GENOMIC RELATIONSHIPS TO CONTROL INBREEDING IN OPTIMUM-CONTRIBUTION SELECTION REALISE MORE GENETIC GAIN THAN PEDIGREE RELATIONSHIPS WHEN INBREEDING CONTROL IS RELAXED AROUND QUANTITATIVE TRAIT LOCI

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SUMMARY

We tested the premise that optimum-contribution selection with genomic relationships to control inbreeding (GOCS) realises more genetic gain (ΔG) than optimum-contribution selection with pedigree relationships (POCS) at the same rate of true inbreeding (ΔF) when we relax inbreeding control in regions of the genome harbouring QTL. We used stochastic simulation to compare ΔG realised by GOCS with POCS at 0.01 ΔF when we relaxed inbreeding control around 18 major QTL. These QTL were unlinked and explained either 100 or 50% of the total additive-genetic variation (V_a) for a trait under selection. We found that GOCS with relaxed inbreeding realised up to 4.7% more ΔG than POCS at 0.01 ΔF when the 18 major QTL explained 100% V_a. When these QTL explained 50% V_a, GOCS with relaxed inbreeding control realised up to 1.1% more ΔG. Even though GOCS with relaxed inbreeding control realised more ΔG than POCS, we were surprised that the amount of extra ΔG was small, given that we simulated simple genetic models. This does not bode well for practical breeding schemes, where most traits under selection are controlled by many linked QTL and we don't know where most of these QTL are located. So, GOCS with relaxed inbreeding control is a concept that realises more ΔG than POCS at the same ΔF, but we have more to learn before it becomes applicable to practical breeding schemes. For these schemes, POCS remains a worthy method of optimum-contribution selection.

INTRODUCTION

Pedigree relationships to control inbreeding in optimum-contribution selection (OCS) realise more genetic gain (ΔG) than genomic relationships at the same rate of true inbreeding (ΔF), where the true inbreeding coefficient of an individual is the observed proportion of loci in its genome with alleles that are identical-by-descent (IBD) (Henryon *et al.* 2019). Using pedigree relationships to control inbreeding in OCS – hereafter referred to as POCS – realises more ΔG because it manages expected genetic drift without restricting selection at QTL. By contrast, genomic relationships – referred to as GOCS – penalises changes in allele frequencies at marker loci generated by genetic drift and selection. Because these marker alleles are in linkage disequilibrium with QTL alleles, GOCS restricts changes in allele frequencies at QTL. This implies that if GOCS is to realise more ΔG than POCS, we should allow changes in allele frequencies at some markers by varying the level of inbreeding control across the genome while controlling ΔF at acceptable levels. This will involve relaxing inbreeding control in regions of the genome that harbour QTL – allowing selection to increase the frequencies of favourable alleles at QTL – while increasing inbreeding control to reduce genetic drift in other regions. This reasoning led us to believe that GOCS realises more ΔG than POCS at the same ΔF when we relax inbreeding control in regions of the genome harbouring QTL. We tested this premise by stochastic simulation.

MATERIALS AND METHODS

Procedure. We used stochastic simulation of animal-breeding schemes to compare ΔG realised by GOCS with POCS at ΔF = 0.01 (0.01 ΔF) when we relaxed inbreeding control around 18 major QTL. These QTL were unlinked and explained either 100 or 50% of the total additive-genetic variation (V_a) for a single trait under selection. GOCS with relaxed inbreeding control was carried out by excluding markers located within 0, 1, 2, 5, 10, 20, 30, 40, and 50 cM of the 18 major QTL from genomic-relationship matrices used to control inbreeding (i.e., excluding markers in genome regions of 0, 2, 4, 10, 20, 40, 60, 80, and 100 cM centred around the 18 QTL). These GOCS are referred to as $GOCS_0$, $GOCS_1$ … $GOCS_{50}$, where $GOCS_0$ includes all markers and is the GOCS used in Henryon *et al.* (2019). ΔF was calculated as the increase in the observed proportion of IBD loci across the genome that were IBD. The trait under selection had a heritability of 0.2. Breeding values for the trait were predicted by GBLUP. Breeding schemes were run for 10 discrete generations ($t = 1 \ldots 10$) and replicated 500 times. Each replicate was initiated by sampling a unique base population from a founder population. Selection candidates were genotyped and phenotyped before selection.

Breeding scheme. A total of 25 matings were allocated to 125 selection candidates by OCS in each generation. There was no upper limit for the number of matings that were allocated to each male; males were allocated 0, 1, 2 … or 25 matings. Twenty-five females were allocated a single mating. The 25 sire and dam matings were paired randomly. Each pair (dam) produced five offspring, resulting in 25 full-sib families and 125 offspring. Offspring were assigned as males or females with a probability of 0.5.

