

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

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11 **Abstract**

12 **Background**

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

19 **Methods**

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

26 **Results**

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

32 **Conclusions**

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

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

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

39 **Background**

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

51

52 **Several authors have proposed methods for including QTL information in breeding**
53 **programs. Many of those approaches focus on the calculation of the additive genetic**
54 **value of a QTL which is then combined with other information using a selection index**
55 **approach [7-10]. Shepherd and Kinghorn [11] have described how QTL information**
56 **can be included in look-ahead mate selection, and that approach has been**
57 **implemented in the Total Genetic Resource Management™ mate selection service**
58 **([12]; <http://www.xprime.com.au/products/tgrm/index.html>). Li et al. [13,14]**
59 **reported that the use of QTL genotypes provides more benefit when utilized in mate**
60 **selection rather than index selection for a variety of modes of inheritance under**

61 several breeding structures. Recently, Van Eenennaam and Kinghorn [15] extended
62 the MatSel program [16] to permit selection against the number of lethal alleles and
63 recessive lethal genotypes.

64

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

75

76 Pryce et al. [18] recently proposed a simple method for controlling the rate of increase
77 in genomic inbreeding by penalizing parent averages (PA) for matings that produce
78 inbred offspring. After PA are adjusted, the bull that will produce the highest PA when
79 mated to a cow is selected in a sequential manner, and the number of matings
80 permitted for each bull is constrained to prevent one bull from being mated to all
81 cows. This method is straightforward to program, and effectively constrains genomic
82 inbreeding at reasonable levels. The objectives of this research were to extend Pryce's
83 method to include information about recessives, and to examine its use in
84 simultaneously accounting for a large number of Mendelian disorders when allocating
85 mates in dairy cattle breeding schemes by means of computer simulation. Managing

86 genetic defects is a tradeoff between avoiding carrier matings in the short term and
87 eliminating defects in the long run, so the simulation model will examine long-term
88 changes in the population.

89 **Methods**

90 **Base population**

91 Base population cows had true breeding values (**TBV**) for lifetime net merit (**NM\$**)
92 that were randomly sampled from a normal distribution with a mean of $\$0$ and a
93 standard deviation of $\$200$, which is similar to the genetic SD of lifetime net merit
94 [19]. Bull TBV were sampled from a normal distribution with a mean of $\$300$ (+1.5
95 genetic SD of NM\$) and a standard deviation of $\$200$. An animal's carrier status for
96 each recessive was constructed by randomly sampling sire and dam alleles using the
97 minor allele frequencies (**MAF**) shown in **Table 1**. Recessives were assumed to be
98 independent of one another, as though each locus was located on a different
99 chromosome. A sex ratio of 0.5 was used, and base population animals were assigned
100 a birth year from -9 to 0 (bulls) or -4 to 0 (cows) by sampling from a uniform
101 distribution.

102

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

109 **Descendants**

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

112
$$TBV_{\text{calf}} = 0.5(TBV_{\text{sire}} + TBV_{\text{dam}}) + MS$$

113 where TBV_{calf} , TBV_{sire} , and TBV_{dam} are the TBV of the calf, its sire, and its dam,
114 respectively, and MS is a random variate drawn from a standard normal distribution
115 ($\sim N(0,1)$) multiplied by the additive genetic SD of NMS (\$200). Sex was assigned
116 randomly with a 50:50 sex ratio. For each recessive in the scenario, an allele was
117 sampled at random from each parent and used to construct the progeny genotype. If
118 the recessive was lethal, an affected (aa) calf was created and marked as dead. Calves
119 were born in the same herd as their dams, and cows did not move between herds.

120 Allele frequencies were updated each generation by counting alleles.

121 **Mating schemes**

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

130

131 In the Pryce scheme, matings were assigned as follows. First, a matrix of parent
132 averages, \mathbf{B}_0 , was constructed with rows corresponding to bulls and columns
133 corresponding to cows. The elements of \mathbf{B}_0 were computed as:

134
$$\mathbf{B}_{ij} = 0.5(TBV_i + TBV_j) - \lambda F_{ij}$$

135 where TBV_i is the TBV for NM\$ of bull i , TBV_j is the TBV for NM\$ of cow j , λ is the
136 inbreeding depression (\$) associated with a 1% increase in inbreeding, and F_{ij} is the
137 pedigree coefficient of inbreeding of the calf resulting from mating bull i to cow j .

138 Recessive genotypes are simulated without error, and it was necessary only to
139 simulate genotypes for recessives because pedigrees are free of errors. A value of \$25
140 for λ was computed by weighting regressions for 1% inbreeding [20] with the 2014
141 lifetime net merit [19] weights; traits for which no inbreeding regressions were
142 available were set to 0. This is similar to the \$23.11 used by Weigel and Lin [21].

143

144 In the fourth scheme, recessives were accounted for by adjusting the elements of \mathbf{B}_0 to
145 account for the recessives carried by the parents as:

146
$$B'_{ij} = B_{ij} - \sum_{r=1}^{n_r} P(aa)_r \times v_r$$

147 where n_r is the number of recessives in a scenario, \mathbf{B}'_{ij} is the PA adjusted for all
148 recessives in a scenario, $P(aa)_r$ is the probability of producing an affected calf for
149 recessive r , and v_r is the economic value of recessive r . $P(aa)$ will be either 0.25, for a
150 mating of two carriers, 0.5, for a mating of an affected animal with a carrier, or 1, for
151 a mating of two affected animals. Non-lethal recessives were entered into the
152 simulation with an economic value of either 0 or a negative number (which increases
153 the PA). The recessives used in each scenario are described in Table 1, which includes
154 the minor allele frequency and the economic value assigned to each. For each
155 recessive there is a correlation of F_{ij} with $P(aa)$ that will result in some double-
156 counting of the economic impact of each locus, and this may produce suboptimal rates
157 of genetic gain.

158

159 Once the matrix of PA (**B or B'**, depending on the scenario) is constructed, a matrix of
160 matings, **M**, is used to allocate bulls to cows. An element, **M_{ij}**, is set to 1 if the
161 corresponding value of **B_{ij}** is the greatest value in column *j* (that bull produces the
162 largest PA of any bull available for mating to cow *j*), and all of the other elements of
163 column *j* are set to 0. If the sum of the elements of row *i* is less than the maximum
164 number of permitted matings for that bull then the mating can be allocated.
165 Otherwise, the bull with the next-highest value of **B_{ij}** in the column is selected, and
166 so-on, until each column has one and only one element in it with a value of 1. This
167 approach overestimates genetic progress because it assumes that selection accuracy is
168 perfect, but it should permit a reasonable comparison of the Pryce and modified Pryce
169 algorithms.

