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2   **Title**: Background selection and the statistics of population differentiation:

3   consequences for detecting local adaptation

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13 **Abstract**

14   Background selection is a process whereby recurrent deleterious mutations cause a

15   decrease in the effective population size and genetic diversity at linked loci. Several

16   authors have suggested that variation in the intensity of background selection could

17   cause variation in F_{ST} across the genome, which could confound signals of local

18   adaptation in genome scans. We performed realistic simulations of DNA sequences,

19   using parameter estimates from humans and sticklebacks, to investigate how

20   variation in the intensity of background selection affects different statistics of

21   population differentiation. We show that, in populations connected by gene flow,

22   Weir & Cockerham's (1984) estimator of F_{ST} is largely insensitive to locus-to-locus

23   variation in the intensity of background selection. Unlike F_{ST}, however, d_{XY} is

24   negatively correlated with background selection. We also show that background

25   selection does not greatly affect the false positive rate in F_{ST} outlier studies. Overall,

26   our study indicates that background selection will not greatly interfere with finding

27   the variants responsible for local adaptation.

28

29   **Introduction**

30   Natural selection affects patterns of genetic diversity throughout the genome. How

31   selection affects genetic diversity on a single isolated locus is relatively easy to

32   model; however, when a large number of linked loci are considered, interactions

33   between evolutionary pressures at different sites render the task of modelling much

34   more difficult.

35   Maynard Smith & Haigh (1974) recognized the influence of selection on linked

36   neutral sites, proposing that strong positive selection could reduce genetic diversity

37   at nearby sites. This process is now referred to as a 'selective sweep'. Much later,

38   Charlesworth et al. (1993) proposed that deleterious mutations could also affect

39   genetic diversity at nearby sites, because some haplotypes would be removed from

40   the population as selection acts against linked deleterious alleles. They named this

41   process background selection (BGS). Both selective sweeps and background

42   selection affect genetic diversity; they both reduce the effective population size of

43   linked loci. Empirical evidence of a positive correlation between genetic diversity

44   and recombination rate has been reported in several species (Cutter and Payseur,

45   2013), including *Drosophila melanogaster* (Begun & Aquadro, 1992; Elyashiv et al.,

46   2016), humans (Spencer et al., 2006), collared flycatchers, hooded crows and

47   Darwin's finches (Dutoit et al., 2017; see also Vijay et al., 2017).

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49   BGS is also expected to affect F_{ST} (Charlesworth et al., 1997; Cutter & Payseur, 2013;

50   Cruickshank & Hahn, 2014; Hoban et al., 2016). At low effective population size,

51   different populations may randomly fix different alleles, increasing F_{ST}, while at high

52   population size, allele frequency changes less through time and different

53   populations are more likely to have comparable allele frequencies, keeping F_{ST} low.

54   This negative relationship between effective population size N_e and F_{ST} is captured

55   in Wright's classical infinite island result; $F_{ST} = \frac{1}{1+4Ne(m+\mu)}$ (Wright, 1943). One

56   might therefore expect that loci under stronger BGS would show higher F_{ST}.

57   Many authors have also argued that, because BGS reduces the within-population

58   diversity, it should lead to high F_{ST} (Cutter & Payseur, 2013; Cruickshank & Hahn,

59   2014; Hoban et al., 2016). Expressed in terms of heterozygosities, $F_{ST} = \frac{H_T - H_S}{H_T} =$

60    $1 - \frac{H_S}{H_T}$, where H_T is the expected heterozygosity in the entire population and H_S is

61   the average expected heterozygosity within subpopulations (H_S and H_T are also

62   sometimes called π_S and π_T; e.g. Charlesworth, 1998). All else being equal, a

63   decrease of H_S would indeed lead to an increase of F_{ST}. However, all else is not equal;

64   H_T is also affected by BGS (Charlesworth et al., 1997). Therefore in order to

65   understand the effects of BGS on F_{ST}, we must understand the relative impact of BGS

66   on both H_S and H_T.

67   Performing numerical simulations, Charlesworth et al. (1997) report that BGS

68   reduces the within population heterozygosity H_S slightly more than it reduces the

69   total heterozygosity H_T, causing a net increase in F_{ST}. The effect on F_{ST} reported is

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70   quite substantial, but, importantly, their simulations were not meant to be realistic.

71   The authors highlighted their goal in the methods:

72   "The simulations were intended to show the qualitative effects of the various

73   forces studied [...], so we did not choose biologically plausible values [...].

74   Rather, we used values that would produce clear-cut effects".

75   For example, talking about their choice for the deleterious mutation rate of 8×10^{-4}

76   per site:

77   "This unrealistically high value was used in order for background selection to

78   produce large effects [...]"

79   Much of the literature on the effect of BGS on F_{ST} is based on the results in

80   Charlesworth et al. (1997), even though they only intended to show proof of concept

81   (see also Zeng & Charlesworth, 2011 and Zeng & Corcoran, 2015). They did not

82   attempt to estimate how strong of an effect BGS has on F_{ST} in real genomes.

83   It is important to distinguish two separate questions when discussing the effect of

84   BGS on F_{ST}; 1) How does BGS affect the average genome-wide F_{ST}? and 2) How does

85   locus-to-locus variation in the intensity of BGS affect locus-to-locus variation in F_{ST}?

86   The second question is of particular interest to those trying to identify loci under

87   positive selection (local selection or selective sweep). Locus-to-locus variation in F_{ST}

88   potentially could be confounded with the F_{ST} peaks created by positive selection. In

89   this paper, we focus on this second question.

90   The identification of loci involved in local adaptation is often performed via F_{ST}

91   outlier tests (Lotterhos & Whitlock, 2014; Hoban et al., 2016). Other tests exist to

92   identify highly divergent loci such as cross-population extended haplotype

93   homozygosity (XP-EHH; Sabeti et al., 2007), comparative haplotype identity (Lange

94   & Pool, 2016), cross-population composite likelihood ratio (XP-CLR; Chen et al.,

95   2010). F_{ST} outlier tests, such as FDist2 (Beaumont & Nichols, 1996), BayeScan (Foll

96   & Gaggiotti, 2008) or FLK (Bonhomme et al., 2010), look for genomic regions

97   showing particularly high F_{ST} values to find candidates for local adaptation. If BGS

98   can affect F_{ST} unevenly across the genome, then regions with a high intensity of BGS

99   could potentially have high F_{ST} values that could be confounded with the pattern

100   caused by local selection (Charlesworth et al., 1997; Cruickshank & Hahn, 2014).

101   BGS could therefore inflate the false positive rate when trying to detect loci under

102   local selection.

103   The potential confounding effect of BGS on signals of local adaptation has led to an

104   intense effort trying to find solutions to this problem (Bank et al., 2014; Huber et al.,

105   2016). Many authors have understood from Cruickshank and Hahn (2014) that d_{XY}

106   should be used instead F_{ST} in outlier tests (e.g. McGee et al., 2015; Yeaman, 2015;

107   Whitlock & Lotterhos, 2015; Brousseau et al., 2016; Picq et al., 2016; Payseur &

108   Rieseberg, 2016; Hoban et al., 2016; Vijay et al., 2017; see also Nachman & Payseur,

109   2012). F_{ST} is a measure of population divergence relative to the total genetic

110   diversity, while d_{XY} is an absolute measure of population divergence defined as the

111   probability of non-identity by descent of two alleles drawn in the two different

112   populations averaged over all loci (Nei, 1987; Nei, 1987 originally called it D_{XY} but,

113   here, we follow Cruickshank and Hahn's, 2014 terminology by calling it d_{XY}). The

114   argument is that because F_{ST} is a measure of divergence relative to the genetic

115   diversity and d_{XY} an absolute measure of divergence and because BGS reduces

116   genetic diversity, then BGS must affect F_{ST} but not d_{XY}, a claim that we will

117   investigate in this paper.

