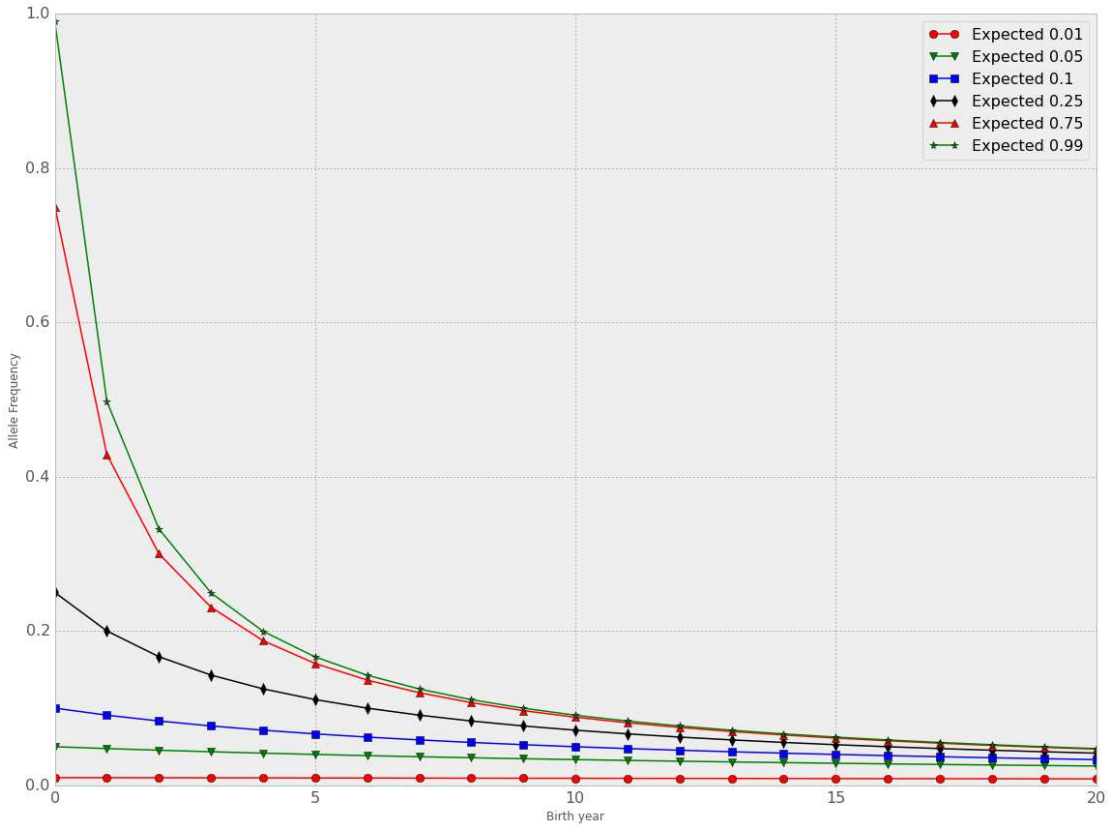


Figure 2 - Observed allele frequencies for Holstein recessives

Observed changes in minor allele frequencies for BLAD, brachyspina, CVM, DUMPS, HH1–HH5, mulefoot, and red coat color over 20 years under random selection, truncation selection, Pryce's method for controlling genomic inbreeding, and Pryce's method accounting for recessives.