170

171 Each step in the simulation represents 1 year of calendar time. New animals are born
172 at the beginning of each year, affected calves die, and surviving animals are culled on
173 age, to maintain population size, and at random (when enabled) at the end of each
174 round (year) of simulation. Generations overlapped, and bulls and cows could have
175 offspring in multiple years. Bulls were culled first for age, with a maximum age of 10
176 years, and then on TBV (lowest-ranking animals culled first) to maintain a maximum
177 population size. Cows were first culled for age, with a maximum age of 5 years. After
178 age-related culling, animals were culled involuntarily. Finally, cows were culled at
179 random to maintain population size, if necessary. The time (generation) and reason for
180 culling was added to each record, and records for dead bulls and cows were moved
181 from live to dead animal lists. Animals were not culled based on carrier status, and
182 cows were not culled due to abortions or stillbirths.

183 **Recessive scenarios**

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

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

199 **Holstein recessives.** Twelve recessives currently segregating in the US Holstein
200 population were grouped together in order to determine how the modified Pryce
201 method will perform in a commercial livestock population: bovine leukocyte adhesion
202 deficiency (**BLAD**), brachyspina, complex vertebral malformation (**CVM**), deficiency
203 of uridine monophosphate synthase (**DUMPS**), Holstein haplotypes 1 through 5
204 (**HH1–HH5**), horned, mulefoot, and red coat color). Three scenarios that used the 12
205 Holstein recessives, but which differed in the economic value assigned to each locus,
206 were used to determine the sensitivity of matings to different prices. In the normal
207 scenario, prices were assigned based on the effect of the recessive and the timing of
208 occurrence. For example, early embryonic lethals (e.g., HH1–HH5) were assumed to

209 have smaller costs than those that result in late-term abortions or stillbirths (e.g.,
210 BLAD, brachyspina, mulefoot). In the zero-cost scenario all economic values were set
211 to \$0. In the high-cost scenario the prices used for the normal scenario were
212 multiplied by 3. Allele frequencies for the 12 recessives were taken from [22].

213

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

219 **Horned and other high-frequency non-lethal recessives.** Not every recessive in a
220 livestock population is lethal to homozygotes, one example being the horned locus in
221 cattle. Because the horned condition in cattle is due to the action of a recessive allele
222 [23], although it has a very high frequency, it was included in the simulation in place
223 of polled with an allele frequency of $1 - 0.0071 = 0.9929$. Based in part on the work of
224 Widmar et al. [24], who calculated average expected costs for dehorning and polled
225 genetics of \$11.79 and \$10.73, respectively, a value of \$40 was assumed for horned to
226 also account for breeders' preferences and premium marketing opportunities. Recall
227 that a positive value reduces the PA in the modified Pryce method, resulting in this
228 case in a lower frequency of horned.

229 **Analysis**

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

234

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

235 where p_t is the frequency of the major allele at time t , q_t is the frequency of the minor
236 allele at time t , and t is the time in **years** (ranging from 1 to 20). The minor allele
237 frequency at time 0 was the value used in each scenario for each recessive, and the
238 major allele frequency was calculated by subtracting the minor allele frequency from
239 1 (Figure 1). Expected allele frequencies for non-lethals was calculated based on
240 Hardy-Weinberg proportions [26] as:

241

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

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

249 **Computing environment**

250 Simulations were carried out using programs written in Python 2.7.9
251 (<http://www.python.org/>) as packaged in the Anaconda 2.1.0 distribution (Continuum
252 Analytics, Austin, TX). Results were analysed in IPython 2.2.0 notebooks
253 (<http://ipython.org/notebook.html>) using pandas 0.15.2 [28] and visualized using
254 matplotlib 1.4.0 [29]. The programs used to conduct the simulations, resulting data
255 files, and notebooks used for data analysis are available in a GitHub repository
256 (<https://github.com/wintermind/multiple-recessives>). All programs in the repository

257 are in the public domain. INBUPGF90 version 1.27 [30] was used to compute
258 coefficients of inbreeding for the Pryce scenario, and is available for download from
259 the University of Georgia ([http://nce.ads.uga.edu/wiki/doku.php?](http://nce.ads.uga.edu/wiki/doku.php?id=readme.inbugf90)
260 [id=readme.inbugf90](http://nce.ads.uga.edu/wiki/doku.php?id=readme.inbugf90)).

261

262 All simulations were performed on a Pogo Linux Atlas 1205 (Pogo Linux, Inc.,
263 Redmond, WA) computer with an 8-core AMD Opteron 6328 processor with a clock
264 speed of 3.2 GHz, 64 GB of DDR3 1600 MHz RAM, and 64-bit CentOS Linux EL6
265 (Red Hat, Inc., Raleigh, NC), and a Thinkmate RAX QS6-4210 (Thinkmate, Inc.,
266 Waltham, MA) workstation with four 12-core AMD Opteron 6344 processors with a
267 clock speed of 2.6 GHz, 256 GB of DDR3 1600 MHz RAM, and CentOS Linux EL7.
268 Data analysis and visualization were performed on a MacBook Pro with two Intel
269 Core i7 processors running at 2.9 GHz, 8 GB of DDR3 1600 MHz RAM, and Mac OS
270 X 10.7.5 (Apple Inc., Cupertino, CA).

271

272 Computation time for the random mating scheme averaged less than 9 minutes per
273 replicate in a one-recessive scenario (high frequency, high cost) and a 12-recessive
274 scenario (Holstein recessives). There was considerable variation in time required for
275 the truncation selection scheme, averaging 174 minutes in the one-recessive scenario
276 and 14 minutes in the Holstein scenario. This may reflect contention for I/O because
277 all simulations ran simultaneously on the same machine, and files were written to the
278 same RAID array. The time needed for the Pryce and modified Pryce schemes
279 averaged 514 minutes and 491 minutes in the one-recessive scenario, and 544 and 555
280 minutes in the Holstein scenario. Operations for the Pryce and modified Pryce
281 scenarios include allocation of large arrays, and the creation of large output files that

282 are not part of the random mating or truncation selection schemes. If matings are done
283 within herd, the memory used for 1 herd can be reused for the next to keep memory
284 requirements low. The time required for processing 1 generation rather than 20 should
285 be very reasonable.