Genetic models. The founder population was established using a Fisher-Wright inheritance model to generate linkage disequilibrium between QTL and markers. The genome was 30 M and consisted of 18 pairs of autosomal chromosomes; each chromosome was 167 cM long. The 18 major QTL were located on separate chromosomes. Each of these QTL had a minor-allele frequency of 0.25 (approx.) and explained equal proportions of V_a in the founder population. They each explained $\frac{1}{18}V_a$ when the 18 major QTL explained 100% V_a. When the major QTL explained 50% V_a, each QTL explained $\frac{1}{36}$ V_a; the remaining 50% V_a was explained by an additional 7684 minor QTL that were randomly distributed across the genome. The genome also contained 54218 biallelic markers that were randomly distributed across the genome. These markers were distinct from QTL and used in GOCS and GBLUP. A total of 6012 IBD loci were placed evenly across the genome in base populations. Unique alleles at these loci were used to calculate ΔF.

Optimum-contribution selection. POCS was carried out by maximising $\mathbf{U}_t(\mathbf{c}) = \mathbf{c}'\hat{\mathbf{a}} - \omega\mathbf{c}'\mathbf{A}\mathbf{c}$, where **c** is a vector of genetic contributions to the next generation, â is a vector of GBLUP-EBV, ω is a penalty applied to the average-estimated relationship of the next generation, and **A** is a pedigree-relationship matrix (after Henryon *et al.* 2019). The penalty, ω, was constant across generations. It was calibrated to realise 0.01 ΔF. GOCS was carried out by replacing **A** with a genomic-relationship matrix, **G**. **G** was constructed as described by VanRaden (2008) using marker-alleles frequencies in the base populations.

Data analyses. ΔG was calculated as the linear regression of G_t on *t*, where G_t is the average breeding value of animals born at times $t = 4 \ldots 10$. ΔG realised by POCS and GOCS differed when the 18 major QTL explained 100 and 50% V_a. We scaled ΔG by setting ΔG realised by POCS to 100 in the two genetic models. ΔF was calculated as 1-exp(β), where β is the linear-regression coefficient of $\ln(1-F_t)$ on *t,* and F_t is the average coefficient of true inbreeding for animals born at times $t = 4 \ldots 10$ (after Sonesson *et al.* 2004). We also present IBD profiles for POCS, $GOCS_0$, and $GOCS_{10}$ on chromosome 3 when the 18 major QTL explained 100% V_a. IBD profiles are presented as the change in realised IBD from generations $t = 4$ to 10 at the 6012 IBD loci. Scaled ΔG and IBD profiles are presented as means of the 500 replicates.

RESULTS AND DISCUSSION

Our findings supported our premise that GOCS realises more ΔG than POCS at the same ΔF when we relax inbreeding control in regions of the genome harbouring QTL. We found that $GOCS_5$ … $GOCS_{40}$ realised 2.7-4.7% more ΔG than POCS at 0.01 ΔF when 18 major QTL explained 100% V_a (Figure 1). When these QTL explained 50% V_a, $GOCS_{10}$ and $GOCS_{20}$ realised 0.3 and 1.1% more ΔG than POCS. Clearly, GOCS with relaxed inbreeding control – where we removed the penalty applied to changes in allele frequencies at markers located around major QTL – is a concept that worked. It worked for two reasons. First, selection increased the frequency of the favourable allele at each of the 18 major QTL with POCS and GOCS with relaxed inbreeding-control, but GOCS with relaxed inbreeding control allowed selection to increase the frequencies of favourable alleles more than POCS. Second, GOCS with relaxed inbreeding control allowed selection to generate more IBD in genome regions around the major QTL than POCS. This was illustrated by our IBD profiles on chromosome 3 when the 18 major QTL explained 100% V_a (Figure 2). $GOCS_{10}$ generated a higher IBD peak around the major QTL on chromosome 3 than POCS and $GOCS_0$. At the same time, $GOCS_{10}$ generated, on average, less IBD than POCS and $GOCS_0$ in regions of the genome that lacked major QTL. It must have generated less IBD in these regions because the area under an IBD profile increases at the same rate at the same ΔF. These two reasons tell us that GOCS with relaxed inbreeding control allows more IBD in regions of the genome where we want to increase the frequency of favourable alleles at QTL, while controlling IBD and genetic drift in other regions. It is exactly how we want to control inbreeding in animal breeding when the aim is to maximise ΔG at acceptable ΔF. So, GOCS with relaxed inbreeding control realises more ΔG than POCS at the same ΔF because it allows inbreeding in regions of the genome that realise ΔG and controls it in other regions.

