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Breeding a better cow—Will she be adaptable?[1]

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ABSTRACT

Adaption is a process that makes an individual or population more suited to their environment. Long-term adaptation is predicated on ample usable genetic variation. Evolutionary forces influencing the extent and dynamics of genetic variation in a population include random drift, mutation, recombination, selection, and migration; the relative importance of each differs by population (i.e., drift is likely to be more influential in smaller populations) and number of generations exposed to selection (i.e., mutation is expected to contribute substantially to genetic variability following many generations of selection). The infinitesimal model, which underpins most genetic and genomic evaluations, assumes that each quantitative trait is controlled by an infinitely large number of unlinked and non-epistatic loci, each with an infinitely small effect. Under the infinitesimal model, selection is not expected to noticeably alter the allele frequencies, despite a potential substantial change in the population mean; the exception is in the first few generations of selection when genetic variance is expected to decline, after which it stabilizes. Despite the common use of the heritability statistic in quantitative genetics as a descriptor of adaption or response to selection, it is arguably the coefficient of genetic variation that is more informative to gauge adaptation potential and should, therefore, always be cited in such studies; for example, the heritability of fertility traits in dairy cows is generally low, yet the coefficient of genetic variation for most traits is comparable to many other performance traits, thus supporting the observed rapid genetic gain in fertility performance in dairy populations. Empirical evidence from long-term selection studies, across a range of animal and plant species, fails to support the premise that selection will deplete genetic variability. Even after 100 yr (synonymous with 100 generations) of selection in corn for high protein or oil content, there appears to be no obvious plateauing in the response to selection. Although populations in several selection experiments did reach a selection limit after multiple generations of directional selection, this does not equate to an exhaustion of genetic variance; such a declaration is supported by the observed rapid responses to reverse selection once implemented in long-term selection studies. New technologies such as genome-wide enabled selection and genome editing, as well as having the potential to accelerate genetic gain, could also increase the genetic variation, or at least reduce the erosion of genetic variance over time. In conclusion, there is no evidence, either theoretical or empirical, to indicate that dairy cow breeding programs will be unable to adapt to evolving challenges and opportunities, at least not because of an absence of ample genetic variability.
Key words: evolution, dairy, genetic, selection, genomic

INTRODUCTION

Adaption is a process that makes an individual or population better suited to their environment. Adaptation itself refers to both the current state of being adapted, as well as the dynamic evolutionary process that leads to the adaptation. The effect of recent artificial selection in various animal breeding programs is well established and proven (Merks, 2000; Chen et al., 2003; Havenstein et al., 2003; Macdonald et al., 2008). In a controlled experimental study comparing grazing Friesian dairy cows representative of germplasm from the 1970s (n = 45) versus the 1990s (n = 60), Macdonald et al. (2008) documented a 23% greater fat plus protein lactation yield in the latter when evaluated at 6 t of DM offered per cow. Figure 1 illustrates the change in phenotypic milk yield per cow in the US Holstein population (https://queries.uscdcb.com/eval/summary/trend.cfm) and apportions it out to genetic and nongenetic influences. The slope of a simple linear regression fitted through the annual phenotypic and genetic means from the years 1970 to 2015 is 305 lb (i.e., 138 kg) and 173 lb (i.e., 78 kg), respectively, implying that genetic gain has accounted for over half

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the gains in phenotypic milk yield; the R^2 of the regression on genetic merit for milk yield was 0.998, implying very little deviation from linearity. It should be noted, nonetheless, that the observed annual gain in nongenetic performance (Figure 1), is in part attributable to genetic improvement, and vice versa. For example, the highly energy-dense diets fed to the modern dairy cows would elicit little milk output advantage if the cow was not bred to exploit such a diet. Therefore, in dairy cow production systems, genetic merit and environment are actually co-evolving. In fact, the environment can have quite a considerable effect on the population dynamics of genetic variance. Certain environmental conditions can favor particular genotypes, thus affecting the genetic variability within the population; this is especially true for relatively rapid and acute changes in the environmental conditions where adaptation of the entire population through genetic change is simply not fast enough. Similarly, a relatively stable environment such as confinement production systems (or indeed vaccination and reproduction synchronization) can, in some instances, reduce selection pressures on a population.

A question that is often raised, however, is if the heretofore observed year-on-year rate of improvement in performance from (dairy cow) breeding programs is sustainable, or if there is a risk of exhausting the genetic variability and thus adaptation capacity. On closer examination of the first derivative of the US Holstein milk yield genetic (and nongenetic) trends in Figure 1, there is a noticeable erosion in the rate at which the annual genetic gain is increasing from the mid-1970s; the first derivative of the annual genetic gain is still positive though, implying that genetic gain in milk production is at least still occurring. Historical genetic trends are a function of the available exploitable genetic variance (and covariances with other traits such as survival) as well as the relative selection pressure on the trait(s). Although one may initially consider a deceleration in genetic gain to be synonymous with an exhaustion of genetic variability, this may not necessarily be true. Exhaustion of genetic variability, in the absence of evolutionary forces that introduce new variability (discussed later), will indeed reduce the rate of genetic gain; in contrast, however, an observed reduction in genetic gain does not necessarily imply an exhaustion of genetic variability (discussed in detail later), and therefore even if the rate of genetic gain diminishes, it does not equate to an inability of a population to adapt, either phenotypically or genetically.

This review will focus on the theory and evolutionary forces underpinning genetic variability and the ability of an animal to adapt, as well as providing empirical evidence of long-term sustainable genetic gain in a range of different animal and plant species. The review concludes with speculation on the possible contributions of developments in key technologies to building a more adaptable cow for the future, as well as strategies that can be exercised to mitigate the risk of breeding a cow that cannot readily adapt to ensuing challenges and opportunities.

IMPORTANCE OF ADAPTATION, AND EVIDENCE OF SUCH IN DAIRY COWS

Agricultural practices in the past century have changed dramatically, and dairy production is no exception (VandeHaar and St-Pierre, 2006). The dairy cow has had to adapt to such changes, the greatest of which in most countries has probably been a change from low-input pasture-based production systems to higher input, highly energy-dense diets fed in confinement. The consequence of aggressive single-trait selection for increased milk production in (predominantly Holstein) dairy cows was a very noticeable deterioration in cow reproductive performance (Berry et al., 2014), the rationale for which has been extensively discussed elsewhere (Berry et al., 2016). The ensuing erosion in farm profit necessitated the adaption or evolution of the Holstein to become more fertile. Figure 2 illustrates the phenotypic change in daughter pregnancy rate in US dairy cows from 1957 to 2015 (https://queries.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.d#StartBody); genetic merit for reproductive performance declined until approximately the year 2010, after which it improved. Similar trends in reproductive performance in dairy cows have been observed in other international populations, signifying that, despite the low heritability for reproductive performance in dairy cows, (rapid) gains in reproductive performance were achieved (Berry et al., 2014).

Climate change will affect dairy cattle production directly (i.e., heat stress, exotic vector-borne diseases) as well as indirectly (e.g., water and feed quality as well as quality). Furthermore, not only are ruminant production systems affected by climate change, but these production systems themselves are cited as contributing substantially to such climate change (Opio et al., 2013). The consequences and challenges of climate change for dairy cow production have been documented elsewhere (Gauly et al., 2013) and the necessity for ruminant production systems to adapt, in the pursuit of reducing environmental footprint, has also been extensively discussed (Monteny et al., 2006; Weiske et al., 2006). The greater competition for water, energy, and land supply (owing to urbanization and population growth) will require a further adaptive capacity in dairy cows.

Nongenetic interventions or strategies (e.g., nutrition, vaccination) can undoubtedly help circumvent