286 **Results and discussion**

287 **Holstein recessives**

288 **Normal costs.** Observed allele frequency changes for 11 of the 12 recessives from the
289 four mating schemes are shown in Figure 2. Horned is not shown because the allele
290 frequency remained above 99% in all 4 schemes, and its inclusion in the plot obscured
291 the changes in alleles at low frequency. The frequency of the 10 lethals generally
292 decreased over time in all scenarios. The frequencies of HH2, HH4, HH5, CVM, and
293 red decreased significantly faster ($P < 0.05$ after a Bonferroni correction) under
294 Pryce's method than under the modified Pryce's method, while the frequency of HH3
295 decreased faster under the latter scenario. Several allele frequencies decreased at a
296 faster rate than expected under the Pryce's (Figure 3) and modified Pryce's (data not
297 shown) schemes. A clear advantage of the modified Pryce approach is that it
298 maintains the frequency of desirable recessives, such as red coat color, in the
299 population. In the Pryce scheme, the frequency of red decreased over time because
300 there is no mechanism in that scenario to balance undesirable economic effects of
301 inbreeding against the desirable economic value of some recessives. In the modified
302 Pryce scheme the positive economic value of red coat color offsets the inbreeding
303 penalty and maintains a relatively constant gene frequency over time. **Avoidance of**
304 **genomic inbreeding limits homozygosity, but eventually the population should**
305 **become homozygous for the favorable allele.**

306

307 Average TBV for the total merit index under selection were similar among the
308 schemes over time. The difference between cows in year 20 of the two schemes was
309 \$85, \$4,016 versus \$3,931 for Pryce and modified Pryce, respectively. Bulls in
310 generation 20 differed by only \$84 on average (\$4,016 versus \$3,932). These
311 differences are relatively small when compared to the overall genetic gain in the
312 population, which averaged approximately \$185 per year. The decrease in TBV after
313 the first 5 generations of selections is due to the mating of bulls to the first generation
314 of calves produced, which have lower TBV than the bulls and bull dams simulated as
315 the base population, and includes all animals, including calves that died and cows and
316 bulls that were culled without producing any offspring.

317

318 Average coefficients of inbreeding by generation for cows and bulls are shown in
319 Figure 4 for the all Holstein recessives scenario using the modified Pryce's method for
320 mate assignment. Inbreeding increased by approximately 0.8% per year in both the
321 cow and bull populations. The increase was constant in cows, but more variable in
322 bulls, which reflects the small number of bulls relative to cows, as well as changes in
323 the bull portfolio available over time. The same general pattern was observed across
324 all scenarios and mate allocation schemes (data not shown). A value of λ of \$25 was
325 used, which is similar to the \$23.11 calculated by [21], and higher than the \$12
326 reported by Smith et al. [31] and the AUS\$5.00 value used by Pryce et al. [18].

327

328 **Zero costs.** The scenario in which all recessives have an economic value of \$0 is
329 equivalent to assuming that all recessives have equivalent values and changes over
330 time should be driven principally by allele frequencies, with similar trends expected
331 for the Pryce and modified Pryce schemes. The observed allele frequency changes in

332 this scenario were similar to those noted in the normal price scenario (Figure 2), with
333 the lethals generally decreasing in frequency over time in all scenarios. Minor allele
334 frequencies decreased faster in the Pryce and modified Pryce schemes than under
335 random mating or truncation selection, and the rates were significantly faster than
336 expectations for all traits but red coat color ($P < 0.05$). The frequencies of
337 brachyspina, HH3, HH4, and horned decreased significantly faster in the modified
338 Pryce scheme, while red decreased faster using Pryce's method. The rates of change
339 of the other recessives did not differ. In both schemes, there was generally good
340 correspondence between the observed and expected changes for each recessive for
341 Pryce's method.

342

343 In generation 20, average TBV were \$143 higher for bulls and \$167 higher for cows
344 under the Pryce scenario than the modified Pryce scenario. The difference was larger
345 for bulls than under normal pricing, and slightly smaller for cows. In generation 0,
346 both populations had similar average TBV, so these differences represent the
347 cumulative effect of a slightly higher genetic trend under the Pryce scenario, probably
348 because matings of carrier cows to high genetic merit bulls were not penalized for the
349 economic consequences of producing affected calves.

350

351 **High costs.** In this scenario, the economic value of each recessive was increased by a
352 factor of 3 over the base scenario. The observed allele frequencies shown in Figure 5
353 show a surprising and unexpected increase in the frequency of HH4 under both the
354 Pryce and modified Pryce schemes, but not under the random mating or truncation
355 selection cases. There were also rapid decreases in the frequency of BLAD and
356 brachyspina, both with economic values of \$450 in this scenario, relative to the other

357 two mate allocation methods. The extreme value placed on BLAD and brachyspina
358 relative to HH4 may have resulted in more selection against the former two recessives
359 than the latter. It is possible that a method such as linear programming, which has
360 previously been applied to mate allocation [32,33], or an evolutionary algorithm [15,
361 16] would do a better job of preventing such a rapid increase in the frequency of a
362 lethal.

363 **Hypothetical recessives**

364 **High frequency, lethal recessives.** The rate of allele frequency change was similar for
365 both the low (\$20; Figure 6) and high (\$200; data not shown) value scenarios. This
366 suggests that at minor allele frequency the change from generation to generation is
367 driven principally by genotype frequencies, not by economic value. The fit of the
368 observed to expected allele frequency changes was very good in both scenarios (data
369 not shown).

370

371 **Medium frequency, lethal recessives.** Results for a minor allele with an initial
372 frequency of 0.50 and an economic value of either \$20 or \$200 were very similar to
373 those for the previous section. The economic values were again dwarfed by the allele
374 frequency, and a different mate allocation strategy will be needed to decrease the
375 allele frequency more quickly.

376

377 **Low frequency, lethal recessives.** The two low-frequency scenarios discussed in this
378 section are perhaps the most representative of the deleterious recessives seen most
379 commonly in livestock populations [22], that is, harmful alleles with low frequencies
380 (< 0.05). Both the Pryce and modified Pryce methods are successful at decreasing the
381 allele frequency over time when the value of the recessive is high, and they do so

382 more quickly than expected. However, the modified Pryce's method appears to be
383 more effective than random mating, truncation selection, or Pryce's method schemes
384 at lowering the allele frequency when the economic value of the recessive is low. It is
385 not clear why the modified Pryce's method performed so much better than Pryce's
386 method in the latter scenario because, at low allele frequency, the only way to increase
387 the frequency of the minor allele is either through inbreeding, or the spread of a *de*
388 *novo* mutation by a popular sire. While mutation is included in the simulation, each
389 replicate uses a different seed for the random number generator, so new mutations are
390 not expected to arise at the same time across different runs of the program.

391

392 ***Six hypothetical, lethal recessives.*** All four systems of mate allocation had similar
393 changes in allele frequencies over time similar results when the recessives all were
394 present in the population as the individual scenarios. Pryce's method and the modified
395 Pryce's method do produce slightly lower frequencies for some of the alleles that had
396 high or medium initial frequencies, but there was no apparent pattern based on the
397 economic value of each locus. Observed allele frequencies showed much better fits to
398 the predicted values than in the scenarios based on the actual Holstein recessives, but
399 that is expected when alleles have initial frequencies greater than 0.20.

400

401 There was no apparent difference between the change in allele frequencies over time
402 even though there was a tenfold difference between the high- (\$200) and low-valued
403 (\$20) recessives. When the minor allele frequency is high, many of the potential mate
404 pairs in the population will have their parent averages reduced, but the loci with large
405 values will be decreased more than those with low values, which should result in few
406 carrier-to-carrier matings.