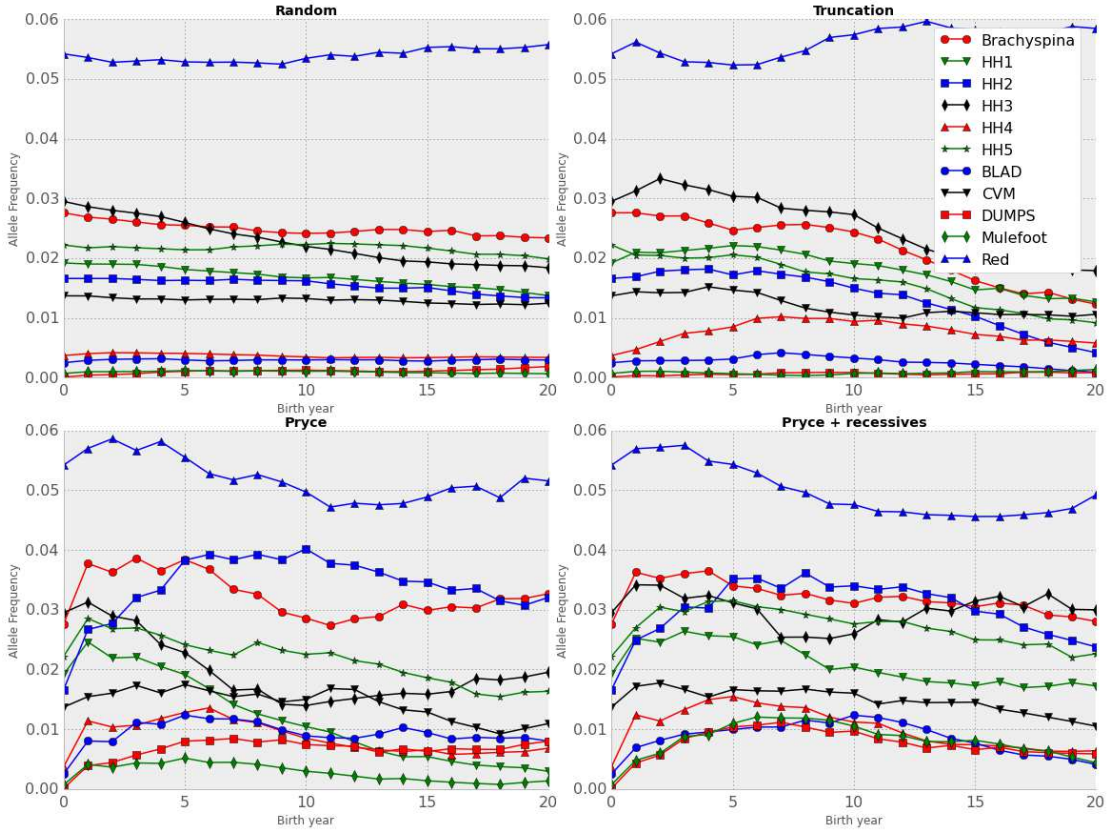


Figure 3 - Observed versus expected allele frequencies under the Pryce scenario

Observed versus expected allele frequencies under the Pryce scenario. Observed versus expected changes in minor allele frequencies for BLAD, brachyspina, CVM, DUMPS, HH1–HH5, horned, mulefoot, and red coat color over 20 years using Pryce's method for controlling genomic inbreeding. Note that the horned subplot is scaled differently on the y axis than the other subplots because of its allele frequency.