118   Whether BGS can affect genome-wide F_{ST} under some conditions is not in doubt

119   (Charlesworth et al., 1997), but whether locus-to-locus variation in the intensity of

120   BGS present in natural populations substantially affects variation in F_{ST} throughout

121   the genome is very much unknown. Empirically speaking, it has been very difficult

122   to measure how much of the genome-wide variation in genetic diversity is caused by

123   BGS, as opposed to selective sweeps or variation in mutation rates (Cutter &

124   Payseur, 2013; see also attempts in humans by Cai et al., 2009 and McVicker et al.

125   2009). We are therefore in need of realistic simulations that can give us more

126   insight into how BGS affects genetic diversity among populations and how it affects

127   the statistics of population divergence.

128   In this article, we investigate the effect of BGS in structured populations with

129   realistic numerical simulations using parameter estimates from humans and

130   stickleback. Our two main goals are 1) to quantify the impact of locus-to-locus

131   variation in the intensity of BGS on d_{XY} (Nei, 1987) and F_{ST} (Weir & Cockerham,

132   1984) and 2) to determine whether BGS inflates the false positive rate of F_{ST} outlier

133   tests.

134   **Methods**

135   Our goal is to perform biologically plausible simulations of the local genomic effects

136   of background selection. BGS is expected to vary with gene density, mutation rate

137   and recombination rate across the genome. We used data from real genomes to

138   simulate realistic covariation in recombination rates and gene densities. We chose

139   to base our simulated genomes on two eukaryote genomes, sticklebacks and

140   humans, because these two species have attracted a lot attention in studies of local

141   adaptation and because sticklebacks have a variance in recombination rate which is

142   almost 15 times higher than humans (data not shown), allowing us to test vastly

143   different types of eukaryotic genomes. The recombination rate variation in humans

144   is extremely fine scale, but it presents the potential issue that it is estimated from

145   linkage disequilibrium data. As selection causes linkage disequilibrium to increase,

146   estimates of recombination rate at regions under strong selection may be under-

147   estimated, hence artificially increasing the simulated variance in the intensity of

148   BGS. Although the recombination map for stickleback is much less fine scaled, the

149   estimates are less likely to be biased as they are computed from pedigrees.

150   Our simulations are forward in time and were performed using the simulation

151   platform SimBit version 3.69. The code and user manual are available at

152   https://github.com/RemiMattheyDoret/SimBit. To double check our results, we

153   also ran some simulations with SFS_code (Hernandez, 2008), confirming that we get

154   consistent distributions of genetic diversity and of F_{ST} among simulations (results

155   not shown). Generations are non-overlapping, individuals are hermaphrodites,

156   mating is random within patches and selection occurs before dispersal.

157   *Genetics*

158   For each simulation, we randomly sampled a sequence of about 10 cM coming either

159   from the stickleback (*Gasterosteus aculeatus*) genome or from the human genome

160   (see treatments below) and used this genomic location to determine the

161   recombination map and exon locations for a simulation replicate. For the stickleback

162   genome, we used the gene map and recombination map from Roesti et al. (2013).

163   Ensembl-retrieved gene annotations were obtained from Marius Roesti. For the

164   human genome, we used the recombination map from The International HapMap

165   Consortium (2007) and the gene positions from NCBI and positions of regulatory

166   sequences on Ensembl (Zerbino et al., 2017). We excluded sex chromosomes to

167   avoid complications with haploid parts of the genomes. As estimates of mutation

168   rate variation throughout the genome are very limited, we assumed that the haploid

169   mutation rate varies from site to site following an exponential distribution with

170   mean of 2.5×10^{-8} per generation (Nachman & Crowell, 2000).

171 More specifically, we first randomly sampled a sequence of 10^5 nucleotides, which

172 we will refer to as the focal region. All of the statistics (defined under the section

173 *Statistics* below) are calculated only on the focal region of each simulation.

174 Nucleotides that occur in locations determined to be exons in the sampled genomic

175 map are subject to selection (see *Selection*), while all other nucleotides are assumed

176 to be neutral. The focal region itself contained on average ~0.44 genes for the

177 human genome and ~3.15 genes for the stickleback genome.

178 We simulated a 5 cM region on each side of the focal region (resulting in a window

179 of 10 cM plus the recombination rate present in the specific focal region of 10^5 sites)

180 in order to capture the local effects of background selection. In these 10 cM flanking

181 regions, we only tracked exons. In the nearest 1 cM on each side of the focal region,

182 as well within the focal region, we individually simulated each nucleotide with a bi-

183 allelic locus. On the remaining outer 4 cM, to improve the speed and RAM usage of

184 the process, we tracked the number of mutations in blocks of up to 100 nucleotides.

185 For these blocks, we tracked only the number of mutations but not their location

186 within the block. Ignoring recombination within a block likely had little effect on the

187 results because the average recombination distance between the first and last site of

188 a block is of the order of 10^{-6} cM. The expected number of segregating sites within a

189 block is $4N\mu \sum_{i=1}^{2N-1}(1/i)$, which for a mutation rate per block of 10^{-6} and a

190 population size of $N = 10,000$ is ~0.42. The probabilities of having more than one

191 mutation and more than two mutations (based on a Poisson approximation) are

192   therefore only approximately 6.7% and 0.9%, respectively. Overall, the level of

193   approximation used is very reasonable.

194   *Selection*

195   As we are interested in the effect of BGS, we modelled the effects of purifying

196   selection against novel deleterious mutations. Each nucleotide in the exons (and

197   regulatory sequences for the human genome) is subject to purifying selection with a

198   selection coefficient against mutant alleles determined by a gamma distribution

199   described below. For focal regions that include exons, statistics are computed over a

200   sequence that is at least partially under direct purifying selection.

201   To create variance in selection pressures throughout the genome, each exon (and

202   regulatory sequence for the human genome) has its own gamma distribution of

203   heterozygous selection coefficients *s*. The mean and variance of these gamma

204   distributions are drawn from a bivariate uniform distribution with correlation

205   coefficient of 0.5 (so that when the mean is high, so is the variance) bounded

206   between 10^{-8} and 0.2 for both the mean and the variance. These bounds were

207   inspired by the methodology used in Gilbert et al. (2017). The gamma distributions

208   are bounded to one. Figure S1 shows the overall distribution of selection coefficient

209   *s*, with 2% of mutations being lethal and an average deleterious selection coefficient

210   for the non-lethal mutations of 0.07. To improve the performance of our

211   simulations, we used multiplicative dominance, where the fitness of heterozygotes

212   is at locus *i* is 1- s_i and the fitness of the double mutant is $(1- s_i)^2$.

213   As a consequence of our parameter choices, our genome-wide deleterious mutation

214   rate was about 1.6 in sticklebacks and about 3 in humans. 9.4% of the stickleback

215   genome and 2.6% of the human genome was under purifying selection. For

216   comparison, the genome-wide deleterious mutation rate is estimated at 2.2 in

217   humans (Keightley, 2012) and 0.44 in rodents (Keightley & Gaffney, 2003). To our

218   knowledge, there is currently no such estimation for sticklebacks. Note however

219   that the above estimates cannot reliably detect mutations that are quasi lethal ($s \ll$

220    $1/2N$). By our distribution of selective coefficients, 49% of all deleterious mutations

221   have a heterozygote selective coefficient lower than $1/2N_e$ when N_e = 1,000 (42%

222   when N_e = 10,000).

223   It is worth noting however that, in rodents, about half of the deleterious mutation

224   rate occurs in non-coding sequences (Keightley & Gaffney, 2003). Our simulations

225   using human genome had all exons and all regulatory sequences under purifying

226   selection. With our simulations based on the stickleback genome, however, only

227   exons were under purifying selection. It is therefore possible that we would have

228   over-estimated the deleterious mutation rate in gene-rich regions and under-

229   estimated the deleterious mutation rate in other regions, especially in stickleback.

230   This would artificially increase the locus-to-locus variation in the intensity of BGS in

231   our simulations.