407 **Horned and other high-frequency non-lethal recessives**

408 The horned allele is present at a frequency greater than 99% in the US Holstein
409 population, and there is increasing interest in reducing its frequency to improve
410 animal welfare. Spurlock et al. [34] recently studied three breeding schemes for
411 increasing the frequency of polled animals, concluding that it is possible to
412 substantially increase the number of polled animals in the population over a
413 reasonable time horizon. One of the key challenges is that there are few polled bulls,
414 but a haplotype test for polled **added** to the US genomic evaluation program **in 2013**
415 **now makes** it easier to identify heterozygous **and homozygous polled** animals for
416 mating. A scenario including only the horned recessive was simulated to determine if
417 the modified Pryce's scheme is an effective tool for increasing the frequency of polled
418 animals in the population.

419

420 Including horned with a value of \$40 was not effective in reducing the minor allele
421 frequency, **which remained essentially unchanged over 20 years of selection.** This is
422 probably because the frequency of the polled allele is so low that carriers were
423 unlikely to be one of the top-ranked bulls by TBV, and even if one was, the simulation
424 included a limit of 5,000 matings per bull per generation. That limited a single bull to
425 only being mated to 5% of the cow population in a generation. A second horned
426 scenario in which the economic value was increased from \$40 to \$400 was run to
427 determine if a higher cost would increase the rate of change. The second scenario was
428 also unsuccessful in changing the frequency of horned. These results are consistent
429 with the results from scenarios that included 12 Holstein recessives described above,
430 in which there was not appreciable change in the frequency of horned. A more
431 sophisticated approach for selecting mate pairs that will either produce polled
432 offspring or heterozygotes, **such as a scheme described by Li et al. [13,14] or**

433 Spurlock et al. [34] or the use of tools for non-meiotic allele introgression [35], will
434 be needed to effectively increase the frequency of polled (decrease the frequency of
435 horned) cows in the national dairy herd.

436 **Mating schemes**

437 As expected, there was negligible genetic trend under the random mating scheme
438 except in scenarios in which lethals had initial minor allele frequencies greater than
439 20%, which suggests that the simulation was performing reasonably. The results from
440 the truncation selection scheme were generally similar to the Pryce's and modified
441 Pryce's schemes for lethals, and to random mating for non-lethal recessives. This is
442 reasonable because the allele frequency of the lethals is expected to decrease over
443 time even if no additional selection pressure is imposed, and the threshold that retains
444 the top 10% of bulls for breeding ensures that genetic trend is positive. The truncation
445 selection scheme loosely resembles current mating strategies used on large
446 commercial dairies in North America.

447

448 More affected calves were observed in the Pryce's and modified Pryce's schemes than
449 in the random mating and truncation selection schemes. Figure 7 shows the proportion
450 of simulated calves that are culled due to recessive genotypes; results were similar for
451 the high value, high frequency and low value, low frequency scenarios (data not
452 shown). This is expected because a bull can have genetic superiority over his
453 contemporaries that exceeds the economic value assigned to the recessive alleles that
454 he may carry. Selection for reduced allele number rather than reduced frequency of
455 recessive genotypes could result in fewer embryonic losses [15]. There also is conflict
456 between the goal of eliminating recessives from the population, which involves fixing

457 associated haplotypes in a homozygous state, and minimizing inbreeding, which seeks
458 to avoid such increases in homozygosity.

459 **Mate allocation**

460 Mate allocation, the process of selecting mating pairs from a population of female and
461 some portfolio of males, has a long history in animal breeding programs in both
462 general [16,32,36,37] and trait-specific [38] applications. Many artificial insemination
463 firms provide recommended mate allocations to their customers as part of their
464 services, but the algorithms used are usually very simple. In 2012, Pryce et al. [18]
465 proposed the use of a simple sequential method that maximizes the parent average of
466 a mating after adjusting for any inbreeding of the offspring, subject to constraints on
467 the number of matings per bull per generation, and showed that their method
468 effectively constrains inbreeding when genomic relationships are used. Sun et al. [33]
469 recently showed that rates of genetic gain can be further increased when genomic
470 relationships are used and matings are allocated using linear programming to
471 simultaneously account for all desired constraints. The modified Pryce's method
472 proposed in this paper uses a sequential allocation method that also accounts for the
473 economic effect of recessives in the population. This may be a more practical
474 approach to account for recessives than to include them in selection indices because
475 of the difficulty of obtaining the marginal cost of a recessive independent of all other
476 costs already accounted for by the other traits in the index, although the possibility of
477 double-counting costs remains.

478

479 An advantage of the modified Pryce method over Pryce's original method is that the
480 former can be used to maintain the frequency of desirable recessives, such as red coat
481 color, in the population. There are other recessives, such as slick hair coat [39], that

482 are segregating in some lines of Holstein that are desirable to producers in sub-
483 tropical regions, and the modified Pryce's method could be used to increase the
484 frequency of that allele in the general population.

485

486 Pryce's method and the modified Pryce's method described in this paper also suffer
487 from order-dependence, that is, if the cows are reordered before bulls are allocated the
488 mate pairs change. This is probably not a serious problem if the elite bulls in the
489 population have similar breeding values, but could be important if there is a small
490 group of, for example, elite young genomic bulls that have much higher breeding
491 values than other active bulls. The use of linear programming (LP) rather than
492 sequential allocation of mate pairs **could** eliminate this problem, at the cost of some
493 added complexity in the implementation phase. **Sun et al. [33] found in simulation**
494 **that expected progeny differences were slightly higher for Holsteins (\$494 versus**
495 **\$474) when using LP compared to Pryce's method, and the Pryce strategy gave only**
496 **72% of the LP benefit over random mating. Progeny inbreeding also was slightly**
497 **lower (5.17 versus 6.03) using LP. This is similar in magnitude to the gains using LP**
498 **reported by Weigel and Lin [21].**

499

500 **Unlike an evolutionary algorithm-based approach, sequential allocation as used in the**
501 **Pryce and modified Pryce algorithms cannot account for a situation in which the value**
502 **of one mating is affected by other matings. This situation is common, for example,**
503 **when matings on multiple farms are considered simultaneously or when management**
504 **of parental coancestry is desired. Van Eenennaam and Kinghorn [15] recently**
505 **extended the MatSel program [16], which is based on an evolutionary algorithm, to**
506 **permit selection against the number of lethal alleles and recessive lethal genotypes**

507 considering either 6 or 100 lethal loci in high and low SNP frequency situations. Their
508 results show that the amount of genetic progress foregone in order to decrease the
509 incidence of lethal homozygous progeny is dependent upon allele frequencies, the
510 number of lethal loci, and the emphasis that is placed on avoiding embryonic deaths.
511 The approach they propose is theoretically more desirable than the modified Pryce
512 algorithm presented in this paper, but there is often considerable reluctance by
513 breeding organizations in the US to modify their software. Because of this, ease-of-
514 implementation is often accorded more importance than theoretically optimal
515 properties, and it is better to have an imperfect mate allocation tool used than no tool
516 at all.