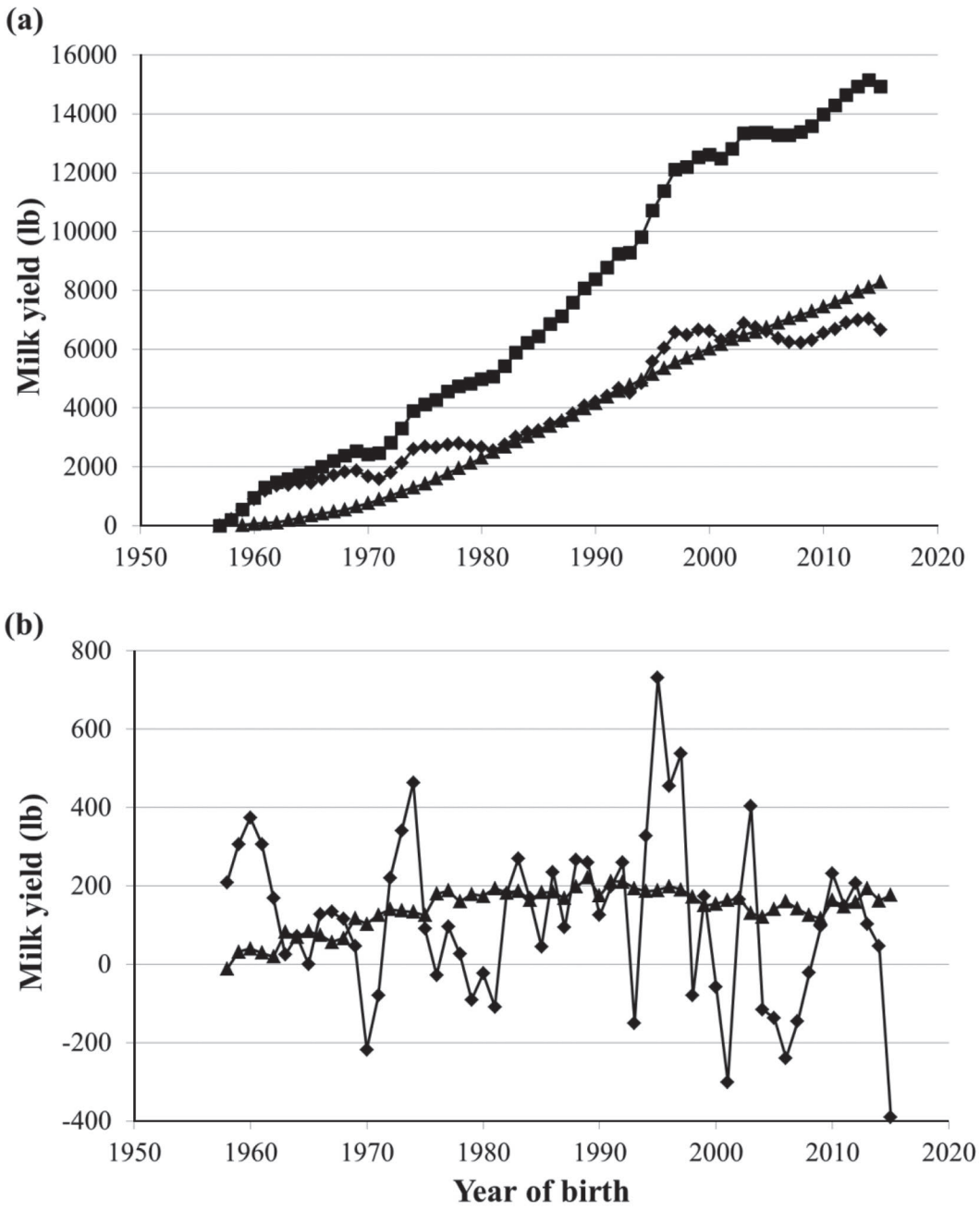

Figure 1. (a) Annual phenotypic (squares), genetic (triangles), and environmental (diamonds; i.e., phenotypic trends minus genetic trends) for milk production in US Holsteins; (b) first derivative trends of the annual genetic (triangles) and environmental (diamond) trends (https://queries.uscdcb.com/eval/summary/trend.cfm). One pound (lb) is equal to 0.4536 kg.

many of the anticipated challenges, or to seize emerging opportunities, especially those of rapid onset. Such strategies may not always be (economically) feasible and, in their own right, could actually generate consequences themselves; 2 examples include (1) the effect of excessive antibiotic usage in animals on respective residues in animal-derived foods and associated antimicrobial resistance, and (2) increasing the energy density of the cow diet through the use of supplementation that could have been used to feed the human population. Recurrent genetic selection over generations, however, has the benefit of accumulated genetic gain with the parents of each generation benefiting from the gain of previous generations.

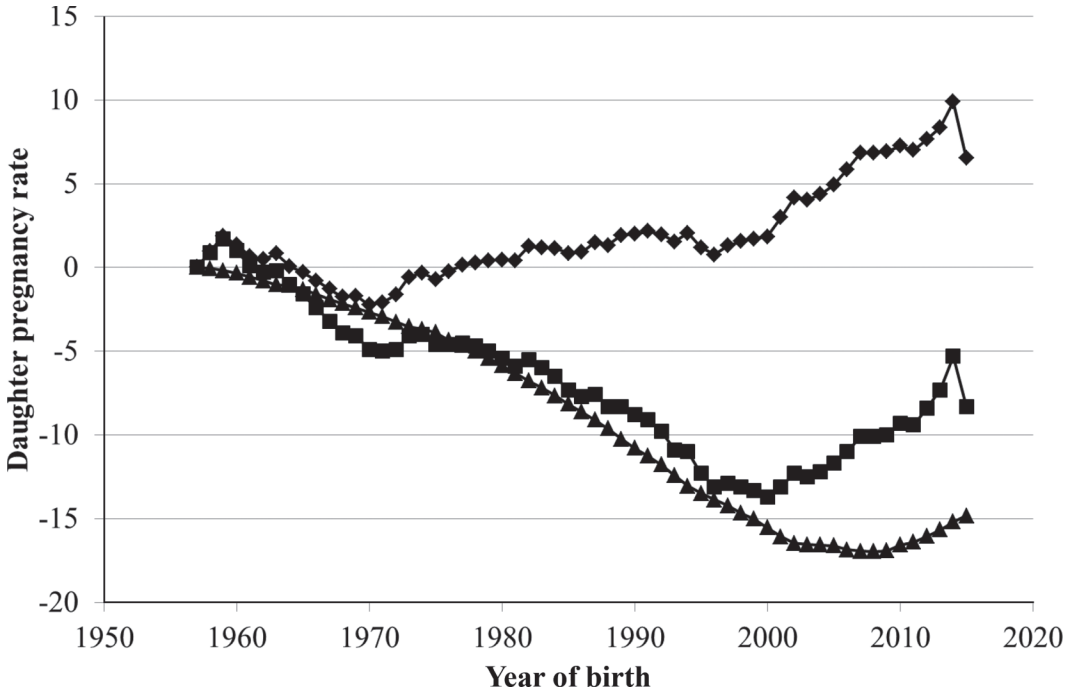

Figure 2. Annual phenotypic (squares), genetic (triangles), and environmental (diamonds; i.e., phenotypic trends minus genetic trends) for daughter pregnancy rate in US Holsteins (https://queries.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.d#StartBody).

THE INFINITESIMAL MODEL

The infinitesimal model (Fisher, 1918) constitutes the cornerstone of almost all modern-day genetic (and most genomic) evaluations for most performance traits. The infinitesimal model assumes that a trait is controlled by an infinitely large number of unlinked and nonepistatic loci, each with an infinitely small effect. Based on the assumptions of the infinitesimal model, allele frequencies do not noticeably change with selection, despite large possible changes in the population mean. This can occur because the small allele frequency changes are occurring across an infinitely large number of loci. Based on the infinitesimal model, in a random mating population with no selection, no covariance is expected to exist among genotypes at different loci and thus the total genetic variance is simply the sum of the variance components at each locus. This principle of a change in mean with no change in allele frequency under the infinitesimal model can then be easily illustrated (Lynch and Walsh, 1998), where we assume there are n loci with genotypes AA, AB, and BB, the allele substitution effect is a, and the frequency of the A allele is p. The effect at the locus is 2ap, and thus the mean of the population across all n loci is n2ap with a population-level genetic variance of $n2p(1 - p)a^2$ (Falconer and Mackay, 1996) assuming loci are in what is termed linkage equilibrium; linkage equilibrium is the nonrandom association of alleles at different genomic locations (i.e., loci). For the genetic variance to remain constant as the number of loci (i.e., n) increase, the allele substitution effect per locus (i.e., a) must therefore be $n^{-1/2}$. Based on this, the change in population mean following 1 generation of selection ($\Delta\mu$) may be calculated as

$$\Delta\mu = n2a\Delta p,$$

where Δp is the change in allele frequency following selection at each of the n loci with an allele substitution effect of a, or in other words:

$$\Delta p = \frac{\Delta\mu}{n2a},$$

where $\Delta\mu$ is the change in the mean of the population following 1 generation of selection based on n loci each with an allele substitution effect of a. Because the allele substitution effect for n loci is $n^{-1/2}$, Δp approaches zero as the number of loci approach infinity (i.e., the infinitesimal model). Therefore, quite clearly, under the assumption of Fisher's infinitesimal model, a change in population mean can occur without an appreciable change in allele frequency. Using a very simple numerical example considering 10,000 loci (which is far from infinity) with an allele substitution effect of each 0.01

standard deviation units, a change in allele frequency across all loci of just 1 percentage unit (i.e., 0.50 to 0.51) will equate to a large change in the mean of 2 standard deviation units; a 5 percentage unit change in the allele frequency at all loci will equate to a change in the population mean of 10 standard deviations!

Lynch and Walsh (1998) deterministically quantified the effect of selection, under the assumptions of the infinitesimal model, on genic variance (i.e., additive genetic variance in the absence of linkage disequilibrium). Assuming the allele frequency after 1 generation of selection (p') is $p + \Delta p$, then the change in genic variance $\left(\Delta\sigma_a^2\right)$ can be defined as

$$\Delta\sigma_a^2 = n2a^2p'\left(1-p'\right) - n2a^2p\left(1-p\right),$$

where $\Delta\sigma_a^2$ is the change in genic variance, p is the allele frequency in the original population, p' is the allele frequency after 1 generation of selection, n is the number of loci, and a is the allele substitution effect. This equation approximates to $a(1 - 2p)\Delta\mu$; because the allele substitution effect (i.e., a) is $n^{-1/2}$, then the change in genic variance due to changes in allele frequency is approximately the reciprocal of the square root of the number of loci. This therefore implies that, under the assumptions of the infinitesimal model, a large change in the mean of the population can occur with selection but with negligible change in the genic variance. Using the simple example previously described with 10,000 loci and an allele substitution effect of 0.01 units, then a change in allele frequency of 0.01 (i.e., from 0.50 to 0.51) will equate to a reduction in genic variance of just 0.0002 units from the previous generation with an original variance of 0.5. Note, if the frequency of the favorable alleles is less than 0.5, say 0.3, selection assuming the same parameters will actually increase the genic variance by 0.0078; this is because the variance of a binomial (i.e., A or B allele) asymptotes at a frequency of 0.5.

Changes in additive genetic variance due to selection, however, can occur for reasons other than through changes in the allele frequency patterns across the genome. The genetic variance can also be altered by linkage disequilibrium between alleles at different loci (Bulmer, 1980) where negative inter-loci covariances can develop as a result of selection. Changes in the covariance between 2 loci are approximately n^{-2} (Bulmer, 1980; Turelli and Barton, 1990), and because, as previously stated, there are n loci, there are n^2 possible 2-way interactions between loci; hence, the contribution of linkage disequilibrium to the genetic variance is n^2 times n^{-2}, which does not go to zero as the number of loci (i.e., n) goes to infinity. The Bulmer effect (Bulmer, 1971) is the term commonly used to describe the reduction in response to selection where negative disequilibrium exists, thereby depleting the genetic variance. Under truncation selection (i.e., only the top proportion of animals from the normal distribution of candidates are selected as parents of the next generation) most of the disequilibrium is created by generation 5 after which it stabilizes (Walsh, 2004). The reduction in response to selection due to the Bulmer effect is greatest when the proportion of individuals selected as parents of the next generation gets smaller or for higher heritability traits (Walsh, 2010). Crucially, however, linkage disequilibrium can be broken down during meiotic recombination, thereby actually releasing again the genetic variance (discussed later).

