Selection on Recombination Rate to Increase Genetic Gain

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ABSTRACT: Recombination leads to more genetic variation being available for selection. In this paper simulation was used to quantify the effect of increased recombination on the response to selection. The rate of response to selection for a polygenic trait of interest was studied with various scenarios of recombination rate and selection intensity. Increased recombination rate decreased the loss in genetic variance. This facilitated the use of higher selection intensity without increasing the rate of loss in genetic variance. Consequently, the genetic gain was higher for the same proportion of genetic variance lost. However using selection to increase the rate of recombination was challenging. A selection index that placed 30% of its weight recombination rate increased it by 150% after five generations. Much higher increases in recombination rate are required to enable it deliver meaningful increases in the rate of improvement.
Keywords: Breeding program; Genetic gain; Recombination rate

Introduction

The amount of genetic variation available to be selected upon is an important determining factor for the rate of response to selection in livestock breeding programs. In a breeding program this is affected by the number of causal variants, their frequency and size, and the degree to which they are linked to each other.

In the most general form of the infinitesimal model of Bulmer (1971), causal variants for a quantitative trait were assumed unlinked and inherited independently. From these assumptions the Bulmer effect was derived, which described the reduction in variance arising from selection and how this reduction in variance arose from negative joint disequilibrium. Thus an individual's genotype at one locus is negatively correlated with its genotype at another.

However, causal variants are not inherited independently because they are linked on chromosomes, and meiotic recombination is relatively rare; e.g. 30 recombinations occur per individual are expected for a 30 Morgan genome. Inheritance of alleles is then constrained by the existing disposition of alleles along the gametes in any given generation, and the loci cannot be utilized in an independent manner for selection. Thus the negative correlations are more persistent and hence the genetic variation in a population is more strongly constrained.

The rate of recombination is under both genetic and environmental control (Kong et al., 2014). This rate is thought to be important for evolution because it enables Figure 2. Response to selection for the target trait when the selection index includes or excludes recombination rate.directional selection when negatively correlated causal variants are physically close together on a chromosome, as might be expected in breeding programs. For example, wild ancestors of domesticated plants have higher rates of recombination than wild plants that have not been domesticated (Ross-Ibarra, 2004) and domesticated pigs have higher rates of recombination than their wild relatives (Ollivier, 1995).

Because recombination is under genetic and environmental control it can be manipulated. Such manipulations could be used in livestock breeding programs to release more standing genetic variation in each generation and thus enable greater short-term and long-term response to selection. The objective of this paper was to use simulation to explore the potential of manipulating recombination for increasing the rate of genetic gain in livestock breeding programs.

Materials and Methods

Simulated data: Several scenarios were simulated as described later. In each scenario twenty generations of selection were undertaken, phenotypes were simulated for a polygenic trait of interest with a h^2=0.5, and the trait was controlled by 10,000 causal variants whose effects were sampled from $N(0,1)$.

Each individual had 10 chromosomes and the number of recombinations for each chromosome was simulated from a Poisson distribution and uniformly distributed across the gametes. The mean of the Poisson distribution was either fixed to a certain value for all individuals or was simulated to be under partial genetic control and selected upon. When it was under genetic control recombination was simulated to have h^2=0.5 with 10,000 causal variants whose effects were sampled from $N(0,1)$. In the first generation the mean of the Poisson was the same for all individuals, but in subsequent generations the number of recombinations per gamete (r_i) was simulated from a Poisson distribution with a gamete specific recombination rate (λ_i) [1] taking into account the average recombination rate in a population (μ) and the breeding value for recombination of the parent $(a_{p(i)})$ [2]. The variance of additive genetic effects (σ_a^2) for recombination was scaled to match the assumed heritability [3,4] following Foulley et al. (1987).

$$r_i \sim Poisson(\lambda_i) \quad [1]$$

$$log(\lambda_i) = \mu + a_{p(i)} \quad [2]$$

$$h^2 = \frac{\sigma_a^2}{\sigma_a^2 + {}^1/_{\lambda_i}} \quad [3]$$

$$\sigma_a^2 = \frac{h^2 \times {}^1/_{\bar{\lambda}_t}}{1 - h^2} \qquad [4]$$

In each generation selection was carried out on the basis of: (i) true breeding values (TBV) for the trait of interest; (ii) a selection index that comprised TBV both for the trait of interest and for recombination; and (iii) a selection index that comprised estimated breeding values (EBV) both for the trait of interest and for recombination. EBV were estimated at each generation using genomic best linear unbiased prediction (GBLUP) in which 20,000 single nucleotide polymorphisms and the phenotypes of the individuals in the previous generation were used to develop the prediction equation. The simulations were undertaken using the AlphaDrop (Hickey and Gorjanc, 2012) software package. Twenty replicates of each scenario were simulated, where 50 sires were mated to 5 dams each. The number of offspring per dam was varied across scenarios to enable selection intensity be manipulated.