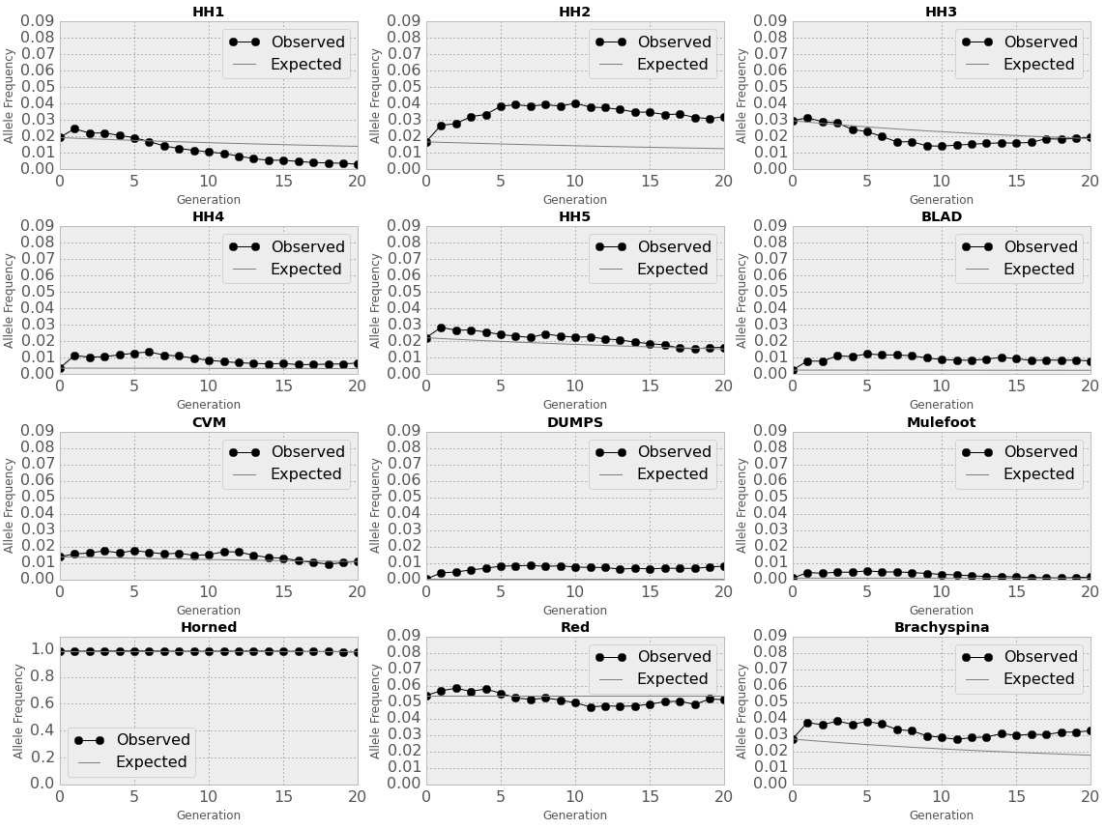


Figure 4 - Observed allele frequencies for Holstein recessives with high economic values

Observed changes in minor allele frequencies for BLAD, brachyspina, CVM, DUMPS, HH1–HH5, mulefoot, and red coat color over 20 years under random selection, truncation selection, Pryce's method for controlling genomic inbreeding, and Pryce's method accounting for recessives.