EVOLUTIONARY FORCES ACTING ON GENETIC VARIABILITY

The extent of genetic variability in a population is a function of the evolutionary forces of random drift, migration (also called gene flow), mutation, recombination, and (natural) selection.

Random Drift

Random genetic drift occurs when the frequency of alleles at a locus change across generations, solely by chance alone, although the likelihood can increase with inbreeding which contributes to a smaller effective population size (Crow and Kimura, 1970). In the absence of other evolutionary forces, in non-overlapping generations, the mean number of generations before a neutral allele (i.e., an allele with no effect on fitness or survival) in linkage equilibrium is lost through genetic drift may be estimated as

$$\overline{T_{LOST}} = \frac{-4N_e p}{1-p}\log_e(p),$$

where $\overline{T_{LOST}}$ is the mean number of expected generations before the neutral allele is lost, N_e is the effective population size, and p is the frequency of the allele in the population. This simplifies to

$$\overline{T_{LOST}} = 2\frac{N_e}{N}\log_e(2N)$$

when a de novo mutation appears in a very large population of size N so that p is negligible. In contrast, the number of generations for a de novo mutation in a very large population (i.e., p is negligible) to become fixed (i.e., $\overline{T_{FIX}}$) is

$$\overline{T_{FIX}} = 4N_e,$$

where N_e is the effective population size. The effect of drift on genic variance at generation t [i.e., $\sigma_a^2(t)$], in the absence of dominance and epistasis, can be predicted as (Walsh, 2010)

$$\sigma_a^2(t) = \sigma_a^2(0)\left(1 - \frac{1}{N_e}\right)^t,$$

where $\sigma_a^2(0)$ is the genic variance in the base population, N_e is the effective population size, and t is the number of generations. The effect of drift can be illustrated by a very simple example of a single biallelic locus in a population of n individuals where the frequency of the A allele is p; therefore, the frequency of the a (i.e., alternative) allele is $(1 - p)$. Assuming generations do not overlap, and that each allele in the next generation is randomly sampled from the previous generation, the probability of exactly k copies of the A allele appearing in the next generation of N individuals can be calculated using the binomial coefficient

$$\binom{2N}{k} p^k q^{2N-k}.$$

Assuming the population size is 10 (i.e., n = 10, which therefore contains 2N times alleles), p (and therefore q which is 1 − p) is 0.5, and k is 10 (i.e., the same as the previous generation), then the probability of this occurring is just 17.6%; hence, the probability of not having a 0.5:0.5 frequency is 82.4% (i.e., 100–17.6%). If the actual frequency of the A allele was 0.6, then the expected frequency of the next generation reflects this; the probability of randomly drawing an A allele has increased from 0.5 to 0.6. Therefore, the effect of the (random) change in allele frequency in 1 generation has ramifications for the subsequent generations.

(Effective) population size is one of the factors of greatest influence on random genetic drift and the effect of drift on allele frequency per generation in a population of 10, 100, or 1,000 individuals is illustrated in Figure 3 based on just a single replicate of a simulation. The frequency of the A allele per generation is more erratic with the smaller population sizes, especially the population with 10 individuals. Moreover, the A allele reaches fixation in the population of 10 animals at generation 13, whereas fixation did not occur within 30 generations for either of the 2 other larger populations. Of course, despite fixation, the a allele can reappear if introduced through one of the other evolutionary forces (e.g., mutation, migration) as well as through human intervention (e.g., genome editing).

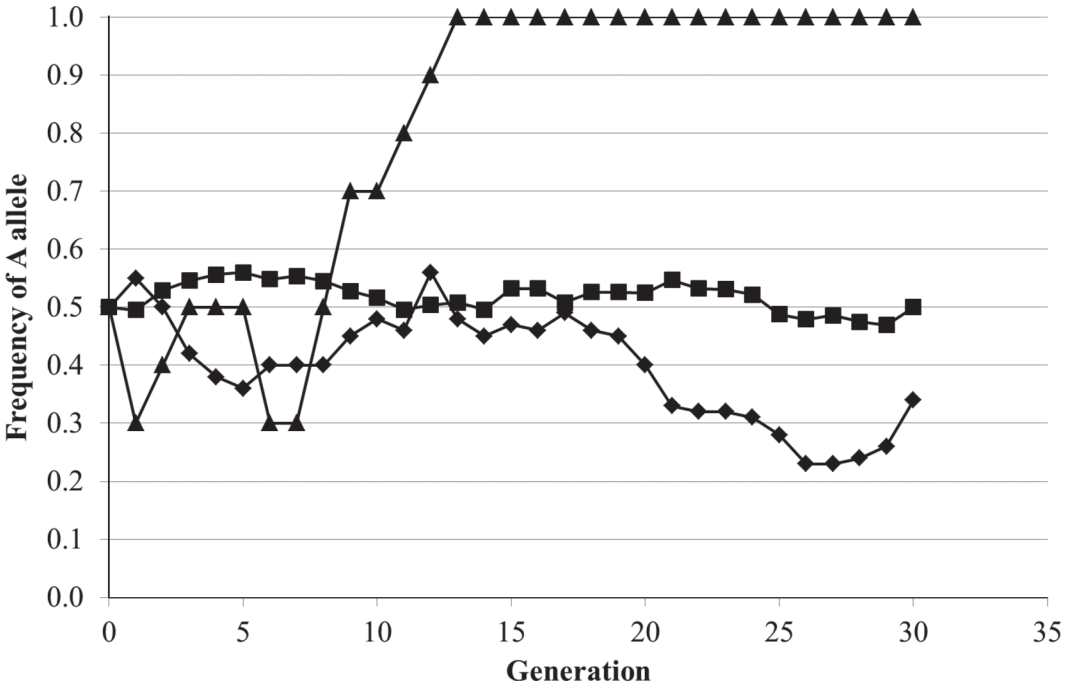

Figure 3. Frequency of an allele by generation, where the base allele frequency (i.e., generation 0) is 0.5, based on one replicate of a simulation of random genetic drift where the population size is 10 (triangle), 100 (diamond), and 1,000 (square).

Despite the large global Holstein population, it may be somewhat surprising that genetic drift has had a noticeable effect, especially on the reproductive performance of the breed. Several known lethal recessive mutations (i.e., variants that do not appear in the homozygous state because such a state is lethal) exist, 2 of which, complex vertebral malformation (**CVM**) and bovine leukocyte adhesion deficiency (**BLAD**), originate from the same family line that includes Penstate Ivanhoe Star; Penstate Ivanhoe Star received the BLAD mutant allele from his dam Penstate Lucifer Anna and the CVM mutant allele from his sire Osborndale Ivanhoe. The prevalence of CVM in the German Holstein herd in 2002 was 8.3%, whereas the prevalence of BLAD in the German Holstein herd in 1997 was 9.4% (Schütz et al., 2008). Kearney et al. (2005) reported that 16 of the top 100 Holstein sires for production in the United Kingdom in 2004 were CVM carriers. There appears to be no (large) favorable allele effect of milk production in the vicinity of each mutation; this suggests therefore that the spread of these mutations was due to random drift attributable to genetic superiority of the Ivanhoe line for milk production.

Migration

Gene flow or migration is the transfer of genetic variation from one population to another. The effect of migration on allele frequency can be illustrated using a simple, single locus model (Falconer and Mackay, 1996). The allele frequency at a single locus in a population following migration (q_1) is

$$q_1 = mq_m + (1 - m)q_0 \text{ or } q_1 = m(q_m - q_0) + q_0,$$

where q_1 is the allele frequency in the first generation following migration, m is the proportion of the new population that are immigrants [and therefore (1 − m) is the proportion of the new population that are natives], q_m is the allele frequency in the immigrant population for that locus, and q_0 is the frequency of the allele in the original native population for that locus. Therefore, the change in allele frequency at a given locus following migration (Δq) is simply

$$\Delta q = m(q_m - q_0),$$

signifying that the change in allele frequency of a population in the first generation following migration is a function of the difference in allele frequency between the native and immigrant population (i.e., $q_m - q_0$) and the immigration rate (i.e., m). Unlike mutation (discussed later), the migration rate can be substantial and thus the change in allele frequency can accordingly be great. As breeds become more extreme, however, as could be said of the Holstein breed relative to other dairy breeds, the usefulness of migration through breed substitution or crossbreeding with other breeds diminishes, although migration from other populations of Holstein (e.g., New Zealand Holsteins introduced to Ireland; Horan et al., 2006) is still a viable option.

Mutation

A mutation is a heritable change that occurs in a DNA sequence. Mutations occur due to either external environmental factors (e.g., UV radiation) or when errors happen during DNA replication. Mutation rate is defined as the probability that a copy of an allele changes to another allelic form in one generation (Griffiths et al., 2000). Mutational variance may be defined as the new additive genetic variance entering a population each generation due to mutations (Hansen, 2006). Mutational variance generally introduces variability and is thought to be the main contributing force to continued response to selection in populations that have been exposed to multiple generations of selection (Hill, 1982). Mutational variance has been estimated to contribute 0.1% of the environmental variance per generation (Lynch and Walsh, 1998), giving a "mutational heritability" (i.e., $\frac{\text{Mutational variance}}{\text{Environmental variance}}$; Hill, 2010) of 0.001; this implies an increase in overall heritability of approximately 0.1% per generation.