517 **Integration with on-farm systems**

518 As of 25 August 2014 there were 722,093 genotypes in the National Dairy Database
519 maintained by the Council on Dairy **Cattle** Breeding (Reynoldsburg, OH, USA), of
520 which 555,981 were from females (https://www.cdcb.us/Genotype/cur_freq.html).
521 There is considerable interest from the farmers who have invested in those data in
522 using them to make optimal management and breeding decisions. Initial research
523 focused on increased genetic gains from the use of genomic information for early
524 culling decisions [40], but there also is interest in using those data with integrated on-
525 farm decision support systems. Gaddis et al. [41] showed that genotype information
526 may have value in predicting changes in health status, and it **is** reasonable to assume
527 that similar approaches can be used to make decisions about what animals to breed
528 based on fertility status, or what animals to dry-off or cull based on predicted future
529 performance. The modified Pryce's method described in this paper can easily be
530 integrated into existing herd management and mate planning software, where it could
531 be used to better inform culling decisions or identify matings that should be avoided.

532 In the case of some haplotypes, such as A2 beta-casein and polled, this may be a
533 useful tool for increasing allele frequencies without sacrificing substantial cumulative
534 genetic gain. It has been suggested that selecting for the number of alleles rather than
535 the frequency of homozygous genotypes might provide greater power for changing
536 allele frequencies.

537 **Tradeoffs and limitations**

538 Van Eenennaam and Kinghorn [15] found that the compromise between genetic gain
539 and the incidence of lethal homozygotes depends upon allele frequencies, the number
540 of deleterious loci, and the relative weighting that is placed on avoiding embryonic
541 mortalities. Selection against low-frequency alleles at 6 loci had little effect on genetic
542 gain, but gain decreased to 94% when selecting against lethal genotypes (their closest
543 scenario to the modified Pryce method). Genetic gain increased as the number of loci
544 increased, as did parental coancestry, and in their 100-locus situation it was not
545 possible to reduce embryo mortality to 0. Under the modified Pryce scenario it was
546 possible to reduce but not eliminate embryonic mortality. As the relative weighting
547 (economic value) of loci increases the foregone genetic progress also will increase.
548 MacArthur et al. [42] recently estimated that human genomes contain approximately
549 100 loss-of-function, and about 20 genes that are completely inactivated. While not all
550 of those mutations are lethal, it suggests that the 100-locus scenario of Van
551 Eenennaam and Kinghorn [15] represents a plausible limit to the selection problem.
552 Segelke et al. [43] suggested that a genetic index including haplotypes of interest
553 should be used when selecting females for mating and breeding values should be used
554 to select bulls in order to balance selection for specific alleles with genetic gain. As
555 the number of known recessives continues to increase it will be increasingly difficult
556 to assign proper weights to each of them because individuals will be more likely to be

557 carriers of multiple lethals, and the marginal value of each recessive will be difficult
558 to calculate without double-counting.

559 **Conclusions**

560 A modified version of Pryce's method [18] that accounts for the economic effects of
561 recessive conditions was developed and compared with random mating, truncation
562 selection, and Pryce's method for several different scenarios, including hypothetical
563 alleles as well as 12 recessives currently segregating in the US Holstein population.

564 The new method appears capable both of reducing the frequency of undesirable
565 recessives with low frequencies and maintaining or increasing the frequency of
566 desirable recessives. The method can easily be implemented in software used for mate
567 allocation, and the code used in this study is freely available for use as a reference
568 implementation.

569 **Competing interests**

570 The author declares that he has no competing interests.

571 **Authors' contributions**

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

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585 for the purpose of providing specific information and does not imply recommendation
586 or endorsement by the US Department of Agriculture. The USDA is an equal
587 opportunity provider and employer.

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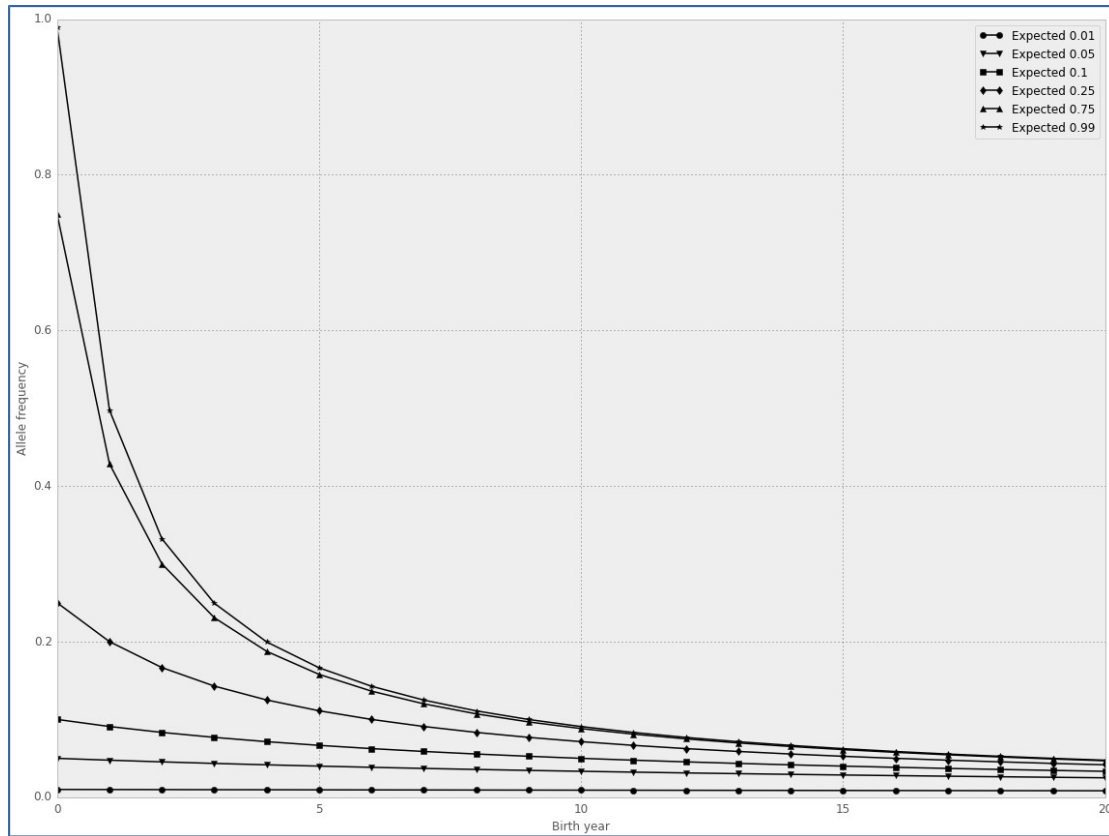
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710 **Figures**