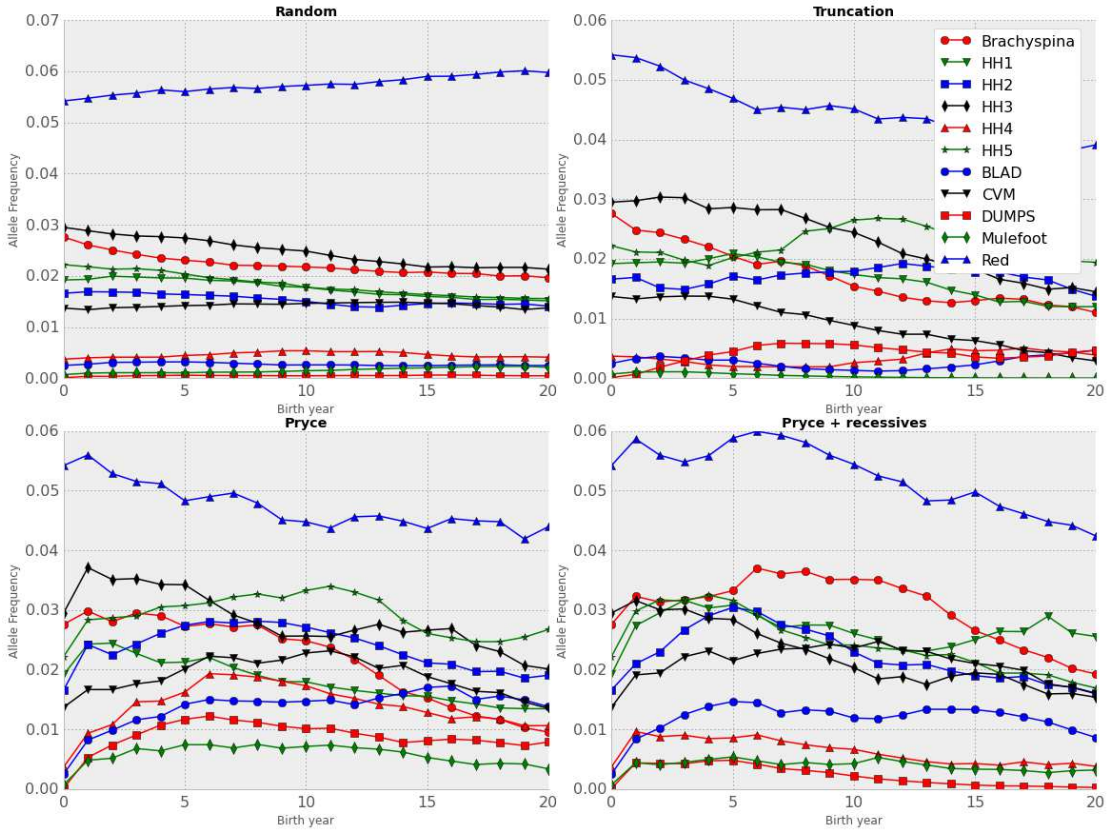


Figure 5 - Observed allele frequencies for a hypothetical recessive with a high frequency and low value

Observed changes in minor allele frequency for a hypothetical recessive with a starting frequency of 0.90 and an economic value of $20 over 20 years under random selection, truncation selection, Pryce's method for controlling genomic inbreeding, and a modified Pryce's method that accounts for recessives.

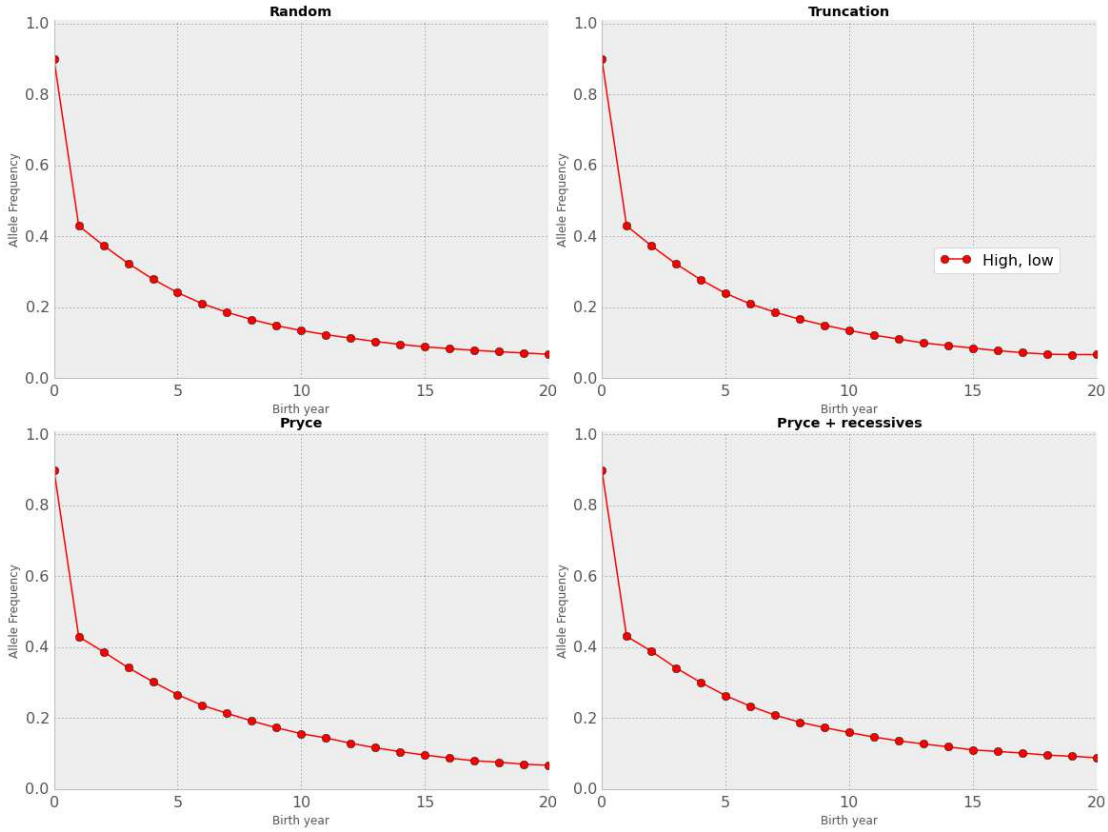


Figure 6 - Embryonic deaths by birth year

Proportion of embryos in each birth year that died due to the effects of recessive genotypes.