A 0.1% increase in heritability per generation due to mutations may seem small, but of course it accumulates over time. Based on this statistic, coupled with empirical evidence, Brotherstone and Goddard (2005) proposed that normal amounts of genetic variance for quantitative traits can be maintained by effective population sizes even less than 1,000. Assuming a global dairy cow population of 270 million (https://dairy.ahdb.org.uk; accessed May 2017), and an average mutation rate in cattle similar to in humans of 1.1×10^{-8} per base per generation (Nachman and Crowell, 2000), this equates to almost 3 de novo mutations per nucleotide per generation; in the US dairy cow population of 9.1 million cows, this equates to 1 mutation every 10 base pairs per generation or 261 million new mutations per generation in the entire US dairy cow population (assuming no animal had the same de novo mutation). Hence, it is not so much that no new genetic variation is being generated, but the issue is how to capture such novel variability, if useful. If p_t is the frequency of the A allele in generation t, and m is the mutation rate at that locus to the a allele, then, in the absence of any

other evolutionary forces, the change in allele frequency from one generation to the next (Δp) is

$$\Delta p = -mp_{t-1}.$$

Hence, as the frequency of p_{t-1} gets smaller, Δp gets smaller and it follows that the frequency of a mutant allele after t generations can be approximated as

$$p_t = p_0 e^{-tm},$$

where p_0 is the frequency of the wild allele in the base generation. Using this equation, which is based on the assumption of no other acting evolutionary forces, even after 10,000 generations of mutations with a mutation rate of 1×10^{-4}, the frequency of the A allele (i.e., original allele or wild-type allele) in the population will still be at a high frequency at 0.90.

Recombination

Genetic recombination refers to the process of rearranging alleles at different loci to form combinations novel to those observed in the parents. Recombination creates genetic variation and the creation of genetic variation can be faster than that created from mutations (Griffiths et al., 2000). By breaking up linkage disequilibrium among alleles, selection can target individual loci without any adverse effects of reducing diversity in the neighboring loci, a phenomenon known as the Hill-Robertson effect. Crossover activity in mammals is usually expressed in centimorgans with 1 cM equating to a 1% chance of crossover, or in other words 1 crossover expected per 100 cM. Because the bovine genome is 30 M (i.e., 3,000 cM) in length, this equates to approximately 30 crossover events between parent and offspring; because the bovine genome consists of 30 chromosomes (although they differ in length), a rule of thumb is one crossover event expected per chromosome between parents and offspring. Recombination is particularly useful in releasing adaptation potential (including response to selection) that would not have been possible due to genetic antagonisms caused by linkage between a locus affecting a trait of interest and another locus affecting fitness (or another trait under selection).

Selection

The effect of long-term selection on genetic variability has been discussed at length (Hill, 2010; Lynch and Walsh, 1998), although a consensus has not been reached (Bürger, 2000; Johnson and Barton, 2005; Zhang and Hill, 2005; Hill, 2010). As previously discussed, the effect of selection on allele frequency under the assumptions of the infinitesimal model is expected to be negligible (especially after the first few generations; Bulmer, 1980). Change in allele frequency, in the absence of direct knowledge of the genotype itself, is expected to be slow for most traits, irrespective of whether or not the conditions of the infinitesimal model hold. A good example, which one might expect to lead to rapid purging, or purifying selection, of an unfavorable allele, is that of a lethal recessive allele. Even if no homozygous lethal recessive genotype exists in a population, the deleterious allele will persist in the heterozygous state. Crow and Kimura (1970) showed that the proportion of the recessive allele in generation t (P_t) is equal to

$$P_t = \frac{P_0}{1 + tP_0},$$

where P_0 is the proportion of the recessive allele in generation zero. The frequency of a recessive allele in a population over generations, with different initial frequencies in the base population, is in Figure 4; the rate at which the allele is purged is slow and, even within the 100 generations modeled, is not eliminated (Figure 4).

The selection coefficient, usually denoted s, is a commonly used term when discussing selection, particularly in populations undergoing natural selection. The selection coefficient of a genotype is the proportionate reduction in the average genetic contribution made by that specific genotype, relative to the contribution made by another genotype, usually the most favored. Under natural selection, the selection coefficient (s) of a given genotype, as related to the fitness (denoted W) of that genotype, is defined as

$$s = 1 - W.$$

The values for the selection coefficient range from zero to one; a genotype that has a lethal effect (i.e., $W = 0$) therefore has a selection coefficient of 1. If a particular genotype produces only 65% viable young, its selection coefficient is 0.35 (i.e., 1.00–0.65). Using a simple example, where the genotype frequency of a biallelic SNP in a population before selection is 0.25, 0.50, and 0.25 for AA, AB, and BB, respectively; following one generation of selection, the respective frequencies are 0.35, 0.48, and 0.17. The selection coefficient on the heterozygous AB individuals (i.e., s_{AB}) and BB individuals (i.e., s_{BB}) is then calculated as

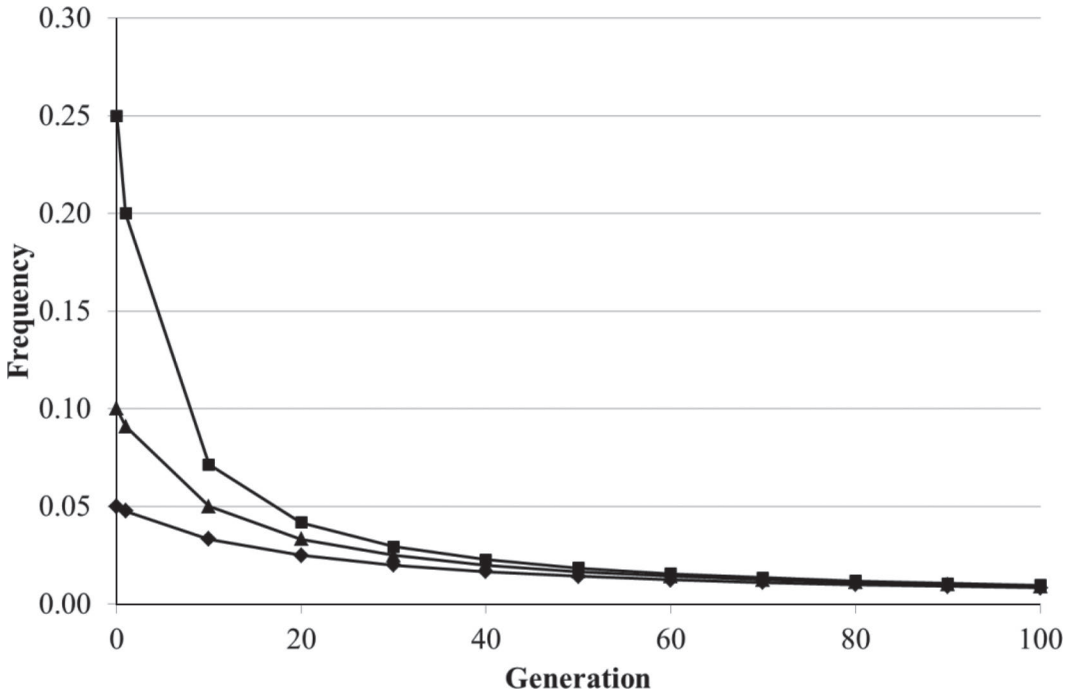

Figure 4. Frequency of a lethal recessive allele by generation when the frequency of the allele in the base population (i.e., generation 0) is 0.25 (square), 0.10 (triangle), and 0.05 (diamond).

$$s_{AB} = 1 - \frac{0.48}{0.5} = 0.04 \quad s_{BB} = 1 - \frac{0.17}{0.25} = 0.32.$$

HERITABILITY, EVOLVABILITY, VARIABILITY, AND THEIR RELEVANCE TO ADAPTATION CAPACITY

Heritability is a statistic commonly used in genetic studies. Heritability depicts the proportion of the phenotypic variance (after adjustment for systematic environmental effects) that is attributable to genetic effects. Studies across different species generally point to low heritability for traits associated with fitness (e.g., fertility) and longevity (Falconer and Mackay, 1996), and dairy cows are no exception (Veerkamp and Beerda, 2007; Berry et al., 2014). Such low heritability estimates have traditionally been interpreted to imply that genetic gain for fitness traits will be slow. However, by definition, the heritability statistic is a ratio trait, and therefore nothing can be deduced on the extent of either the phenotypic or genetic variability in that trait (Houle, 1992).

Houle (1992) described in great detail the concepts of evolvability and variability as alternative measures to heritability for depicting the potential to alter the mean of a population for quantitative traits, or in other words adapt. Houle (1992) argued that it is the coefficient of genetic variation, which is potentially more informative than the heritability to quantify the capacity for genetic change. This is because, when comparing traits for evolvability, it is the proportional change in the mean that is of most interest rather than the absolute change per se; for example, a mean change of 1 kg of live weight is huge for a mouse but tiny for an elephant. Standardizing traits by their mean is also therefore important for comparing the variability that exists in different traits (and populations/species). Based on calculations from a review of 842 multi-species population estimates of means and variances, Houle (1992) concluded that fitness traits have high coefficients of genetic variability and the low heritability commonly cited for such traits is not therefore due to low genetic variation, but instead due to proportionally greater residual variability. In a review of the genetics of reproduction in up to 67 dairy and beef cattle populations, Berry et al. (2014) documented a coefficient of genetic variation up to 7% for female reproductive traits, which is consistent with the documented coefficients of genetic variation for performance traits such as milk yield, live weight, and BCS in dairy cows (Berry et al., 2003a). Thus, considerable adaptation/evolution potential exists for many reproductive and performance traits if considered individually in a breeding program.

The argument of both Houle (1992) and Berry et al. (2014) is clearly demonstrated in Figure 2, which illustrates the change in daughter pregnancy rate in

US Holsteins over the past 7 decades. Despite the heritability of daughter pregnancy in the United States being just 0.04 (VanRaden et al., 2004), a simple linear regression of estimated breeding value for daughter pregnancy rate on phenotypic daughter pregnancy rate across the 41 yr from 1957 to 1997 was 0.843 (SE = 0.04) with an R^2 of 0.93, signifying that almost all of the phenotypic deterioration in reproductive performance over that time period was due to the prevailing breeding programs of that time.