232   *Demography*

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233   In all simulations, we started with a burn-in phase with a single population of N

234   diploid individuals, lasting $5 \times 2N$ generations. The population was then split into

235   two populations of N individuals each with a migration rate between them equal to

236   m. After the burn-in phase, each simulation was run for $5 \times 2N$ more generations for

237   a total of $10 \times 2N$ generations.

238   *Treatments*

239   We explored presence and absence of deleterious mutations over two patch sizes,

240   three migration rates, and two genomes.

241   We do not have a full factorial design. We considered a basic design and explored

242   variations from this design. The basic design had a population size per patch of $N =$

243   1000, a migration rate of m = 0.005 and used the stickleback genome for its

244   recombination map and gene positions. As deviations from this basic design, we

245   explored modification of every variable, one variable at a time. The *Large N*

246   treatment has N = 10000. The *Human* treatment uses the human genome for gene

247   positions, regulatory sequences and recombination map. The treatments *No*

248   *Migration* and *High Migration* have migration rates of $m = 0$ and $m = 0.05$,

249   respectively.

250   To test the robustness of our results and because it may be relevant for inversions,

251   we also had unrealistic simulations where recombination rate for the entire genome

252   was set at zero. As a check against previous work, we qualitatively replicated the

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253   results Charlesworth et al. (1997) by performing simulations with similar

254   assumptions as they used. We named this treatment *CNC97*. In our *CNC97*

255   simulations, N=2000, m=0.001, and 1000 loci were all equally spaced at 0.1 cM apart

256   from each other with constant selection pressure with heterozygotes having fitness

257   of 0.98 and double homozygotes fitness of 0.9 and constant mutation rate μ =

258   0.0004.

259   In all treatments (except *Large N*), we performed 4000 simulations; 2000

260   simulations with BGS and 2000 simulations without selection (where all mutations

261   were neutral). For *Large N*, simulations took more memory and more CPU time. We

262   therefore could only perform 2000 simulations for *Large N*; 1000 simulations with

263   background selection and 1000 simulations without selection. That represents a

264   total of 26,000 simulations for 7 treatments. A full list of all treatments can be found

265   in table 1.

266   We set the generation 0 at the time of the split. The state of each population was

267   recorded at the end of the burn-in period (generation -1) and at generations 0.001×

268    $2N$, $0.05 \times 2N$, $0.158 \times 2N$, $1.581 \times 2N$ and $5 \times 2N$ after the split. For N=1000, the

269   sampled generations are therefore -1, 2, 100, 316, 3162 and 10000.

270   *Predicted intensity of Background Selection*

271   In order to investigate the locus-to-locus correlation between the predicted

272   intensity of BGS and various statistics, we computed B, a statistic that approximates

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273   the expected ratio of the coalescent time with background selection over the

274   coalescent time without background selection $\left(B = \frac{T_{BGS}}{T_{neutral}} \right)$. B quantifies how

275   strong BGS is expected to be for a given simulation (Nordborg et al. 1996). A B value

276   of 0.8 means that BGS has caused a drop of genetic diversity of 20% compared to a

277   theoretical absence of BGS. Lower B values indicate stronger BGS.

278   Both Hudson & Kaplan (1995) and Nordborg et al. (1996) have derived theoretical

279   expectations for B. We applied both methods and found that the predictions of the

280   two formulas are highly correlated (Figure S2). Because the Hudson & Kaplan

281   (1995) approach has been more popular in the literature (cited almost twice as

282   often), we show only the B values computed following Hudson & Kaplan (1995):

283      $$B = \exp\left(-\sum_i \frac{u_i s_i}{(s_i + r_i(1 - s_i))^2} \right)$$

284   where r_i is the recombination rate between the focal site and the ith site under

285   selection, and s_i is the heterozygous selection coefficient at that site. u_i is the

286   mutation rate at the ith site. By this formula, B is bounded between 0 and 1, where 1

287   means no BGS at all and low values of B mean strong BGS. We computed B for all

288   sites in the focal region and report the average B for the region.

289   For the stickleback genome, B values ranged from 2×10^{-6} to 1.0 with a mean of

290   0.937 (Figure S2). For the human genome, B values ranged from 0.45 to 1.0 with a

291   mean at 0.975. There is indeed less variability and much fewer extremely low B

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292   values in the human genome. In the unrealistic *No Recombination* treatment, *B*

293   values range from 0.00003 to 0.84 with a mean of 0.17.

294   *F_{ST} outlier tests*

295   In order to know the effect of BGS on outlier tests of local adaptation, we used a

296   variant of FDist2 (Beaumont & Nichols, 1996). We chose FDist2 because it is a

297   simple and fast method for which the assumptions of the test match well to the

298   demographic scenario simulated here. Because the program FDist2 is not available

299   through the command line, we rewrote the FDist2 algorithm in R and C++. Source

300   code can be found at https://github.com/RemiMattheyDoret/Fdist2.

301   Our FDist2 procedure is as follows; first, we estimated the migration rate from the

302   average F_{ST} ($m = \frac{F_{ST}-1}{8 \cdot F_{ST} \cdot N}$; Charlesworth, 1998) and then running 50000 simulations

303   each lasting for 50 times the half-life to reach equilibrium F_{ST} given the estimated

304   migration rate (Whitlock, 1992). For each SNP, we then selected the subset of FDist2

305   simulations for which allelic diversity was less than 0.02 away from the allelic

306   diversity of the SNP of interest. The *P*-value is computed as the fraction of FDist2

307   simulations within this subset having a higher F_{ST} than the one we observed. The

308   false positive rate is then defined as the fraction of neutral SNPs for which the *P*-

309   value is lower than a given α value. The α values explored are 0.1, 0.05, 0.01, 0.001,

310   0.0001 and 0.00001.

311   For the outlier tests, to avoid issues of pseudo-replication, we considered only a

312   single SNP per simulation whose minor allele frequency is greater than 0.05. Then,

313   we randomly assembled SNPs from a given treatment into groups of 500 SNPs to

314   create the data file for FDist2. We have 4000 simulations (2000 with BGS and 2000

315   without BGS) per treatment (*Large N* is an exception with only 2000 simulations

316   total), which allowed 8 independent false positive rate estimates per treatment (4

317   estimates with BGS and 4 without BGS). In each treatment, we tested for different

318   false positive rate with and without BGS with both a Welch's *t*-test and a Wilcoxon

319   test.

320   *Statistics*

321   F_{ST} and d_{XY} are both measures of population divergence. In the literature there are

322   several definitions of $F_{ST,}$ and we also found potential misunderstanding about how

323   d_{XY} is computed. We want to clarify here these definitions and what we mean when

324   we use the terms F_{ST} and d_{XY}.

325   There are two main estimators of F_{ST} in the literature; G_{ST} (Nei, 1973) and θ (Weir &

326   Cockerham, 1984). In this article, we focus on θ as an estimate of F_{ST} (Weir &

327   Cockerham, 1984). There are also two methods of averaging F_{ST} over several loci.

328   The first method is to simply take an arithmetic mean over all loci. The second

329   method consists at calculating the sum of the numerator of θ over all loci and

330   dividing it by the sum of the denominator of θ over all loci. Weir and Cockerham

331   (1984) showed that this second averaging approach has lower bias than the simple

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332   arithmetic mean. We will refer to the first method as the "average of ratios" and to

333   the second method as "ratio of the averages" (Reynolds et al. 1983; Weir &

334   Cockerham, 1984) . In this article, we use F_{ST} as calculated by "ratio of the averages",

335   as advised by Weir and Cockerham (1984). To illustrate the effects of BGS on the

336   biased estimator of F_{ST}, we also computed F_{ST} as a simple arithmetic mean ("average

337   of the ratio"), and we will designate this statistic with a subscript $F_{ST\ (average\ of\ ratios)}$.