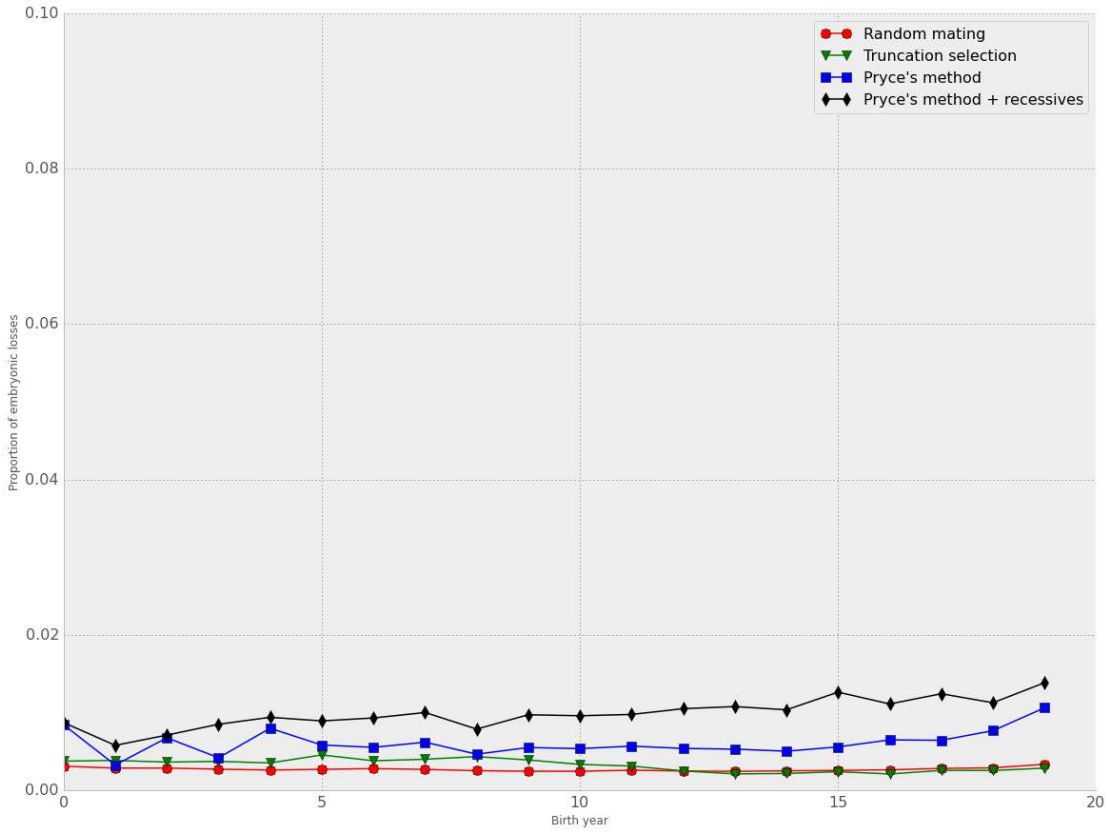
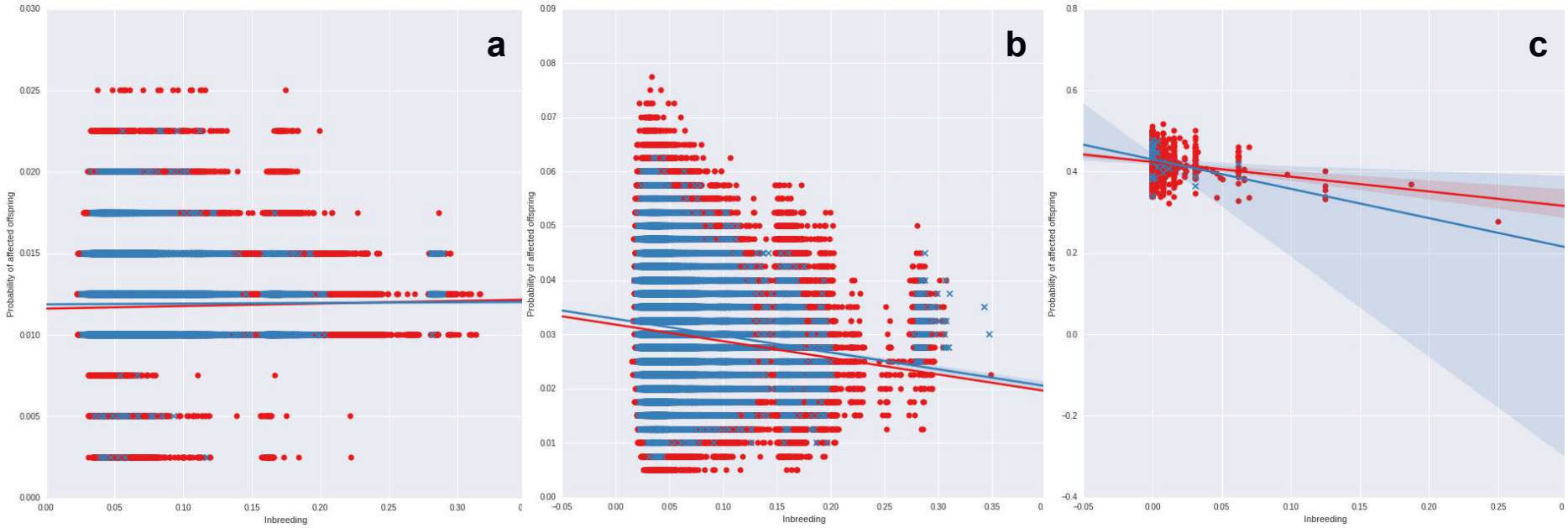