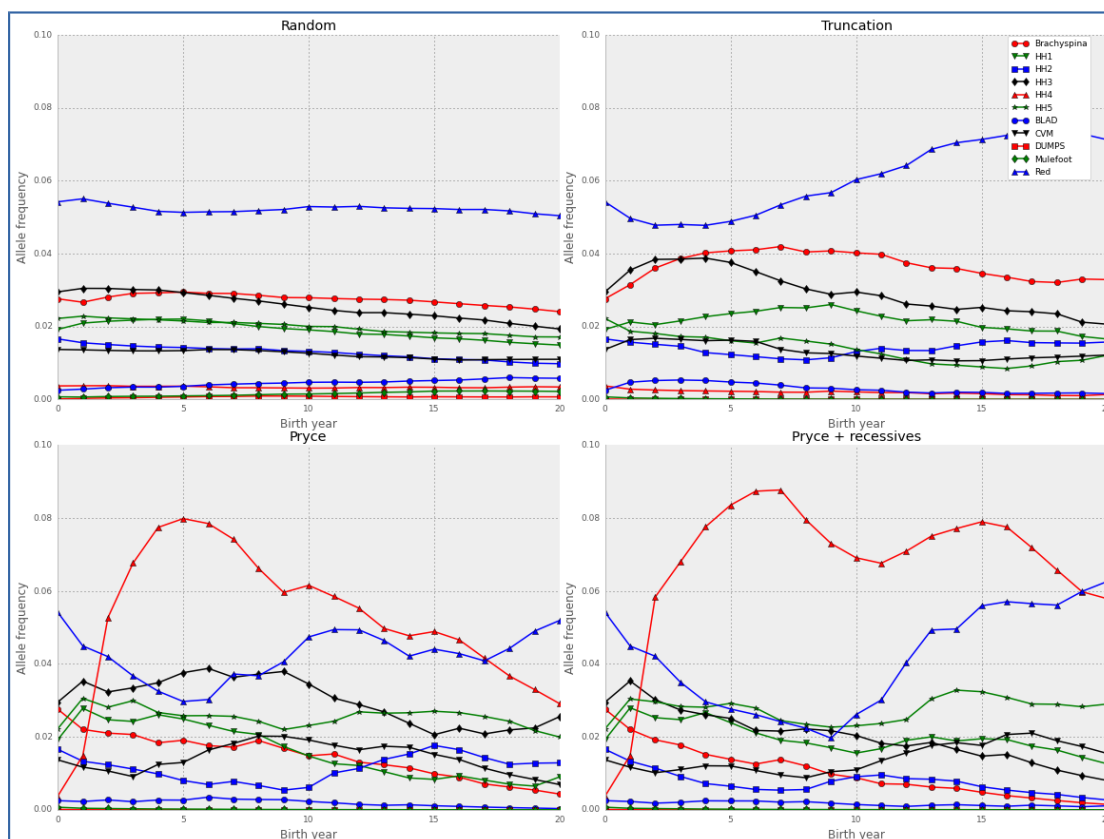
711 **Figure 1 - Expected allele frequencies**

712 The expected decrease in minor allele frequency for lethal recessives with initial

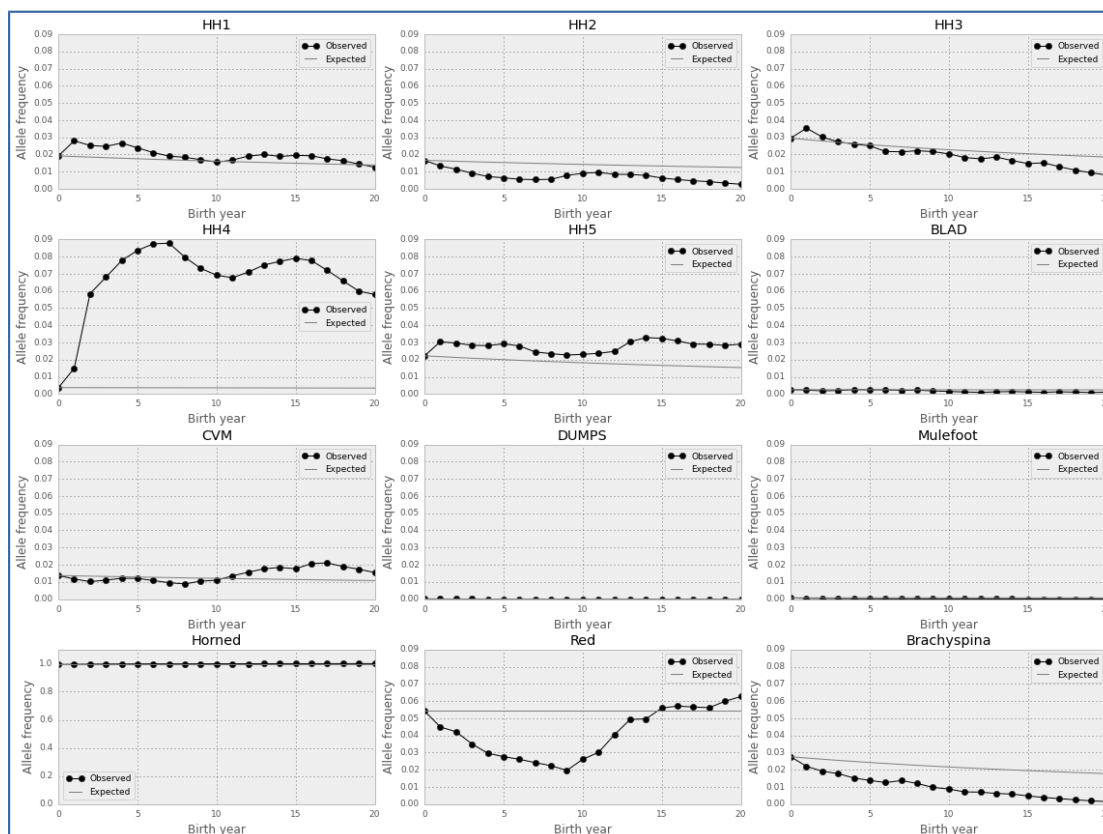
713 frequencies of 0.01, 0.05, 0.10, 0.25, 0.75, and 0.99.



715 **Figure 2 - Observed allele frequencies for Holstein recessives**
 716 Observed changes in minor allele frequencies for BLAD, brachyspina, CVM,
 717 DUMPS, HH1–HH5, mulefoot, and red coat color over 20 years under random
 718 selection, truncation selection, Pryce’s method for controlling genomic inbreeding,
 719 and Pryce’s method accounting for recessives.