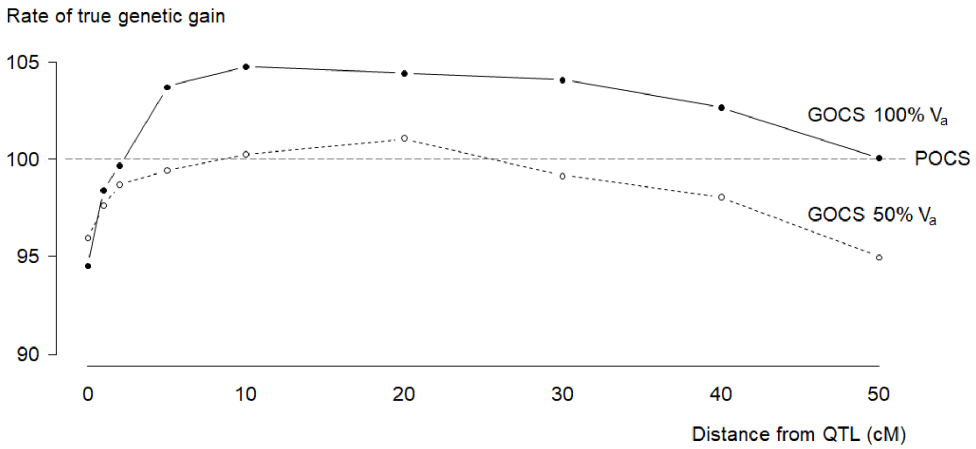

Figure 1. Rates of genetic gain realised by POCS and GOCS with relaxed inbreeding control at 0.01 rate of true inbreeding plotted against distance from 18 major QTL excluded from inbreeding control. The 18 QTL explained 100 and 50% of the additive-genetic variation (100% V_a, 50% V_a) for a single trait under selection. Rates of genetic gain were scaled by setting the rates of genetic gain realised by POCS with 100 and 50% V_a to 100. The rates are means of 500 simulation replicates. SD between the replicates ranged from 12.0-13.7

Even though GOCS with relaxed inbreeding control realised more ΔG than POCS, we were surprised that the amount of extra ΔG was small when we simulated a simple genetic model where 100% V_a was explained by only 18 unlinked QTL with known genome locations. This extra ΔG all but disappeared when the 18 major QTL explained 50% V_a. These findings are important because they imply that GOCS with relaxed inbreeding control only realises more ΔG than POCS at the same ΔF when traits are controlled by few unlinked QTL and we know where these QTL are located on the genome. It does not bode well for practical breeding schemes, where most, if not all, traits under selection are controlled by many linked QTL – each with small effects – and we don't know where most of these QTL are located. So, GOCS with relaxed inbreeding control is a concept that realises more ΔG than POCS, but we have more to learn before it becomes applicable to practical breeding schemes. For these schemes, POCS remains a worthy method of OCS.

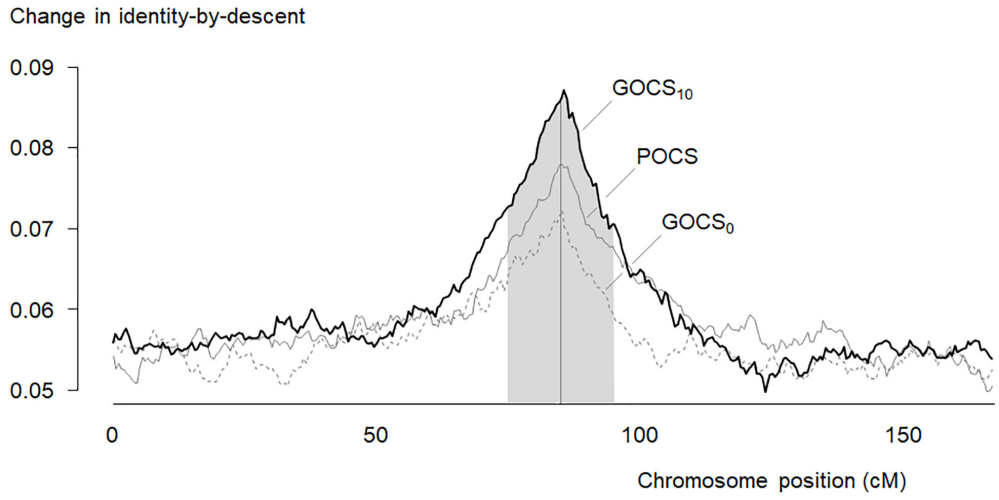

Figure 2. Identity-by-descent profiles for POCS, $GOCS_0$, and $GOCS_{10}$ on chromosome 3 at 0.01 rate of true inbreeding when 18 major QTL explained 100% of the additive-genetic variation for a single trait under selection. The profiles present the change in IBD realised at IBD loci located across the chromosome. The vertical line at 84.8 cM is the position of a single major QTL on chromosome 3; the shaded area represents the region of the genome that is within 10 cM of the major QTL. The profiles are means of 500 simulation replicates

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