EMPIRICAL EVIDENCE FROM OTHER SPECIES OF CONTINUED LONG-TERM RESPONSE TO SELECTION

Long-term selection experiments or trend analyses can provide excellent empirical evidence of the potential that exists to consistently achieve gains in performance, or the potential aptitude for adaptation, even after many generations of (aggressive) directional selection. Selection experiments or analysis of temporal trends, however, should be interpreted with caution. In many instances, especially in selection experiments, selection is unidirectional with a focus on only one trait. Second, many selection experiments are undertaken either within the confines of a controlled laboratory environment, or a relatively controlled field environment. The lack of environmental cues can minimize selection pressures but also negate any expression of genotype-by-environment. Moreover, the existence of nongenetic changes over a long time period (e.g., animal or soil nutrition), as would exist in longitudinal studies, make it sometimes difficult to attribute any changes in the mean performance of a population to genetic change. Finally, most selection experiments originate from a small (effective) sample population size, implying a potentially significant contribution from genetic drift and founder effects. All the same, cautionary examination of such data can provide useful insights into the potential of long-term genetic improvement and adaptation.

Illinois Corn Selection Experiment

The Illinois long-term selection experiment for grain protein and oil concentration in maize is the longest continuous selection experiment in higher plants. The selection experiment began in 1896 with a base population of 163 ears (Moose et al., 2004). Ears divergent for protein content and oil content were chosen to represent a founder population for a high protein, a high oil, a low protein, and a low oil strain (n = 24 ears each). Recurrent selection in these 4 strains occurred almost every year thereafter (with the exception of 3 yr during World War II). Even after 100 yr (synonymous with 100 generations) of selection, there appeared to be no obvious plateauing of the response to selection for either the high protein or high oil strains (Dudley and Lambert, 2004); the low protein and low oil strains have now reached a lower biological limit, however, and are therefore not responding to selection (Dudley and Lambert, 2004). Interestingly, by generation 17, all individuals within a line could be traced back to a single founder ear, with the actual founder differing per line (Winter, 1929); the estimated effective population size of the Illinois long-term selection experiment is 4 to 12 (Walsh, 2004), although the fact that each of the 300 to 500 kernels on a single ear could have different parents suggests the effective population size could be as large as 96.

At generation 48 of the experiment, a reverse selection experiment was imposed with a proportion of the high protein and oil lines bred to have low protein and low oil, respectively (Moose et al., 2004); rapid reverse genetic change occurred (Moose et al., 2004). The mean ear protein and oil content after 100 yr of positive selection was 20 standard deviations greater than the mean of the base population and 4 standard deviations less than the base population where continuous negative selection was practiced (Moose et al., 2004). In conclusion, the Illinois long-term selection experiment suggests that genetic variance in the traits exposed to unidirectional selection remains, even after 100 generations.

Thoroughbred Racing Horses

A consensus is lacking on whether or not thoroughbred racehorses have reached a selection limit for speed (Gaffney and Cunningham, 1988; Denny, 2008; Desgorces et al., 2012; Sharman and Wilson, 2015). The winning times of elite horse races in Great Britain have improved little in recent decades (Gardner, 2006); similarly, Denny (2008) failed to document any improvement in winning speed of 3 prestigious horse races in the United States since the 1970s. A similar observation has been reported globally (Desgorces et al., 2012). Sharman and Wilson (2015) argue, however, that such studies were limited, in that they focused only on a selection of middle and long distance elite races, and no account was taken of confounding temporal variability. Sharman and Wilson (2015) undertook an analysis of 616,084 race times from 70,388 horses over 2,000 races between the years 1850 and 2012; the mixed model they used accounted for many possible confounding fixed effects as well as random horse effects. Least squares means for year of race clearly revealed an improvement in speed (i.e., yards per second) over the period of 1950 to 2012, although the trend was slightly nonlinear with

a slowing down in speed between the period 1910 and 1975. The improvement in speed was greatest in sprint races, increasing by, on average, 0.11% annually from the year 1997. Variability in the observed annual rate of change in speed documented by Sharman and Wilson (2015) should, however, be interpreted with caution as the improvements cannot be unequivocally attributed to genetic change, but instead influential nongenetic improvements such as riding style at key times during the period will likely have caused rapid improvements over a short time period. Furthermore, not all confounding factors affecting speed will have been accounted for in the mixed model; for example, handicap weights were not accounted for in the model although the average weight carried has increased in the more recent years, which would be expected to dilute any gains attributable to genetic improvement in speed. In an attempt to disentangle environment from genetic effects, Gaffney and Cunningham (1988) undertook a genetic analysis of speed in all thoroughbred horses. Based on their genetic trend for performance between the years 1952 to 1977, Gaffney and Cunningham (1988), although acknowledging that winning times were not improving, also failed to support the theory of an exhaustion of genetic variance in performance; their analysis was based on the thoroughbred population as a whole, contrary to most previous analyses, which focused solely on the best horses winning elite races.

It should also, nonetheless, be noted that the thoroughbred horse industry is arguably one of the sectors most focused on family lines and animals conforming to type. Therefore, any horse carrying a mutation contributing to greater speed will have to satisfy breeder and trainer demands and expectations on other attributes such as conformation (Hill, 2008) and, to a lesser extent, pedigree. The conclusion, therefore, from studies on Thoroughbred horses is that, although a selection limit in speed does appear to have been reached, it does not imply that no genetic variability remains within the population.

Drosophila melanogaster

Many selection experiments in *Drosophilia melanogaster* for a range of different traits exist (Yoo, 1980; Luckinbill et al., 1984; Svetec et al., 2015) and therefore the discussion of all experiments are beyond this review. Yoo (1980) documented the effect of selection for abdominal bristles in *Drosophila* over 90 generations. Abdominal bristle number increased almost linearly from just less than 10, to approximately 20 bristles at generation 50, when a large jump in selection response was detected; this was followed by a linear increase in bristle numbers until approximately generation 70 when a large jump in selection response was again observed. It is not clear what caused these jumps in selection response, but they could have been due to factors such as a breakdown of linkage disequilibrium releasing new genetic variance or simply an increase in allele frequency of (de novo) favorable alleles. A selection limit appeared to have been reached at generation 90. However, random mating was implemented after generation 90, contributing to a subsequent rapid decline in bristle number. This therefore suggests that the observed plateau in response in bristle number from directional selection was probably due to an antagonism with fitness contributing to a selection limit; the decline in bristle number once random mating ensued was likely then due to the forces of natural selection. Hence, this is another example of how a selection limit does not necessarily imply an exhaustion of genetic variance or, in other words, is not indicative of an inability to adapt should external factors necessitate it.

Mice

Martinez et al. (2000) reported the effect of 20 generations of selection in mice for either body fat or body lean, and quantified the effect relative to an unselected strain, each based on 3 replicates; selection was based on the ratio of gonadal fat pad to body weight at 10 wk of age. At generation 20, the gonadal fat to BW ratio in the fat-selected lines was twice that of the control line, whereas the ratio in the lean-selected lines was half that of the control line (Martinez et al., 2000). The REML-estimated heritability and genetic variances for the ratio trait did not differ when comparing either the first few generations versus the last few generations, or when comparing the selection lines themselves; this therefore, suggests a minimal effect of selection on genetic variance. Martinez et al. (2000) did, however, observe a decline in the rate of response after generation 16, but this was thought to be mainly attributable to almost a halving of selection differentials from generation 15.

Eisen (1972) undertook a long-term selection experiment based on 2 replicates selecting for increased 12-d litter weight in mice. Eisen (1972) documented an apparent selection limit after 17 generations. This limit, however, is unlikely to be attributable to an exhaustion of genetic variance because, once reverse selection for 12-d BW was invoked on one of the replicates, an immediate response ensued (Eisen, 1972). It is also unlikely that selection favored heterozygotes because reverse selection would not have resulted in such an immediate response (Eisen, 1972). Eisen (1972) proposed that the lack of a response after generation 17 was actually due to an antagonistic genetic correlation

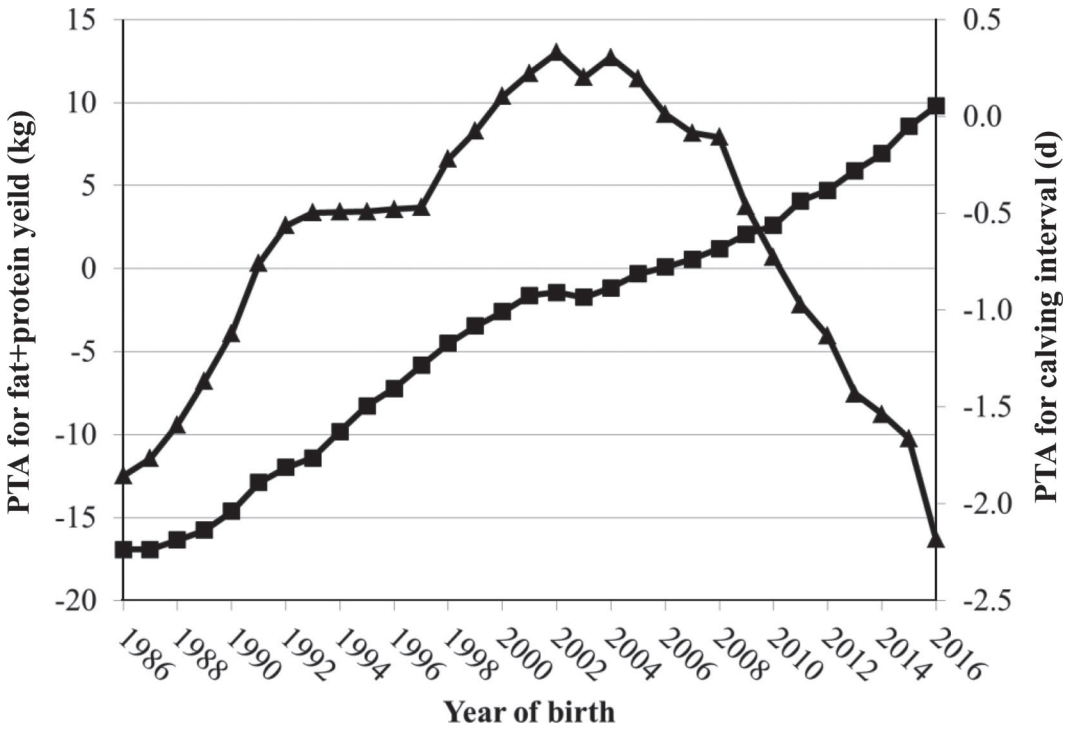

Figure 5. Genetic trends by year of birth of Irish dairy cows for fat plus protein yield (square) and calving interval (triangle).

between direct and maternal genetic effects; the effect of this is the physical inability of the dam to consume sufficient nutrients to feed the growing neonate. Other morphological limits (in other mammalian species) could include size of the uterus and number of teats (Bennett and Leymaster, 1989).