721 **Figure 3 - Observed versus expected allele frequencies under the Pryce**
 722 **scenario**
 723 Observed versus expected allele frequencies under the Pryce scenario. Observed
 724 versus expected changes in minor allele frequencies for BLAD, brachyspina, CVM,
 725 DUMPS, HH1–HH5, horned, mulefoot, and red coat color over 20 years using
 726 Pryce’s method for controlling genomic inbreeding. **Note that the horned subplot is**
 727 **scaled differently on the y axis than the other subplots because of its allele frequency.**

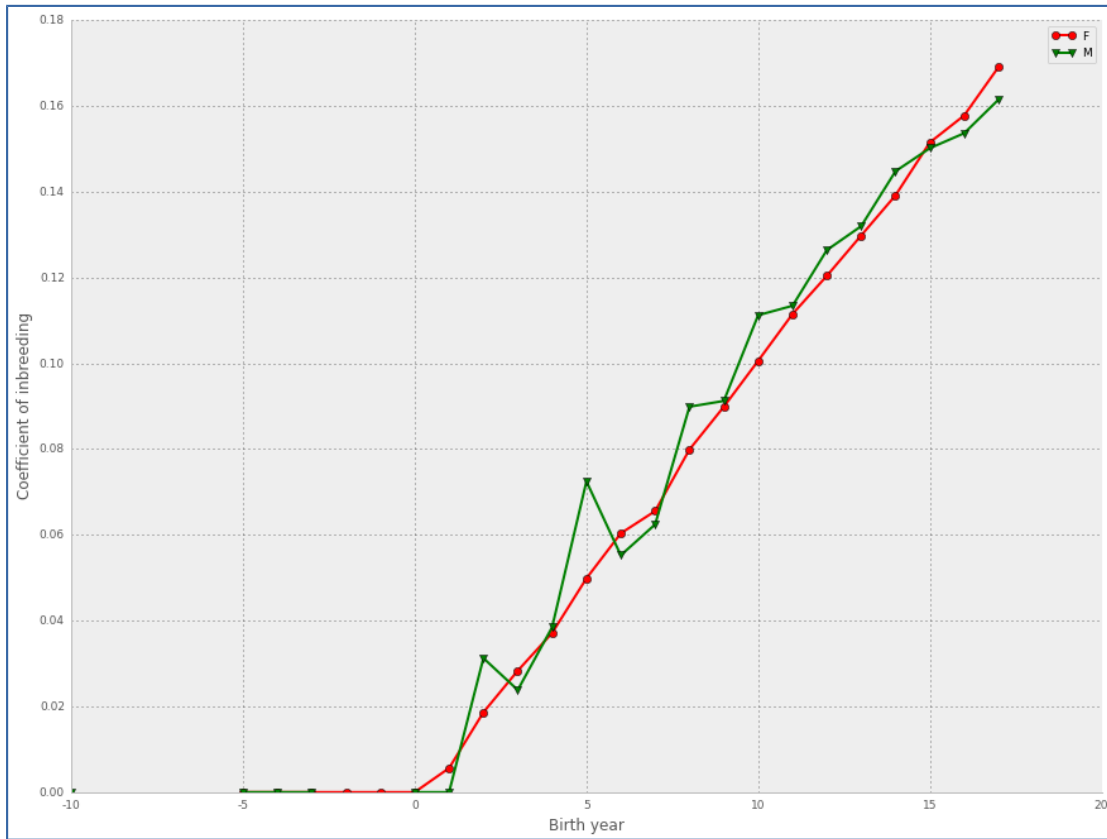


729 **Figure 4 - Inbreeding in Holsteins**

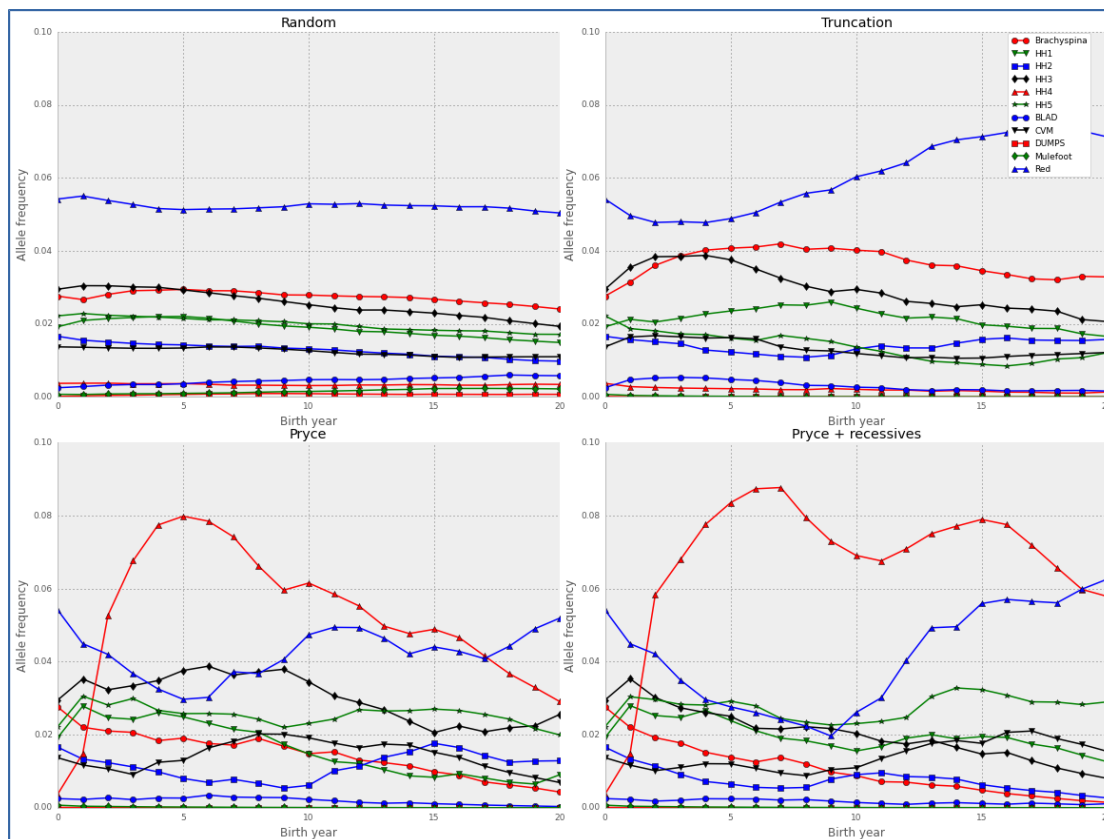
730 Average coefficients of inbreeding for bulls (M) and cows (F) in the all Holstein

731 recessives scenario using Pryce's method accounting for recessives

732 (Pryce+recessives).