338   d_{XY} is a measure of genetic divergence between two populations X and Y. Nei (1987)

339   defined d_{XY} as

340    $$d_{XY} = \frac{\sum_{l=1}^{L}\left(1 - \sum_{k=1}^{A_l} x_{l,k} y_{l,k}\right)}{L}$$

341   where L is the total number of sites, A_l is the number of alleles at the lth site and $x_{l,k}$

342   and $y_{l,k}$ are the frequency of the kth allele at the lth locus in the population X and Y

343   respectively.

344   Some population genetics software packages (e.g., EggLib; De Mita and Siol, 2012)

345   average d_{XY} over polymorphic sites only, instead of averaging over all sites, as in

346   Nei's (1987) original definition of d_{XY}. This measure averaged over polymorphic

347   sites only will be called $d_{XY\text{-}SNP}$; otherwise, we use the original definition of d_{XY} by Nei

348   (1987).

349   The statistics reported are the average F_{ST}, d_{XY}, and within population genetic

350   diversity $H_S = \sum_{l=1}^{L}\left(1 - \sum_{k=1}^{A_l} x_{l,k}^2\right) / L$. For each treatment and at each generation, we

351   computed five independent Pearson correlation tests between B and F_{ST}, $F_{ST\,(average\,of}$

352     $_{ratios)}$, d_{XY}, $d_{XY\text{-}SNP}$ and H_S. We compared our correlation tests with ordinary least

353   squares regressions and robust regressions (using M-estimators; Huber, 1964), and

354   the results were consistent.

355   **Results**

356   Correlations between the statistics H_S, F_{ST}, $F_{ST\,(average\,of\,ratios)}$, d_{XY}, and $d_{XY\text{-}SNP}$ and B, are

357   summarized in tables S1, S2, S3, S4 and S5, respectively. Figure 1 shows the means

358   and standard errors for the treatments *Default*, *High Migration*, *Large N, Human* and

359   *No Migration*. The same graphs for the treatments *No Recombination* and *CNC97* can

360   be found in Figure S3.

361   *Genetic Diversity*

362   Genetic diversity within populations (H_S) is very similar among the treatments

363   *Default, High Migration* and *Human* (around $H_S = 1.9 \times 10^{-4}$) but is about 1.9 times

364   lower in the *No Migration* treatment ($H_S = 1.0 \times 10^{-4}$) and about 10 times higher in

365   the *Large N* treatment ($H_S = 1.9 \times 10^{-3}$; Figure 1).

366   B is significantly correlated with genetic diversity within populations (H_S) for all

367   treatments using the stickleback genome (and at almost all generations) but not

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368   with the *Human* treatment (table S1). Excluding the unrealistic treatments (*No*

369   *Recombination* and *CNC97*), simulations with BGS have a genetic diversity 4% to

370   20% lower than simulations without BGS (Figure 1, right column and Figure S3,

371   right column). In the *Human* treatment, there is no significant correlation of B and

372   H_S. Note that Pearson's correlation coefficients between B and H_S are always very

373   small even when the effect is highly significant. The largest R^2 observed in realistic

374   simulations (excluding in the *No Recombination* and *CNC97* treatments) between B

375   and H_S is $R^2 \approx 0.0121$.

376   *Statistics of population divergence*

377   Figure 2 shows the correlation between B and the statistics F_{ST}, d_{XY} and H_S for

378   *Default* at the last generation. These graphs highlight the general tendencies of the

379   treatments *Default*, *High Migration*, *Large N* and *No Recombination*. The strongest

380   correlation with B is observed for the statistics d_{XY} ($P = 3.28 \times 10^{-5}$, $R = 0.093$) and H_S

381   ($P = 3.1 \times 10^{-5}$, $R = 0.093$). In fact, the two statistics d_{XY} and H_S are very highly

382   correlated ($P < 2.2 \times 10^{-16}$, $R = 0.99$). This high correlation explains the resemblance

383   between the central and right graphs of figure 2. F_{ST} is not correlated with B ($P =$

384   0.99, $R = 10^{-4}$). All correlation tests between B and the statistics F_{ST}, $F_{ST\ (average\ of\ ratios)}$,

385   d_{XY}, $d_{XY\text{-}SNP}$ can be found in Tables S2, S3, S4 and S5, respectively.

386   The *No Migration* treatment is an exception to the other treatments. F_{ST} is not

387   significantly correlated with B at early generations but become slightly correlated as

388   divergence rises to 0.6 and higher. d_{XY} shows an opposite pattern. d_{XY} is very

20

389   significantly correlated with B at early generations and seemingly independent of B

390   at the last generation. Note that for both d_{XY} and F_{ST}, all correlation coefficients are

391   always very small. The largest R^2 observed is $R^2=0.0121$ in realistic simulations

392   (found for F_{ST} *No Migration* and for d_{XY} Large N; Tables S2, S4) and $R^2=0.0256$ for

393   the *No Recombination* treatment (found for d_{XY}; Table S4).

394   As expected, in the *CNC97* simulations, there is a strong difference between

395   simulations with BGS and simulations without BGS for all three statistics (F_{ST}, d_{XY},

396   and H_S) at all generations (Welch's *t*-tests; all $P < 2.2\times10^{-16}$; Figure S3).

397   F_{ST} calculated as advised by Weir and Cockerham (1984) was generally less sensitive

398   to BGS than F_{ST} calculated as an average of ratios (compare tables S2 and S3). Figure

399   S4 illustrates the sensitivity of $F_{ST\ (average\ of\ ratios)}$ in the worst case, the *No*

400   *Recombination* treatment. This sensitivity is driven largely by rare alleles and goes

401   away when minor alleles below a frequency of 0.05 are excluded.

402   *F_{ST} outlier tests*

403   The observed false positive rate is relatively close to the α values except for *No*

404   *Migration* (with and without BGS) and *CNC97* (with BGS). With the exception of

405   treatments *No Migration* and *CNC97*, there is no significant difference in false

406   positive rates between simulations with BGS and those without BGS for α of 0.05

407   (Figure 3). In the treatment, *No Migration*, the false positive rates between

408   simulations with and without BGS are significantly different for the latter

21

409   generations. In this treatment, the false positive rate for both simulations with and

410   without BGS are much higher than the α value of 0.05. Results remain very

411   congruent for other α values (results not shown).

412   **Discussion**

413   Background selection reduces genetic diversity, both within and among populations,

414   but the effect on F_{ST} is rather small. In simulations of interconnected populations

415   with realistic parameters, F_{ST} is insensitive to BGS while the absolute measure of

416   divergence d_{XY} is affected by BGS. On the other hand, in highly diverged populations

417   unconnected by migration, BGS can have a greater impact on F_{ST} and a lower impact

418   on d_{XY}. The effects of BGS, when observed, are always very small with R^2 never over

419   1.1%.

420   BGS impacts both total and within population genetic diversity. Excluding the

421   treatments *No recombination* and *CNC97*, we observe that simulations with BGS

422   have a genetic diversity (whether H_T or H_S; H_T data not shown) 6% to 16% lower

423   than simulations without BGS. Messer & Petrov (2013) simulated a panmictic

424   population, looking at a sequence of similar length inspired from a gene-rich region

425   of the human genome, and reported a similar decrease in genetic diversity. Under

426   the *No Recombination* treatment, this average reduction of genetic diversity due to

427   BGS is 53%. Although empirical estimates are very complex and can hardly

428   disentangle BGS from selective sweeps, our results are also comparable with

429   empirical estimates. Reduction in genetic diversity in humans between regions

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430 under high BGS are estimated at 6% according to Cai et al. (2009) or 19-26%

431 according to McVicker et al. (2009). In *Drosophila melanogaster*, where gene density

432 is higher, the reduction in genetic diversity due to BGS is estimated at 36% when

433 using Kim & Stephan (2000)'s methodology and is estimated at 71% reduction using

434 a composite likelihood approach (Elyashiv et al., 2016) and is hence closer to our *No*

435 *Recombination* treatment than to the other treatments. It is worth noting that,

436 because we were interested in simulating variance among sites in effects of BGS, we

437 only simulated local effects and therefore underestimate the expected genome-wide

438 effect of BGS on H_T.