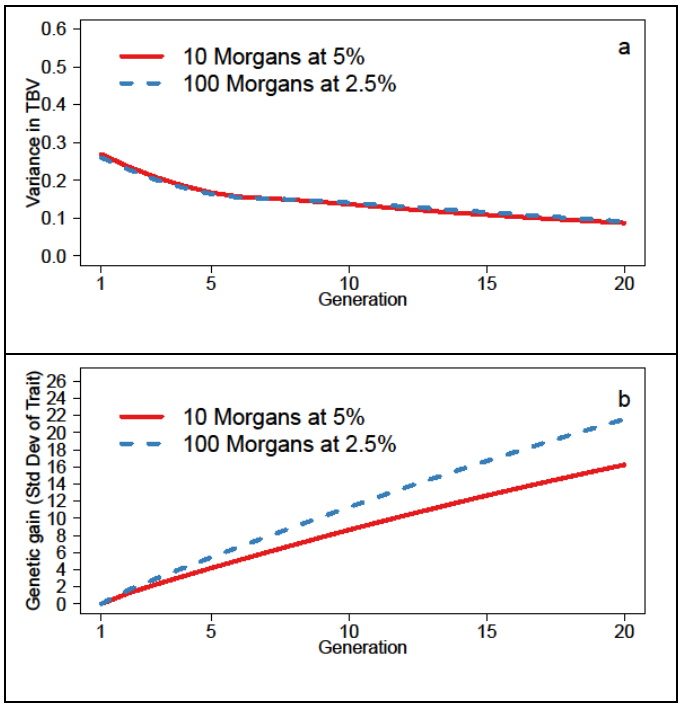
Scenarios: The first scenario (Sc1) aimed to quantify the impact, across a range of selection intensities, of increased recombination rate on the response to selection and the loss of genetic variance due to selection. Twenty generations of selection on TBV were simulated for all combinations of different genome lengths (10, 20, 50, 100 Morgans) and selection intensities (1.25%, 2.5%, 5%, 10%).

The second scenario (Sc2) aimed to demonstrate that recombination can be selected upon as part of an index, and that by increasing recombination rate though selection greater genetic gain for the target traits can be made subsequently. In Sc2 genome length was initialized with 10 Morgans but a selection index placing 0% to 50% of the emphasis on recombination and the remainder on the target trait was used to select sires for the first five generations. This was followed by 15 generations of selection with the emphasis on the target trait increased to 95% and only 5% emphasis on recombination. This index was designed to initially increase recombination rate in the first few generations and then to maintain the increased level for the subsequent generations. A range of selection intensities (1.25%, 2.5%, 5%, 10%) was used.

Results

Sc1 comprised a 4×4 grid of scenarios with different combinations of selection intensity and recombination rate. It showed that these factors impact the rate of both genetic gain and of loss in genetic variance due to selection. A single pair of scenarios from this grid was chosen for illustration because they displayed an almost identical pattern for the loss in genetic variance (Figure 1a). One of these scenarios had a genome length of 100 Morgans and a selection intensity of 2.5% while the other had a genome length of 10 Morgans and a selection intensity of 5%. While both scenarios showed an almost identical pattern for the loss in genetic variance the scenario with greater genome length and could support greater selection intensity and thus result in a greater response to selection (Figure 1b). The results presented are for situations where selection was on TBV. Similar trends were observed for situations where selection was on estimated breeding value from GBLUP.

Figure 1. (a) Variance in true breeding value (TBV) of all individuals in each generation. (b) Genetic gain in each generation.