Genetic Trends

To more properly credit changes in phenotypic performance in an uncontrolled environment to changes in the underlying genetic merit of the individuals, changes in the mean (estimated) breeding values of the population contributing to the phenotype should be plotted across time (or space). The genetic trends for estimated breeding values for milk production and fertility in the US Holstein herd are in Figure 1. A simple linear regression through milk production between the birth years of 1980 through to 2002 yielded a regression coefficient of 190 kg/yr; the regression coefficient fitted through the birth years of 2003 to 2009 (between the introduction of the fertility evaluations and subsequent genomic evaluations), was 149 kg/yr, implying that genetic gain in milk production in more recent years (following the consideration of female fertility in the national breeding goal) is 73% that achieved prior to when female fertility was considered in the national breeding goal. The genetic trends for fat plus protein yield and calving interval for the Irish dairy cow herd are in Figure 5; the rate of genetic gain in fat plus protein yield from the birth year 2001 (introduction of fertility evaluations in the national breeding objective) to 2009 (introduction of genomic evaluations) is 68% of the annual rate of genetic gain in fat plus protein yield from the year 1980 to 2000.

The observed reduction in genetic gain in both populations is not likely due to an exhaustion of genetic variability for milk production, as ample genetic variability is known to exist (Berry et al., 2002); instead the reduction in genetic gain for milk production is likely due to a dilution of selection intensity as selection pressure is placed on ancillary traits (Berry, 2015). This therefore suggests that in some situations, although genetic variability clearly exists in traits under selection, no (or lesser) genetic variability may actually exist in the desired gains for both traits favored in the breeding goal. Such a phenomenon can be illustrated using a simple 2-trait breeding objective (Lande, 1979), assuming a genetic covariance matrix ($\mathbf{G}$) and selection gradient ($\boldsymbol{\beta}$) as follows:

$$\mathbf{G} = \begin{pmatrix} 10 & 20 \\ 20 & 40 \end{pmatrix} \quad \boldsymbol{\beta} = \begin{pmatrix} 2 \\ -1 \end{pmatrix}.$$

The $\boldsymbol{\beta}$ vector signifies that the selection pressure on the second trait is half that of the first trait, but in an op-

posite direction. The anticipated response to selection may be calculated as $\mathbf{R} = \mathbf{G}\boldsymbol{\beta}$, which, in this example, is

$$\mathbf{R} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

implying no response to selection in either trait despite clear genetic variability existing in both traits. This is because the genetic covariance matrix scales the response based on both the extent of genetic variability present for both traits but also the genetic covariance between them. In fact, one of the eigenvalues of the G matrix is zero, which corresponds to the eigenvector directly corresponding to $\boldsymbol{\beta}$. Therefore, no standing genetic variation exists along this selection direction and this is what is termed an absolute constraint (Pease and Bull, 1988). Response will also be small when $\boldsymbol{\beta}$ is just a few degrees from the eigenvector associated with a near-zero eigenvalue. If this trajectory somehow relates to fitness or adaptation, then it follows that adaptive evolution will not be possible.

JUSTIFICATION FOR LONG-TERM RESPONSE TO SELECTION (IN DAIRY COWS) AND THEIR ADAPTATION CAPACITY

Although no consensus exists on the underlying causal factors, and their relative contribution to sustained genetic gain after generations of selection, many possibilities exist and include the following:

1. Standing variation in the founder population: standing variation relates to allelic variability that is present in a population at a given time. If a large number of segregating QTL exists in the founder population with a low allele frequency for the favorable allele, then the scope for genetic gain by selecting for these alleles, especially if additive, can be very large. Because the genetic variance contributed by a locus is proportional to $2p(1 - p)$, where p is the allele frequency (Falconer and Mackay, 1996), then the genetic variance is greatest at an allele frequency of 0.5. A comparison of molecular genetic diversity was undertaken by the International Chicken Polymorphism Map Consortium (2004) between both a modern-day broiler and layer strain with their wild ancestor, the Red Jungle Fowl; results showed that the broiler and layer lines still retain 70 to 80% of the molecular variability observed in the Jungle Fowl. Hence, in a situation with low allele frequency for the favorable alleles, selection for these rare alleles, if assumed in linkage equilibrium with other loci, could actually increase the genetic variability. Standing variation, however, cannot be the only contributing factor to long-term genetic gain because studies that began with completely inbred founder population also exhibited long-term gains.
2. Mutations: mutational variance is thought to contribute 0.1% of the environmental variance per generation (Lynch and Walsh, 1998), implying an increase in heritability of approximately 0.1% per generation (Hill, 2000). Fisher (1930) derived the probability that a random mutation would have a favorable effect on adaptation; in doing so Fisher (1930) showed that, although mutations with a small effect have a 50:50 change of being advantageous, mutations of greater effect are less likely to have a favorable effect and are therefore unlikely to contribute much to adaptation. Kimura (1983) noted, however, that Fisher failed to consider that mutations of larger effect are more likely to become fixed if favorable; once considered, Kimura (1983) proposed that mutations of intermediate effect are most likely to play a greater role in adaptation. Nonetheless, the modeling of the effect of mutations on genetic variance is a function of the parameters used in the mathematical equations, many of which, like the mutation rate itself and fixation probabilities, are unknown.
3. Drift: drift can introduce or deplete genetic variability, but inevitably will erode the genetic variance, as evidenced in Figure 4. The speed at which loss or fixation of alleles occur, is a function of the effective population size (Figure 4). Under the assumption of a neutral model, where only mutation and genetic drift operate, an equilibrium between mutation and drift is expected to be reached when the genetic variance $\left(\sigma_a^2\right)$ is (Lynch and Walsh, 1998):

$$\sigma_a^2 = 2\mathrm{N_e}\sigma_m^2,$$

where $\mathrm{N_e}$ is the effective population size and σ_m^2 is the mutational variance. Therefore, the expected equilibrium heritability $\left(\widetilde{\mathrm{h}^2}\right)$ under such a mutation-drift model would be

$$\widetilde{\mathrm{h}^2} = \frac{2\mathrm{N_e}\mathrm{h}_\mathrm{m}^2}{1 + 2\mathrm{N_e}\mathrm{h}_\mathrm{m}^2},$$

where N_e is the effective population size and h^2_m is the mutational heritability (defined as 0.001 above). Assuming an effective population size of 500, then the heritability of the trait under a mutation-drift model would be 0.5 (i.e., $2 \times 500 \times 0.001 \times \sigma^2_e$); many traits in dairy cattle do not exhibit such large heritability estimates (Berry et al., 2014), thus indicating that selection (and other evolutionary forces) eliminates many of the mutations.

4. Epistasis: epistasis is the phenomonen where the expression of a gene is modulated by another gene (i.e., inter-gene interactions). Epistasis has traditionally been thought to contribute only to the nonadditive genetic variation. Selection, however, may be able to generate new additive genetic variability from previously epistatic effects (Goodnight, 2004; Carlborg et al., 2006); Eitan and Soller (2004) termed this phenomenon "selection induced genetic variation." Based on simulations, Goodnight (2004) stated that the presence of epistasis in a population lengthened the number of generations where a linear rate of genetic gain was achieved, as opposed to actually increasing the rate of response. Eitan and Soller (2004) asserted that genes interact with other genes or with the genetic background. Hence, because selection may alter the allele frequencies at different loci, the genetic background is therefore dynamic and QTL that were neutral in one genetic background may actually have favorable effects in a subsequent genetic background. Because the genetic background is transient under selection, then new genetic variability is constantly being released, thus ensuring a long-term response to selection. Carlborg et al. (2006) provided empirical evidence of such selection induced genetic variability from crosses of high and low BW selected broiler lines.
5. Genetic correlations: genetic correlations are due to either alleles in linkage (i.e., tend to be co-inherited) or pleiotropy. Pleiotropy is when a given locus affects more than one trait; this can contribute to a correlation between traits assuming no other factors negate the pleiotropic effect. The genetic correlation between 2 traits under directional selection (either natural or artificial) is expected to become unfavorable over time; furthermore, selection is more likely than not to contribute to asymmetrical responses to (indirect) selection (Bohren et al., 1966). This is because the pleiotropic alleles acting favorably on both characteristics (i.e., complementary pleiotrophy) will quickly become fixed under selection; these alleles therefore will contribute little to the variation or the covariation between the 2 characters. Alleles that affect both characteristics in opposing directions (i.e., antagonistic pleiotropy), however, will remain in intermediate frequencies and therefore contribute more to the covariance between the traits (Falconer and Mackay, 1996). This phenomenon will contribute to a limit of selection if one of these traits relates to animal fitness; nevertheless, despite the limit to selection (some) genetic variance in fitness will remain as the alleles continue to segregate in the population.
6. Stabilizing selection: stabilizing selection tends to favor individuals of intermediate value and not extreme values. Although higher (i.e., extreme) milk yield in dairy cows is generally favored in most modern-day production systems, in nature an intermediate value of milk yield may be more preferred because too little milk may contribute to the young not thriving, whereas too much milk could compromise the reproductive performance and survival of the dam. An example of a trait in modern dairy production systems that is subjected to stabilizing selection is live weight. Stabilizing selection does not necessarily have to contribute to maintaining genetic variance, however, as alleles favoring opposite extremes may still become fixed with the outcome being an intermediate genotype. Nonetheless, stabilizing selection could contribute to the heterozygote being favored for loci that act additively or that exhibit incomplete dominance. The implications are segregating loci and large associated genetic variance.
7. Balancing selection: unlike directional selection which favors one particular allele (if operating in an additive fashion), thus leading to fixation, balancing selection occurs either where the heterozygous confers a particular advantage over both homozygous states or where the favored allele varies temporally or spatially (i.e., a type of genotype-by-environment). Differentiation between balancing selection and stabilizing selection is that the latter applies to the phenotypic trait whereas the former applies to the given locus. One mechanism conferring heterozygote advantage is over-dominance. This can contribute to multiple alleles (or both alleles in the case of a biallelic SNP) segregating in a population and thus ensuring genetic diversity. Balancing selection is not expected to persist over a long