439 In contrast to measures of heterozygosity, F_{ST} was generally not significantly

440 correlated with B. The only exception is for the *No Migration* treatment, where, after

441 many generations, as the average F_{ST} becomes very high ($F_{ST} > 0.5$), we observe a

442 slight, yet significant, negative correlation between the expected effects of BGS, B,

443 and F_{ST} (intense BGS lead to high values of F_{ST}). This highlights that F_{ST} is not

444 completely insensitive to BGS, but F_{ST} is largely robust to BGS.

445 Future research is needed to attempt a theoretical estimate of the genome-wide

446 effect of BGS. Our work has been restricted to the stickleback and human genomes.

447 While these two genomes are good representatives of many cases of eukaryotic

448 genomes, they are not good representatives of more compact genomes such as

449 bacterial genomes or yeasts. Our simulations used randomly mating diploid

450 populations. Non-random mating, selfing, and asexual reproduction could also affect

451   our general conclusion, and potentially strongly increase the effects of BGS on F_{ST}

452   (Charlesworth *et al.* 1997). We have explored two population sizes, but we could not

453   explore population sizes of the order of a million individuals (like *Drosophila*

454   *melanogaster*) and still realistically simulate such long stretch of DNA. It is not

455   impossible that a much greater population size or a more complex demography

456   could yield to BGS having a greater effect on F_{ST} than what we observed here (Torres

457   et al. 2017).

458   Some have argued that, because BGS reduces the within population diversity, it

459   should lead to high F_{ST} (Cutter & Payseur, 2013; Cruickshank & Hahn, 2014; Hoban

460   et al., 2016). All else being equal, this statement is correct. However, BGS reduces H_T

461   almost as much as H_S (Figure 4). It is therefore insufficient to consider only one

462   component, and we must consider the ratio of these two quantities captured by the

463   definition of F_{ST}, $F_{ST} = 1 - \frac{H_S}{H_T}$. This ratio, as we have shown, appears to be relatively

464   robust to BGS. While genome-wide BGS might eventually be strong enough to cause

465   departures with F_{ST} values, it appears that locus-to-locus variation in the intensity of

466   BGS is not strong enough to have much impact on F_{ST} as long as populations are not

467   too highly diverged.

468   We also investigated the consequences of BGS on the widely-used but imperfect

469   estimator, $F_{ST\ (average\ of\ ratios)}$, for which F_{ST} measures for each locus are averaged to

470   create a genomic average. It is well known that $F_{ST\ (average\ of\ ratios)}$ is a biased way to

471   average F_{ST} over several loci (Weir & Cockerham, 1984); however, its usage is

24

472   relatively common today. In our simulations, $F_{ST \, (average \, of \, ratios)}$ is more affected by

473   BGS than F_{ST}. Interestingly, $F_{ST \, (average \, of \, ratios)}$ is most often higher with weaker BGS.

474   The directionality of this correlation may seem unintuitive at first. To understand

475   this discrepancy, remember that BGS affects the site frequency spectrum; we

476   observed that BGS leads to an excess of loci with low H_T (results not shown but see

477   Charlesworth et al., 1995; see also contrary expectation in Stephan, 2010). Loci

478   associated with very low H_T also have low F_{ST} (figure S5), a well-known result

479   described by Beaumont and Nichols (1996). As BGS creates an excess of loci with

480   low H_T and loci with low H_T tend to have low F_{ST}, BGS can actually reduce $F_{ST \, (average \, of}$

481    $_{ratios)}$. After filtering out SNPs with a minor allele frequency lower than 5%, most of

482   the correlation between $F_{ST \, (average \, of \, ratios)}$ and B is eliminated (Figure S4).

483   The absolute measure of divergence d_{XY} is sensitive to BGS. Regions of stronger BGS

484   are associated with low d_{XY}. The effect, although significant, is of relatively small

485   size. The expected d_{XY} for neutral loci is $d_{XY} = 4N\mu + 2t\mu$ (Nei, 1987), where t is the

486   time in generation since the populations started to diverge. $4N\mu$ is the expected

487   heterozygosity in the ancestral population (before splitting) and $2t\mu$ is the expected

488   number of mutations fixed over time in either population since the population split.

489   BGS does not affect the rate of fixation of mutations arising after the populations

490   diverged, but BGS affects the expected heterozygosity. Therefore, BGS should affect

491   d_{XY} by its effect on the expected heterozygosity, and this effect should be greater

492   early in divergence when the $4N\mu$ term is large relative to the fixation term. This is

493   consistent with the results of our simulations. This result is in agreement with Vijay

494   et al. (2017) who reported a strong correlation between H_S and d_{XY} when F_{ST} is low

495   ($F_{ST} \approx 0.02$), but this correlation breaks down when studying more distantly related

496   populations ($F_{ST} \approx 0.3$).

497   Interestingly, d_{XY} becomes less sensitive to BGS when F_{ST} becomes more sensitive.

498   While our methodology does not allow us to test the efficiency of d_{XY} in outlier tests,

499   it is possible that d_{XY} could be used for highly divergent lineages, but not in cases

500   when divergence is relatively low. Cruickshank and Hahn (2014) suggested relying

501   more on d_{XY} than F_{ST} for finding highly divergent loci. Their conclusion was based on

502   analysis of a dataset involving highly divergent populations only (F_{ST} values range

503   from about 0.38 to about 0.8). Based on our simulations, their conclusion is not valid

504   when populations are not highly diverged.

505   As BGS also leads to a reduction of the number of polymorphic sites, BGS has an

506   even stronger effect on $d_{XY\text{-}SNP}$ than on d_{XY} (Figure S4). (The measure that we call $d_{XY\text{-}}$

507    $_{SNP}$ is d_{xy} improperly calculated based only on polymorphic sites, as is done in some

508   software packages.) This result highlights the importance of not blindly trusting the

509   output of a given software package.

510   Outside the effect of BGS on N_e, there are at least two other possible factors that can

511   potentially affect the correlation between B and μ: the effect of deleterious

512   mutations on the effective migration rate and the auto-correlation of μ. Because

513   most deleterious mutations are recessive (García-Dorado and Caballero, 2000;

514   Peters et al., 2003; Shaw & Chang, 2006), the offspring of migrants, who enjoy an

515   increased heterozygosity compared to local individuals, will be at a selective

516   advantage. The presence of deleterious mutations therefore lead to an increase in

517   the effective migration rate (Ingvarsson & Whitlock, 2000). This increases the

518   effective migration rate and hence, leads to a decrease in F_{ST}.

519   As mutation rate is auto-correlated throughout the genome, neutral sequences

520   closely linked to sequences that frequently receive deleterious mutation are also

521   likely to experience frequent neutral mutations. As a high mutation rate leads to low

522   F_{ST} values ($F_{ST} \cong \frac{1}{1+4Ne(m+\mu)}$, Wright 1943), autocorrelation in mutation rate may

523   also impact the correlation between B and F_{ST}. This effect is likely to be negligible as

524   long as $m \gg \mu$.

525   Recently, evidence of a correlation between recombination rate and F_{ST} has been

526   interpreted as likely being caused by deleterious mutations rather than positive

527   selection, whether the divergence between populations is very high (e.g.

528   Cruickshank & Hahn, 2014), moderately high (Vijay et al., 2017) or moderately low

529   (Torres et al., 2017). Here we showed the BGS is unlikely to explain all of these

530   correlations. It can be hypothesized that positive selection (selective sweeps and

531   local adaptation) could be the main cause of this correlation.

532   McVicker et al. (2009) attempted an estimation of B values in the human genome

533   (see also Elyashiv et al., 2016). They did so using equations from Nordborg et al.

534   (1996). As there is little knowledge about the strength of selection throughout the

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535   genome, to our understanding, this estimation of B values should be highly

536   influenced by the effects of beneficial mutations as well as deleterious mutations.