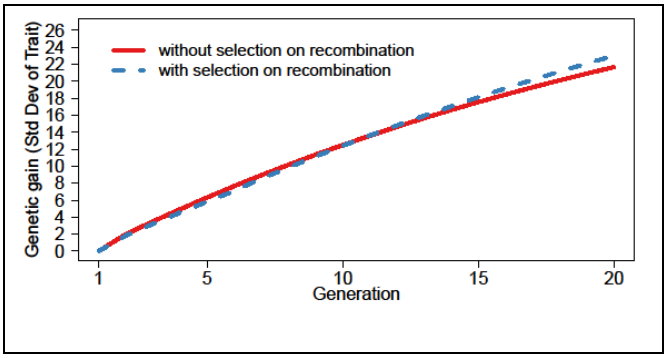


The aim of Sc2 was to use selection to increase the rate of recombination such that it would enable greater response to selection be made for the trait of interest in the subsequent generations. Figure 2 shows the genetic progress for the trait of interest when recombination was included in the selection index with a weight of 30% or excluded from the selection index. Introducing selection on recombination rate increased the rate by about 150%, from an initial value of 10 to 25 Morgans. In comparison to the situation where no selection emphasis was placed on recombination, adding weight to recombination rate enabled a small increase in the amount of genetic improvement for the target in the later generations of selection, with a 6% greater rate by generation 20. The results presented are for situations where selection was on TBV. When selection was on EBV the accuracy of selection reduced more when recombination rate had been increased because of the increase in genome length, and this negated the benefit of having higher recombination rate (results not shown).

Discussion

The results of this study show that higher recombination rate enables the genetic variation that is present in a population to be converted into genetic gain at a faster rate than when recombination rate is lower. This opens up new possibilities both in the short and long term, because it gives a potential new tool to control the conversion rate of genetic variance into gain in breeding programs.

Figure 2. Response to selection for the target trait when the selection index includes or excludes recombination rate.



However, designing breeding programs to take advantage of this potential will not be a trivial task. When a selection index that placed 30% of the emphasis on increasing recombination rate during the first five generations of selection was used recombination rate increased by 150%. However, this level of increase in recombination rate was insufficient to enable a large improvement in the rate of genetic progress to be made for the polygenic trait of interest. In other situations (results not shown) higher emphasis was placed on recombination rate and selection was placed on recombination rate for longer. This led to greater increases in the recombination rate but these scenarios did not result in higher overall genetic improvement for the target trait because the overall selection emphasis on the target trait was reduced too much. Nevertheless if breeding schemes were assessed by gain achieved for a given loss of expressed variance, then selection for recombination rate was almost always beneficial (results not shown), suggesting that including it as an objective when using optimum contribution selection may provide a more complete picture of the potential benefits.

In this study recombination rate was assumed to have a heritability of 0.50 and to be controlled by 10,000 causal variants each with a very small effect (i.e. polygenic). Manipulating a trait with such architecture through selection is a slow process. While the recombination rate is known to be heritable and some causal variants have been identified, in comparison to more intensively studied traits (e.g. height, disease resistance, growth) relatively little is known about the total genetic architecture of recombination rate. It is possible that recombination rate could be controlled by much fewer causal variants, each with larger effects, than typical polygenic traits. If this was the case meaningful benefit be obtained.

With a different architecture other options emerge. A recent study in a human data set found several causal variants that affect recombination rate, including one that increased the rate by 10% (Kong et al., 2014). If causal variants were identified for recombination rate in livestock then these would increase accuracy for recombination rate. One route to achieve greater recombination rate, without having to place heavy selection emphasis upon it, could be through the use of genome editing (GE), which enables modification of genetic material in targeted ways (Niu et al., 2014; Cong et al., 2013). For example, single nucleotide causal variants with large effect on recombination rate could be edited into all sires in a breeding program. There is therefore a synergy for delivering gain between the GE technology and selection for recombination rate.

Higher rates of recombination will present a challenge for genomic selection as it is currently implemented. Genomic selection currently utilizes the correlations between markers and causal variants (i.e. linkage or linkage disequilibrium) to drive accurate predictions of EBV. These correlations are reduced by increasing recombination rate, thus leading to lower accuracy of genomic selection, which in turn would reduce the benefit of increasing the recombination. Therefore huge data sets (i.e. many hundreds of thousands of individuals with sequence and phenotype data) may be needed to maximally benefit from increased recombination rates in breeding programs using genomic selection. Such data sets will ensure that the accuracy of genomic breeding values will depend less on the correlations between markers and causal variants since more will be finely mapped. One benefit from greater recombination rate for statistical estimation of allelic effect will be less confounding due to the less extensive linkage disequilibrium.

Recombination is one of biology's central mechanisms, and extremely high recombination rates are not common in any species. This suggests that there may be something fundamental about having such extensive recombination. Dramatically altering the rate may therefore reduce fitness and risk the survival of a breeding program. However, animal breeders have been dramatically altering the fundamental biology of farmed animals for millennia and perhaps recombination is just one more trait!

Conclusion

The results of this work show that increasing recombination is a potential way to make faster and more sustainable genetic improvement.

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