Figure 7 - Embryo inbreeding and probability of carrying recessives

Relationships of embryo inbreeding with the probability that the embryo will be affected by one or more recessive conditions for (a) Holstein recessives, (b) 100 simulated recessives, and (c) 1,000 simulated recessives. The mating variable distinguishes matings that were not made (red dots) from those that were made (blue crosses).



Tables

Table 1 - Properties of the recessives included in each scenario simulated

			Recessives			
Group	Scenario[1]	N[2]	Frequency	Value ($)[3]	Name	Lethal
Holstein	All recessives	12	0.0276	150	Brachyspina	Yes
			0.0192	40	HH1	Yes
			0.0166	40	HH2	Yes
			0.0295	40	HH3	Yes
			0.0037	40	HH4	Yes
			0.0222	40	HH5	Yes
			0.0025	150	BLAD	Yes
			0.0137	70	CVM	Yes
			0.0001	40	DUMPS	Yes
			0.0007	150	Mulefoot	Yes
			0.9929	40	Horned	No
			0.0542	-20	Red coat color	No
	All recessives, zero cost	12	As above, but all recessives have a value of $0.			
	All recessives, high cost	12	0.0276	450	Brachyspina	Yes
			0.0192	120	HH1	Yes
			0.0166	120	HH2	Yes
			0.0295	120	HH3	Yes
			0.0037	120	HH4	Yes
			0.0222	120	HH5	Yes

			0.0025	450	BLAD	Yes
			0.0137	210	CVM	Yes
			0.0001	120	DUMPS	Yes
			0.0007	450	Mulefoot	Yes
			0.9929	120	Horned	No
			0.0542	-60	Red coat color	No
Hypothetical	High frequency, low value	1	0.90	20	High. low	Yes
	High frequency, high value	1	0.90	200	High, high	Yes
	Medium frequency, low value	1	0.50	20	Medium, low	Yes
	Medium frequency, high value	1	0.50	200	Medium, high	Yes
	Low frequency, low value	1	0.01	20	Low, low	Yes
	Low frequency, high value	1	0.01	200	Low, high	Yes
	All recessives	6	As above.			
Horned	Horned, market value	1	0.9929	40	Horned	No
	Horned, high value	1	0.9929	400	Horned	No

[1]The specific scenario simulated for each trait or group of traits.

[2]The number of recessives in the scenario.

[3]Positive values are undesirable and negative values are desirable.