537   Torres et al. (2017) reused this dataset and found a slight association between B and

538   F_{ST} among human lineages. It is plausible that this correlation between B and F_{ST}

539   could be driven by positive selection rather than by deleterious mutations.

540   Our FDist2 analysis shows that the false positive rate does not differ in simulations

541   with BGS or without BGS. The only exceptions concern the unrealistic *CNC97*

542   treatment and the *No Migration* treatment after many generations (Figure 3). The

543   average F_{ST} at the last generation of the *No Migration* treatment is greater than 0.8.

544   With such high F_{ST} both the simulation without BGS and with BGS lead to very high

545   false positive rates (0.45 without BGS and 0.5 with BGS). This difference in false

546   positive rates is significant, but the observed high false positive rate should make it

547   clear that for such highly diverged populations, F_{ST} outlier tests are not

548   recommended in general.

549   Many authors (e.g. Nachman & Payseur, 2012; Cutter & Payseur, 2013; McGee et al.,

550   2015; Yeaman, 2015; Whitlock & Lotterhos, 2015; Brousseau et al., 2016; Picq et al.,

551   2016; Payseur & Rieseberg, 2016; Hoban et al., 2016) have raised concerns that BGS

552   can strongly reduce our ability to detect the genomic signature of local adaptation.

553   Our analysis shows that BGS is not a strong confounding factor to F_{ST} outlier tests of

554   populations that are not too highly diverged.

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Table 1: Summary of treatments. For all treatments but *CNC97*, the average mutation rate was set to 2.5×10^{-8} per site, per generation and the mean heterozygous selection coefficient to 0.1.

Treatment	N	m	Genome	Recombination	BGS
Default	1000	0.005	Stickleback	Yes	Yes
					No
No Migration	1000	0	Stickleback	Yes	Yes
					No
High Migration	1000	0.05	Stickleback	Yes	Yes
					No
Large N	10000	0.005	Stickleback	Yes	Yes
					No
Human	1000	0.005	Human	Yes	Yes
					No
No Recombination	1000	0.005	Stickleback	No	Yes
					No
CNC97	2000	0.001	NA	Yes	Yes
					No

Figure 1: Comparisons of means F_{ST} (left column), d_{XY} (central column), and H_S (right column) between simulations with (black) and without (grey) BGS. Similar graphs for the treatments *No Recombination* and *CNC97* are in figure S3. Error bars are 95% CI.
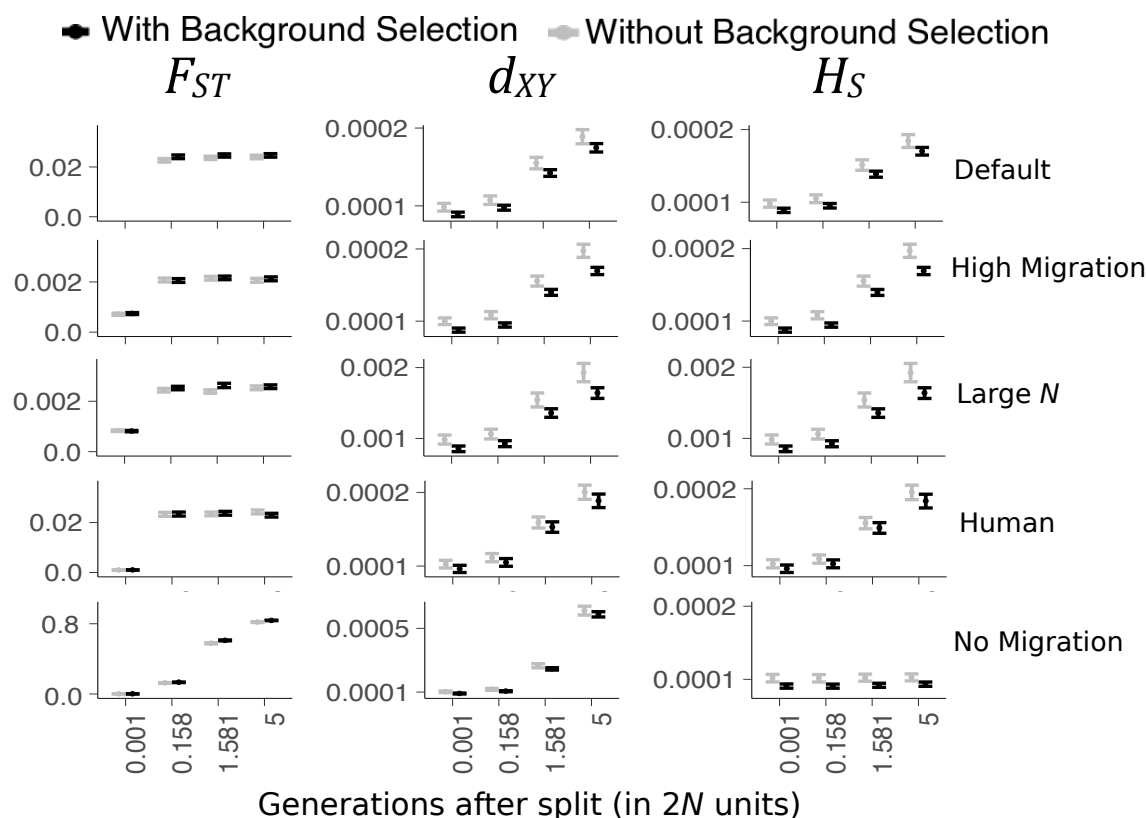
17 Figure 2: Correlation between B and $F_{ST}, H_S,$ and d_{XY} for the last generation ($5 \times 2N$
18 generations after the split) of the *Default* treatment. Each grey dot is a single
19 simulation where there is BGS. The large black dot is the mean of the simulations
20 where BGS was artificially turned off. The *P*-values are computed from a Pearson's
21 correlation test. *P*-values and R are computed on the simulations with BGS (grey
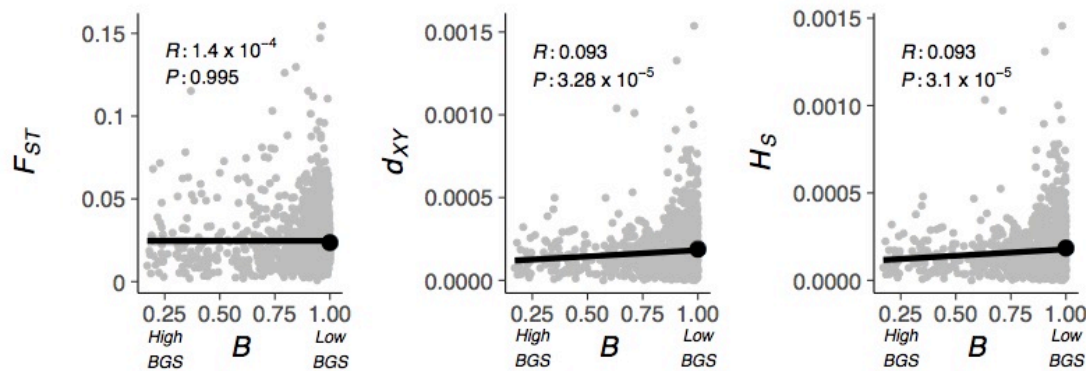22 dots) only.
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26 Figure 3: Comparison of false positive rate (FPR) returned by FDist2 between
27 simulations with BGS (black) and without BGS (grey) for all treatments by
28 generation. The significance level is 0.05 and is represented by the horizontal
29 dashed line. Significance based on a Welch's *t*-test is indicated with stars (2×10^{-16}
30 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1). Significance levels are the same with
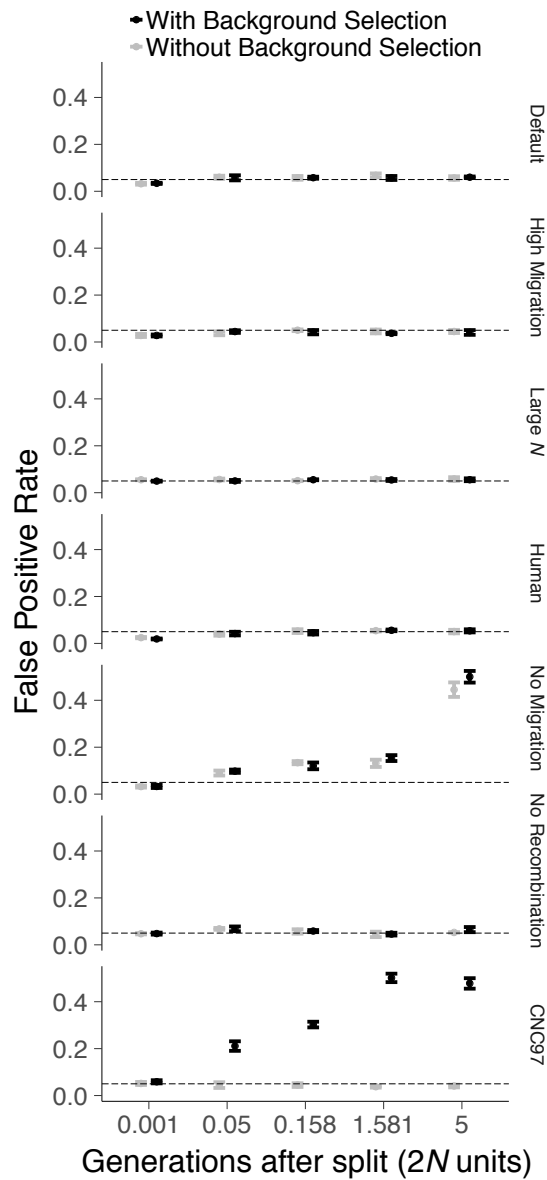31 Wilcoxon tests.