time period as evolutionary mechanisms reduce balancing selection (e.g., the introduction of a new allele that is favored more than the heterozygote). Moreover, loci conferring heterozygote advantage are thought to be relatively few in number (Hedrick, 2012) and such a mechanism is therefore unlikely to play a major role in adaptation. Evidence of balancing selection in dairy cows was recently documented as a 660-kb deletion in Nordic Red cattle (Kadri et al., 2014); the deletion, which is recessively lethal, was actually segregating in a high frequency in the Nordic Red population, possibly because of the favorable effect of the allele on increased milk production.

8. Epigenetics: epigenetics may be defined as the changes in the regulation of gene activity and expression that are not dependent on the gene sequence (Holliday, 2006). Methylation of DNA, although only one form of epigenetic modification, has probably received the most attention. Methylation of DNA is a process where methyl groups attach to the DNA molecule, thus changing the activity of a DNA sequence but without changing the sequence. It follows that each cell type in a given individual possesses its own epigenetic signature that reflects genotype, developmental history, and environmental influences; such signatures affect the phenotype (Morgan et al., 2005). Epigenetic signatures in a cell, however, can undergo epigenetic reprogramming, and new epigenetic marks may replace them (Reik et al., 2001). Some epigenetic signatures however are heritable (Daxinger and Whitelaw, 2012). Genomic imprinting is one form of epigenetic mechanism whereby certain alleles are only expressed depending on which parent they originated from. Thus, epigenetics is one process that can protect some allelic variability against selection, and in doing so, maintain genetic diversity.
9. Environment: genotype-by-environment is the phenomenon whereby the performance of an individual genotype is a function of the environment (Falconer and Mackay, 1996). In the absence of information on the genome of individuals, the extent of genetic variability in a population is generally estimated using either restricted maximum likelihood or Bayesian approaches applied to mixed models (Henderson, 1950). In such approaches, the phenotypic variance is partitioned into its causal variance components, one of which is the additive genetic variance. For a given heritability, therefore, the lower the phenotypic variance, the lower the genetic variance. The environment itself does not alter the actual genome of the individual but instead the expression of the genome (or through epigenetic modifications). There are 2 main types of genotype-by-environment, namely reranking and rescaling. If the variability among environments considered is large enough, reranking and rescaling can both occur. Reranking is where the ranking of genotypes differ by environment, and rescaling is where minimal reranking occurs but the differential in performance between genotypes (i.e., the estimated genetic variance of a population) varies by environment. Rescaling facilitates greater discrimination among genotypes, and greater genetic variance for performance is usually exhibited in management deemed to be superior quality such as more feed offered, a greater quality of feed, or both (Hill et al., 1983; Merila, 1997; Garcia de Leaniz and Consuegra, 2006). The effect of the environment on the expression (and adaptation) of genotypes can be quite substantial and rapid; for example, the environmental pressure of more highly energy-dense diets in US (and other confinement-fed) dairy cows has only been in effect for approximately 10 to 14 generations, yet considerable differences exist among strains of Holstein-Friesian dairy cows (Horan et al., 2006). Reranking can also influence genetic variance through the development of sub-populations. This is an example of the coevolution of genetics and environment.
10. International populations and migration: although Holsteins are ubiquitous in temperate dairy production systems, breeding goals differ by country (Miglior et al., 2005); the extent of the difference in ranking of sires across countries (i.e., genotype by environment) is, however, dependent on the countries compared. For example, the production systems in the United States and Ireland are quite different, thus contributing to different breeding goals. Based on 1,053 Holsteins sires of at least 70% reliability for both the US net merit index (https://queries.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.nm#StartBody; accessed May 8, 2017) and the Irish economic breeding index (https://www.icbf.com/wp/; accessed May 8, 2017), the correlation between the net merit index and the economic breeding index was 0.66. Such differences in sire rankings can lead to the formation of strains of Holstein, and not only will differences exist in the selection coefficient of different loci between populations, but also the same alleles in

different strains are unlikely to be lost by genetic drift. Generating non-intermating sub-populations is actually a useful strategy for maintenance of genetic diversity although the overall population size per sub-population would be smaller exposing them to the effects of evolutionary forces such as random drift. The additive genetic variance in a population declines with the extent of heterozygosity per locus, which affects inbreeding. Therefore, the genetic variance in a population in generation $t\left(\sigma^2_{a_t}\right)$ is

$$\sigma^2_{a_t} = \left(1 - F_t\right)\sigma^2_{a_0},$$

where F_t is the inbreeding coefficient in generation t and $\sigma^2_{a_0}$ is the genetic variance in the base population. The additive genetic variance between populations, however, in generation t $\left(\sigma^2_{Between_t}\right)$ increases at twice the rate:

$$\sigma^2_{Between_t} = 2F_t\sigma^2_{a_0}.$$

Together, the genetic variance both within (e.g., within the United States where confinement and grazing production systems co-exist) and between (e.g., between the United States and Ireland) populations actually increases with inbreeding:

$$\sigma^2_{Total_t} = \left(1 + F_t\right)\sigma^2_{a_0}.$$

11. Crossbreeding: crossbreeding is a form of migration and although common in many farmed species, it is relatively less common in dairy cow populations, with some exceptions (Lopez-Villalobos et al., 2000; Coffey et al., 2016). As well as increasing the genetic diversity in the population, crossbreeding can improve performance through complementarity of breeds as well as through the exploitation of nonadditive genetic variability.

OUTLOOK AND STRATEGIES TO ACHIEVE AN ADAPTABLE COW

The rate of loss in genetic variation in a closed finite population is expected to be proportional to the reciprocal of the effective population size (Hill, 2008); expansion in genetic variation due to mutations is also proportional to the effective population size. Similarly, the within-family genetic variance is expected to decrease with inbreeding. Hence, strategies which maintain, or increase the effective population size are logical strategies to ensure long-term response to selection and adaptation through maintenance of genetic variation.

Genomic Selection Versus Marker-Assisted Selection

Since the publication of the seminal paper on genomic selection by Meuwissen et al. (2001), animal breeding schemes worldwide have been revolutionized. The main implication of the incorporation of genome-wide marker information into genetic evaluations is a massive increase in the rate of genetic gain for a range of different traits and such benefits have been discussed at length elsewhere (e.g., the US Holstein population; García-Ruiz et al., 2016). Rapid selection on a given (few) QTL is generally the strategy advocated with marker-assisted selection (Dekkers, 2004), and this strategy is likely to rapidly fix these favorable alleles (assuming no large and unfavorable pleiotropic or linkage effects with other important traits such as fitness); the consequence is a likely population bottleneck. Population bottlenecks can have a dramatic effect on genetic diversity. One measure of genetic diversity is the extent of heterozygosity and the extent of heterozygosity in generation t may be approximated as

$$H_t = H_0\prod_{i=1}^{t}\left(1 - \frac{1}{2N_{e_i}}\right),$$

where H_0 is the initial heterozygosity and N_{e_i} is the effective population size in generation i. Therefore, the expected level of heterozygosity after 4 generations would be the same in the 2 populations of (1) a population that underwent a population bottleneck resulting in an effective population size of 10 for a single generation followed by an effective population size of 100 for each of the 3 subsequent generations, or (2) a population with an effective population size of 30 for each of the 4 generations.

Aggressive selection for a given locus may also fix flanking DNA sequences in linkage disequilibrium due to hitch-hiking. Selection based on markers spread across the entire genome, however, each having only a small contribution to the estimated breeding value of an animal, is likely to have a less consequential effect on effective population size, and thus genetic variation. Such a strategy of selection for alleles dispersed across the entire genome is the fundamental basis behind what is now commonly known as genomic selection (Meuwissen et al., 2001). Relative to traditional non-genome-based selection, however, the shorter generation intervals pos-

sible in dairy cattle with genomic selection (Schaeffer, 2006) can contribute to an increase in the annual rates of inbreeding.

Optimal Contribution Theory to Constrain the Accumulation of Inbreeding

Although there is a general acceptance that inbreeding causes a reduction in performance (Mc Parland et al., 2007b, 2008), if the accumulation of inbreeding is slow, then the effect of inbreeding can actually be favorable at a population level (Mc Parland et al., 2009). Inbreeding is nonetheless unavoidable in a finite population; each animal has a maximum of 2^t possible ancestors t generations deep, so it is not long before 2^t is greater than the actual population size of some breeds, thus implying that some common individuals have to occur in the pedigree. It is the rate of accumulation of inbreeding rather than the level of inbreeding which is an important and relevant descriptor of a population, as the former determines the effective population size, which is subsequently known to relate to the population dynamics of genetic variation (Hill, 2008).