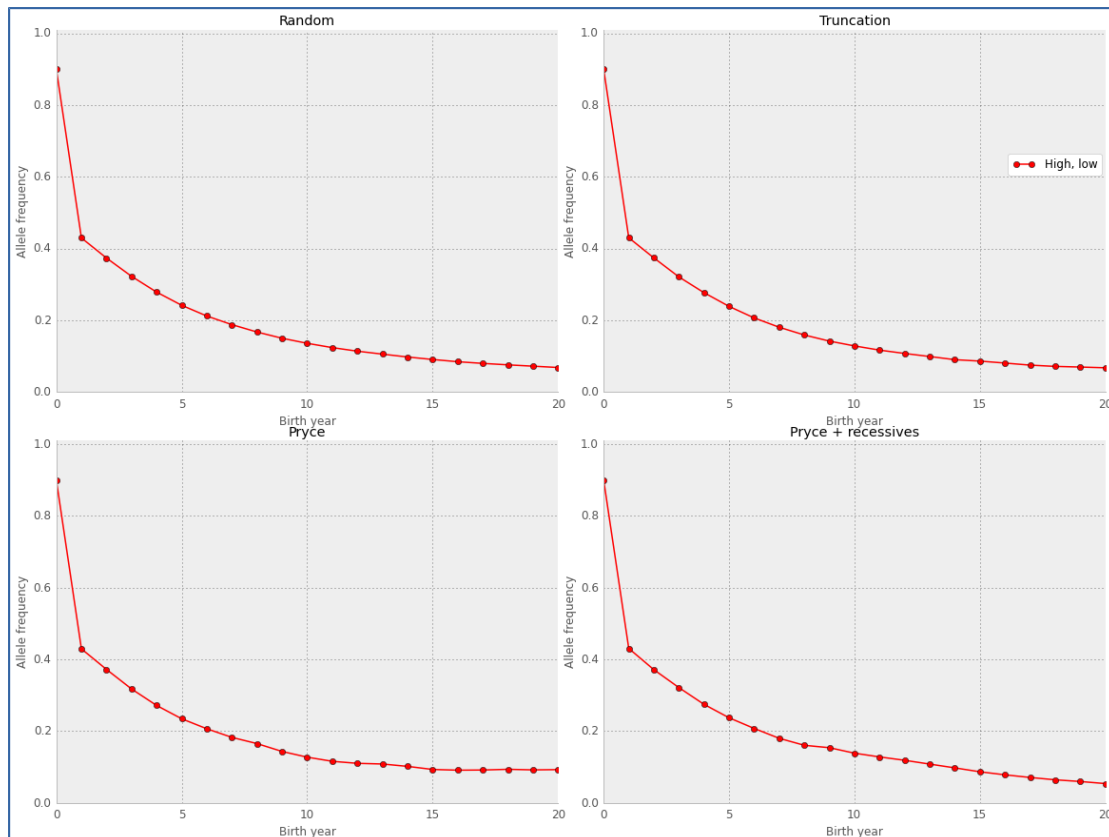


734 **Figure 5 - Observed allele frequencies for Holstein recessives with high**
 735 **economic values**
 736 Observed changes in minor allele frequencies for BLAD, brachyspina, CVM,
 737 DUMPS, HH1–HH5, mulefoot, and red coat color over 20 years under random
 738 selection, truncation selection, Pryce’s method for controlling genomic inbreeding,
 739 and Pryce’s method accounting for recessives.

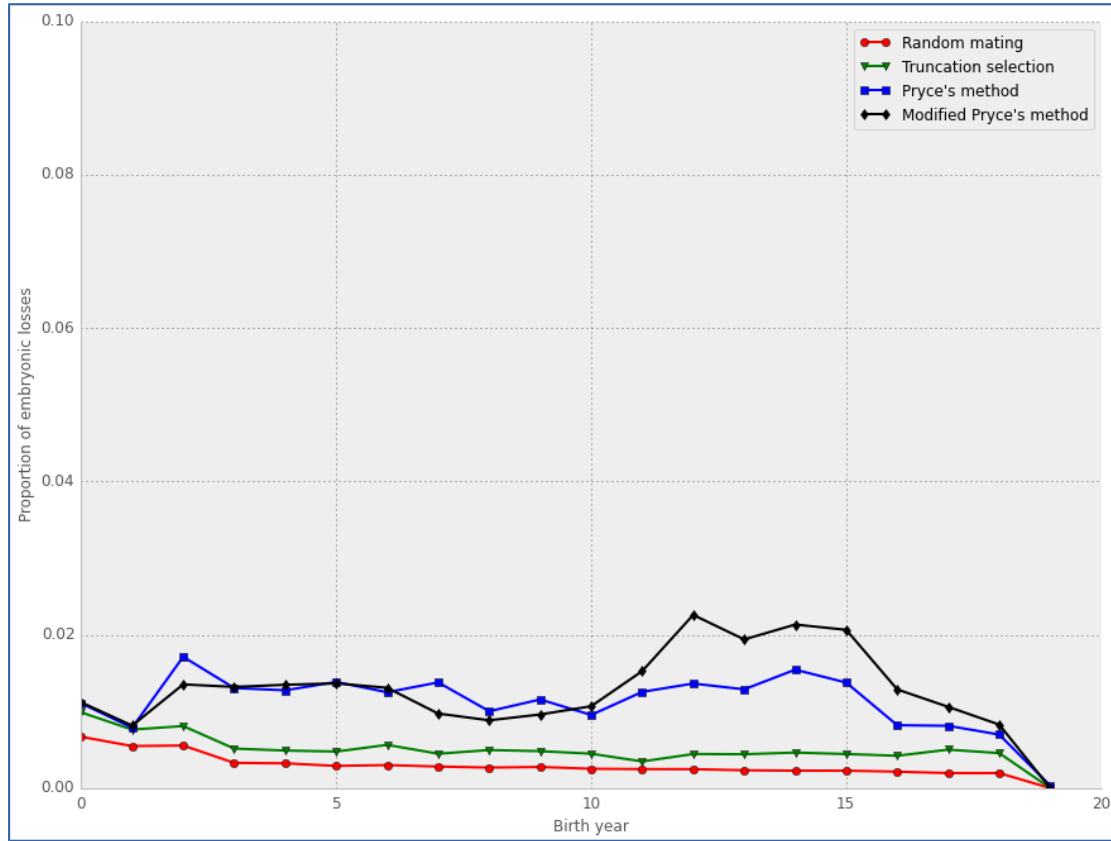


741 **Figure 6 - Observed allele frequencies for a hypothetical recessive with a high**
742 **frequency and low value**

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



748 **Figure 7 - Embryonic deaths by birth year**
749 Proportion of embryos in each birth year that died due to the effects of recessive
750 genotypes.



752

753 **Tables**

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

Group	Scenario ¹	N ²	Frequency	Recessives		
				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	
Hypothetical	1	0.90	20	High, low	Yes	
		0.90	200	High, high	Yes	
		0.50	20	Medium, low	Yes	
		0.50	200	Medium, high	Yes	
		0.01	20	Low, low	Yes	
		0.01	200	Low, high	Yes	
		All recessives	6	As above.		
Horned	1	0.9929	40	Horned	No	
		0.9929	400	Horned	No	

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

756 ²The number of recessives in the scenario.

757 ³Positive values are undesirable and negative values are desirable.