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36   Figure 4: Regressions of total (H_T; upper line) and within (H_S; lower line) population
37   expected heterozygosity on the coefficient of BGS (B) for the last generation of the
38   *Default* treatment. The two regression lines are not exactly parallel with H_S tending
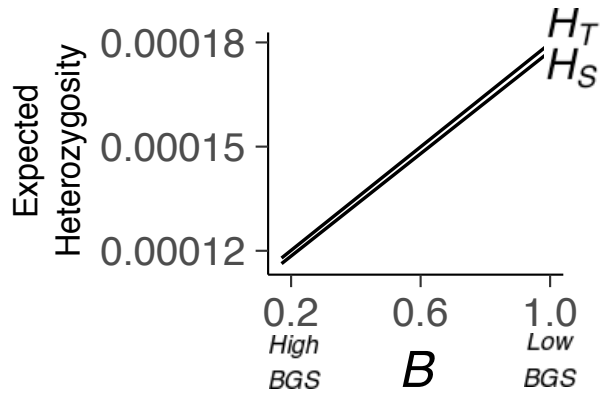39   to H_T as B goes to low values (more intense BGS).
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Table S1: Pearson's correlation tests for the association between the coefficient of background selection (B) and H_S. P-values and R are computed on the simulations with BGS only.

Treatment	Generation after split	R	P	Bonferroni correction
Default	1	0.085	1.4×10^{-4}	**
	5	0.083	1.9×10^{-4}	**
	158	0.082	2.4×10^{-4}	**
	1581	0.096	1.8×10^{-5}	***
	10000	0.093	3.1×10^{-5}	**
High Migration	1	0.056	0.01	
	5	0.054	0.02	
	158	0.056	0.01	
	1581	0.062	5.3×10^{-3}	
	10000	0.079	4.4×10^{-4}	*
Human	1	-0.036	0.11	
	5	-0.039	0.09	
	158	-0.047	0.04	
	1581	-0.067	2.7×10^{-3}	.
	10000	-0.036	0.11	
Large N	10	0.097	2.2×10^{-3}	.
	50	0.096	2.3×10^{-3}	.
	1580	0.091	0.4×10^{-2}	
	15810	0.087	5.6×10^{-3}	
	100000	0.11	5.8×10^{-4}	*
No Migration	1	0.088	7.7×10^{-5}	**
	5	0.088	8.4×10^{-5}	**
	158	0.095	1.9×10^{-5}	***
	1581	0.089	6.2×10^{-5}	**
	10000	0.09	5.9×10^{-5}	**
No Recombination	1	0.086	1.3×10^{-4}	**
	5	0.086	1.3×10^{-4}	**
	158	0.088	9.1×10^{-5}	**
	1581	0.1	4.9×10^{-6}	***
	10000	0.16	1.9×10^{-12}	***

Table S2: Pearson's correlation tests for the association between the coefficient of background selection (B) and F_{ST}. P-values and R are computed on the simulations with BGS only.

Treatment	Generation after split	R	P	Bonferroni correction
Default	1	0.012	0.6	
	5	0.029	0.2	
	158	-0.015	0.49	
	1581	-0.021	0.35	
	10000	0.00014	0.99	
High Migration	1	-0.017	0.45	
	5	0.013	0.56	
	158	0.045	0.04	
	1581	-0.0023	0.92	
	10000	-0.0037	0.87	
Human	1	-0.012	0.6	
	5	0.033	0.14	
	158	-0.019	0.39	
	1581	0.028	0.22	
	10000	0.0077	0.73	
Large N	10	0.0084	0.79	
	50	-0.034	0.28	
	1580	-0.02	0.52	
	15810	-0.026	0.4	
	100000	-0.035	0.27	
No Migration	1	0.0061	0.78	
	5	0.028	0.21	
	158	-0.065	3.5×10^{-3}	
	1581	-0.053	0.02	
	10000	-0.11	6.3×10^{-7}	***
No Recombination	1	0.0058	0.8	
	5	-0.039	0.08	
	158	-0.0011	0.96	
	1581	-0.0048	0.83	
	10000	-0.0055	0.81	

Table S3: Pearson's correlation tests for the association between the coefficient of background selection (B) and $F_{ST\,(average\ of\ ratios)}$. P-values and R are computed on the simulations with BGS only.

| Treatment	Generation after split	R	P	Bonferroni correction
Default	1	0.032	0.15	
	5	0.065	3.6×10^{-2}	
	158	0.04	0.07	
	1581	0.028	0.20	
	10000	0.051	0.02	
High	1	-0.013	0.57	
	5	0.023	0.31	
	158	0.058	9.4×10^{-3}	
	1581	0.012	0.6	
	10000	0.041	0.07	
Human	1	-0.011	0.62	
	5	0.064	4.5×10^{-3}	
	158	0.022	0.32	
	1581	0.036	0.11	
	10000	0.031	0.17	
Large N	10	0.048	0.13	
	50	0.038	0.23	
	1580	0.038	0.23	
	15810	0.027	0.4	
	100000	0.04	0.2	
No Migration	1	0.014	0.54	
	5	0.073	1.1×10^{-3}	*
	158	0.022	0.32	
	1581	0.038	0.09	
	10000	-0.0012	0.96	
No Recombination	1	0.016	0.48	
	5	0.035	0.12	
	158	0.092	4.3×10^{-4}	**
	1581	0.097	1.5×10^{-5}	***
	10000	0.11	5.0×10^{-7}	***

Table S4: Pearson's correlation tests for the association between the coefficient of background selection (B) and d_{XY}. P-values and R are computed on the simulations with BGS only.