Optimal contribution theory (Meuwissen, 1997; Meuwissen and Sonesson, 1998) attempts to maximize long-term genetic gain by weighting genetic gain against contribution to an accumulation of inbreeding over time; in essence, optimal contributions tend to equalize better the usage of individual parents of the next generation. Based on simulations, which mimicked dairy cattle nucleus schemes, Meuwissen and Sonesson (1998) reported 44% greater long-term genetic gain (up to 20 yr) when a predefined rate of inbreeding was considered compared with direct selection on just breeding values alone. The benefit of their dynamic rules for maximizing genetic gain while limiting the average relationship in the population, relative to no such restriction, was lesser in larger populations or where more conservative levels of inbreeding were allowed. The benefits of optimal contribution to achieving genetic gain without large associated increases in the rate of inbreeding have been widely documented (Sonesson and Meuwissen, 2000), including when the relationships are derived using genomic information (Clark et al., 2013).

Cryopreservation

Several strategies and discussions exist on conservation (Oldenbroek, 2007) as a means of retaining genetic diversity to ensure population adaptation potential. Conservation is especially a relevant strategy for smaller dairy breeds. For major dairy breeds, however, cryopreservation is a more likely strategy. Cryopreservation is a process where individuals (or any biological construct) are preserved by cooling to very low temperatures. In the context of animal breeding and genetic diversity, cryopreservation strategies may relate to embryos and semen; semen cryopreservation may be the most logical because semen from all bulls in AI are already cryopreserved so therefore a cryopreservation strategy would simply entail the storage (and associated logistics such as cataloguing and routine sample quality testing) of samples from animals of interest. Cryopreservation strategies, and the appropriate selection of candidate farm animals, have been discussed at length elsewhere (Oldenbroek, 2007). Semen from least related sires in each new generation should be cryopreserved; this is to ensure the genetic lag between the cryopreserved sires and the current generation is minimized.

Multi-Trait Breeding Goals

Genetic evaluations are based on best linear unbiased prediction (**BLUP**), which exploits information from relatives to generate an unbiased estimate of the genetic merit of an individual. For example, in the absence of any information on an individual, other than its parents, the estimated genetic merit of that individual is simply the average of the genetic merit of its parents. Therefore, in such situations BLUP evaluations contribute to strong correlations of estimated breeding values among close relatives, resulting in high co-selection probabilities. In general, the lower the heritability of a trait under selection, the greater the extent of between-family selection; this has repercussions for subsequent genetic diversity, the implications of which for adaptability have already been discussed at length.

Dairy cow breeding goals of the past in many countries, with some exceptions, were almost exclusively based on the output traits of milk production. Milk yield and composition traits are moderately heritable (Berry et al., 2003a). In the late 1990s and early 2000s, dairy cow breeding goals were broadened to include functional traits (Miglior et al., 2005); functional traits are less heritable than milk production traits (Berry et al., 2014), thus contributing to a reduction in the heritability of the overall breeding goal. Changes to the dairy cow breeding goals in the past 2 decades has generally been confined to low heritability traits (e.g., fertility, health) or traits that are difficult to measure (e.g., feed intake complex) and thus of low reliability. Such additions revert to placing greater emphasis on between family variability, thus potentially contributing to reduced diversity in the selected lines. Progeny testing of individuals contributes to less reliance on family information, once the candidate bulls themselves have, however, been selected. The incorporation of genomic

information into breeding schemes can, nonetheless, help alleviate these issues. Changes to breeding objectives over time can also introduce new family lines.

Moreover, a breeding objective is a linear combination of component traits and therefore 2 animals can have the same breeding objective value, yet this can be due to a different combination of traits; for example, one animal could be excellent for milk production but relatively poor for fertility, whereas the other animal could be relatively poor for milk production but excellent for fertility. Such a characteristic of broad breeding goals could therefore contribute to an enlarging of the germplasm that rank highly on the breeding objective; similarly, a broad breeding objective may actually contribute to animals from more than one breed ranking high, thus promoting the use of other breeds/crossbreeding, which will increase genetic diversity through migration.

Reaction Norms

Reaction norms are often used as descriptors of phenotypic plasticity across a gradient of environmental conditions. In animal breeding, the reaction norm (i.e., the plotted line) can be generated if an animal itself is exposed to a variety of different environments, although it is more common for reaction norms, in dairy cattle at least, to be generated at a sire level where half-sib progeny of the sire (each assumed to have a covariance of $\geq$0.25), produce in multiple different environments (Hayes et al., 2003; Mulder, 2016). If the reaction norm for the individual (or sire) is horizontal, then the phenotype does not vary across the range of environmental conditions examined; such an individual is said to be a generalist for that trait (Levins, 1968; Friggens et al., 2017), or indeed said to have low environmental sensitivity for that trait. A nonhorizontal line implies that the expression of the genotype is a function of the environment; if the reaction norm is relatively steep, then the individual is said to be a specialist (i.e., it performs better in some environments; Friggens et al., 2017) or suffer from high environmental sensitivity for that trait.

Random regression models are used in many populations to estimate the genetic covariance function for performance along a trajectory of environments (Kolmodin et al., 2002; Berry et al., 2003b; Mulder, 2016), and the coefficients of the random regressions can be used to draw animal-specific reaction models (Berry et al., 2003b). Nguyen et al. (2016) proposed using such random regression methodology to generate estimates of the sensitivity of individual dairy animals to heat tolerance. Whether an animal being more or less sensitive to an environment is the more adaptive is not, however, clear. An animal with low environmental sensitivity (if associated with a high intercept) will produce equally well irrespective of the environment (i.e., it adapted to the environment and thus performance was not affected); an animal with high environmental sensitivity, however (if associated with a favorably sloped reaction norm), will also usually adapt to the prevailing environmental conditions maximizing performance based on the available resources. If, however, the fixed and random regression slopes on environment are linear, steep, and positive, then although the animal performance will improve in light of improving environmental conditions (e.g., higher concentrate input), it will also suffer (linearly) with dis-improving environments (e.g., less concentrate input due to high concentrate feed prices). Nonetheless, once the necessary data are available (i.e., performance in multiple environments) then breeding values of the slope of the reaction norm can be generated and made available; how they are eventually used may depend on the trait by environment combination as well as their relative importance for the individual producer. The use of reaction norms for heat tolerance could be particularly informative given the reported warming of climates that is expected to continue into the future. Incorporation of genomic information into evaluations can further augment the response to selection in the presence of genotype-by-environment interactions (Mulder, 2016).

Genome Editing

Genome-editing technologies enable the modification of a genome in a targeted way by inserting, deleting, or replacing DNA. The potential for genome editing in (dairy cow) breeding programs includes (1) the rapid removal of alleles conferring recessive defects or large unfavorable effects, (2) the opposite by fixing the favorable alleles of monogenic traits, (3) increasing the frequency (and possibly fixing) of the allele conferring favorable attributes for polygenic traits, assuming no repercussions via pleiotropy on other traits, (4) minimizing a loss in selection intensity when attempting to retain favorable permutations of desired alleles because of the rarity of meiotic recombination during gametogenesis, and (5) resolving genetic antagonisms among traits due to linkage. The approach for increasing the frequency of favorable alleles for polygenic traits has been labeled promotion of alleles by genome editing (**PAGE**; Jenko et al. 2015). Targeted genome editing, in principle (i.e., ignoring off-target effects) affects just the locus itself, thereby avoiding correlated responses in the trait itself or other traits owing to alleles in (tight) linkage disequilibrium with the focal locus; these loci would normally tend to be co-inherited, resulting in

correlations due to linkage, which can only be resolved (in the absence of genome editing) by recombination. From an adaptation perspective, this targeted genome editing will safeguard against depletion in genetic variance in flanking genomic regions due to hitch-hiking effects or the Hill-Robertson effect (Hill and Robertson, 1966).

Based on a simulated data set, Jenko et al. (2015) reported up to 4 times greater genetic gain using a combination of both PAGE and genomic selection over and above using solely genomic selection; in their simulation, the accuracy of the genomic predictions was 100%. Their genome editing strategy was imposed on sires and, unsurprisingly, the benefit of PAGE was greatest when more sires were edited and more quantitative trait nucleotides per sire were edited (Jenko et al., 2015). When all sires were edited, there was no difference in the rate of accumulation of inbreeding when comparing genomic selection alone versus genomic selection in combination with PAGE (Jenko et al., 2015). Again, unsurprisingly, when the edits were restricted to just a few sires, the rate of increase in inbreeding accelerated (Jenko et al., 2015).

Several factors, however, currently impede the widespread use of genome editing in routine breeding programs: (1) regulatory policy and associated consumer/stakeholder concerns including apprehension of bioterrorism (Gurwitz, 2014), (2) possible off-target edits, although these are expected to be minimum and may be detectable (Hendel et al., 2015), (3) the cost of undertaking many edits at once with a high degree of success, (4) the heretofore lack of success of detecting causal variants explaining (a decent proportion of) polygenic variability, (5) the effect of editing sequences with pleiotrophic effects, and (6) only really applicable for alleles that operate additively unless large-scale editing at an individual (i.e., producing female) level is feasible. With the exception of where antagonistic pleiotropic effects exist, however, all other factors are likely to be surmountable.

CONCLUSIONS

Adaptation, both in terms of acclimatization to environmental perturbation or opportunities, as well as response to selection, is predicated on the presence of useful and usable genetic variability. Such variability is under the influence of the 5 evolutionary forces of drift, migration, mutation, recombination, and selection. Although many populations may reach a selection limit after multiple generations of directional selection, this does not necessarily imply a depletion of genetic variance. In fact, empirical evidence to date from long-term selection studies clearly show that genetic variance is not easily exhausted through evolutionary forces; this is true because rapid changes in the population mean have been observed once reverse selection is imposed. There is therefore minimal reason for concern that the modern-day dairy cows will be unable to adapt to (relatively slow) changes in the prevailing environmental conditions.

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