Treatment	Generation after split	R	P	Bonferroni correction
Default	1	0.085	1.35×10^{-4}	**
	5	0.084	1.35×10^{-4}	**
	158	0.082	2.46×10^{-4}	**
	1581	0.095	2.12×10^{-5}	***
	10000	0.093	3.28×10^{-5}	**
High Migration	1	0.056	0.01	
	5	0.054	0.02	
	158	0.056	0.01	
	1581	0.062	5.26×10^{-3}	
	10000	0.079	4.36×10^{-4}	*
Human	1	-0.036	0.11	
	5	-0.037	0.10	
	158	-0.047	0.03	
	1581	-0.067	3.0×10^{-3}	
	10000	-0.036	0.11	
Large N	10	0.097	2.2×10^{-3}	.
	50	0.096	2.3×10^{-3}	.
	1580	0.091	4.0×10^{-3}	
	15810	0.087	5.7×10^{-3}	
	100000	0.11	5.8×10^{-4}	*
No Migration	1	0.088	7.6×10^{-5}	**
	5	0.089	6.7×10^{-5}	**
	158	0.086	1.2×10^{-4}	**
	1581	0.052	0.02	
	10000	0.029	0.20	
No Recombination	1	0.086	1.3×10^{-4}	**
	5	0.085	1.6×10^{-4}	**
	158	0.088	8.8×10^{-5}	**
	1581	0.1	4.9×10^{-5}	***
	10000	0.16	2.3×10^{-12}	***

Table S5: Pearson's correlation tests for the association between the coefficient of background selection (B) and $d_{XY\text{-SNP}}$. P-values and R are computed on the simulations with BGS only.

Treatment	Generation after split	R	P	Bonferroni correction
Default	1	0.15	3.1×10^{-11}	***
	5	0.12	8.9×10^{-8}	***
	158	0.14	5.3×10^{-10}	***
	1581	0.16	2.8×10^{-13}	***
	10000	0.15	5.8×10^{-12}	***
High Migration	1	0.075	8.1×10^{-4}	*
	5	0.088	7.5×10^{-5}	**
	158	0.09	5.5×10^{-5}	**
	1581	0.12	5.7×10^{-8}	***
	10000	0.17	5.4×10^{-14}	***
Human	1	0.071	1.6×10^{-3}	.
	5	0.062	5.6×10^{-3}	
	158	0.053	0.02	
	1581	0.023	0.3	
	10000	0.067	2.7×10^{-3}	.
Large N	10	0.22	6.4×10^{-12}	***
	50	0.21	1.2×10^{-11}	***
	1580	0.2	6.6×10^{-11}	***
	15810	0.19	2.2×10^{-9}	***
	100000	0.25	2.7×10^{-15}	***
No Migration	1	0.15	2.3×10^{-11}	***
	5	0.16	1.5×10^{-12}	***
	158	0.14	1.2×10^{-10}	***
	1581	0.048	0.03	
	10000	-0.0014	0.95	
No Recombination	1	0.18	6.3×10^{-16}	***
	5	0.16	4.0×10^{-13}	***
	158	0.18	2.7×10^{-15}	***
	1581	0.22	3.6×10^{-23}	***
	10000	0.3	6.6×10^{-42}	***

1   Figure S1: Overall distribution of selection coefficient in the heterozygotes. There
2   are 2% lethal mutations, and the average selection coefficient of the non-lethal
3   mutations is approximately 0.07.

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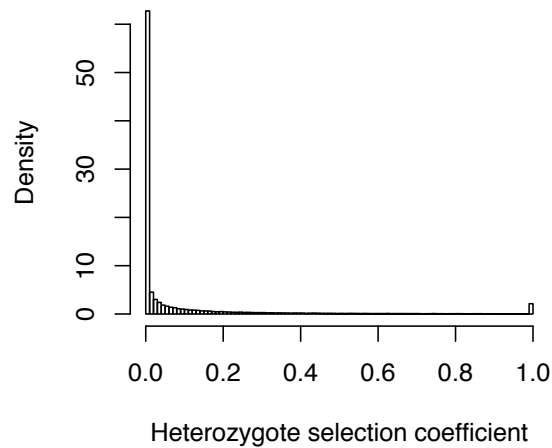
9   Figure S2: Relationship between B values computed for all simulations using the
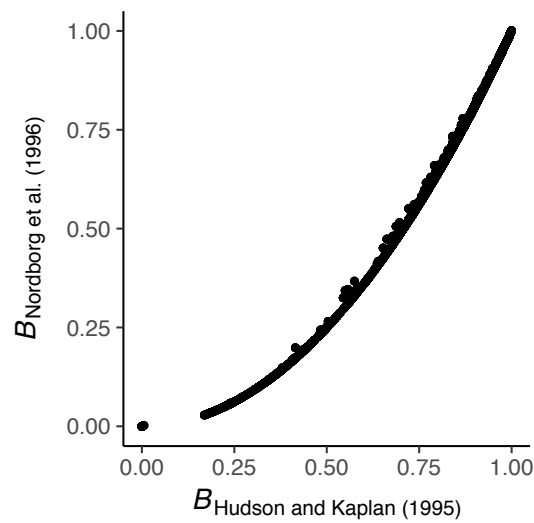10 stickleback genome using the methods of Hudson and Kaplan (1996) and Nordborg
11 et al. (1997).

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14 Figure S3: Comparisons of means F_{ST} (left column), d_{XY} (central column), and H_S
15 (right column) between simulations with (black) and without (grey) BGS for all
16 unrealistic treatments. Realistic treatments (*Default*, *No Migration*, *High Migration*,
17 *Human* and *Large N*) are in Figure 1 in the main text. Error bars are 95% confidence
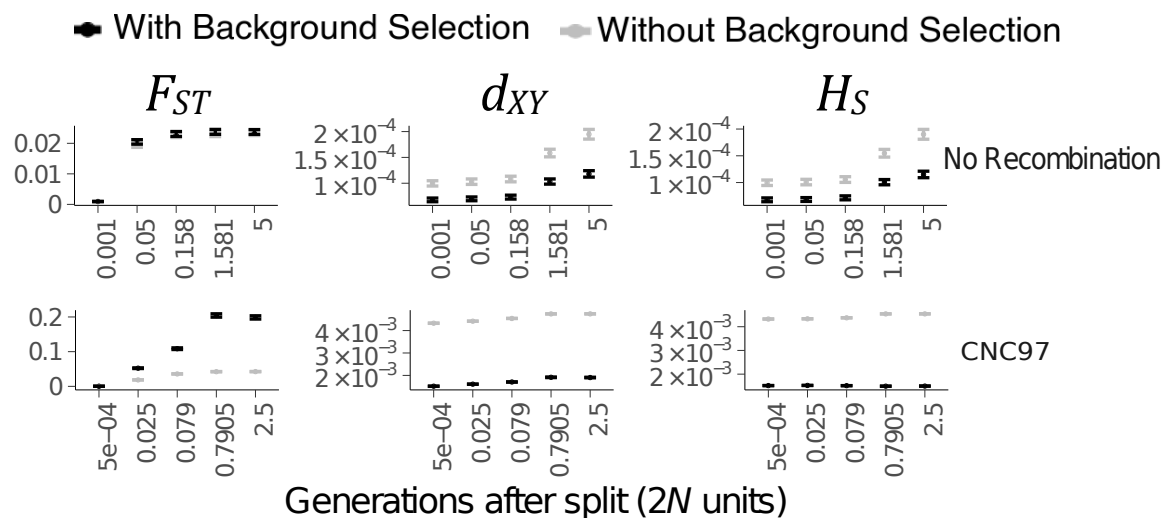18 intervals.
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28   Figure S4: Correlations between B and F_{ST}, d_{xy}, $F_{ST \text{ (average of ratios)}}$, $d_{xy\text{-SNP}}$, and $F_{ST \text{ (average}}$
29   $_{\text{of ratios)}}$ after removing all loci that have minor allele frequency (MAF) lower than
30   0.05 (called MAF - $F_{ST \text{ (average of ratios)}}$) for the treatment *No Recombination* only at the
31   last generation (5 x 2N generations after the split). Each grey dot is a single
32   simulation with BGS. The large black dot is the mean of all simulations without BGS.
33   The *P*-values are computed from a Pearson's correlation test. *P*-values and R are
34   computed on the simulations with BGS (grey dots) only.
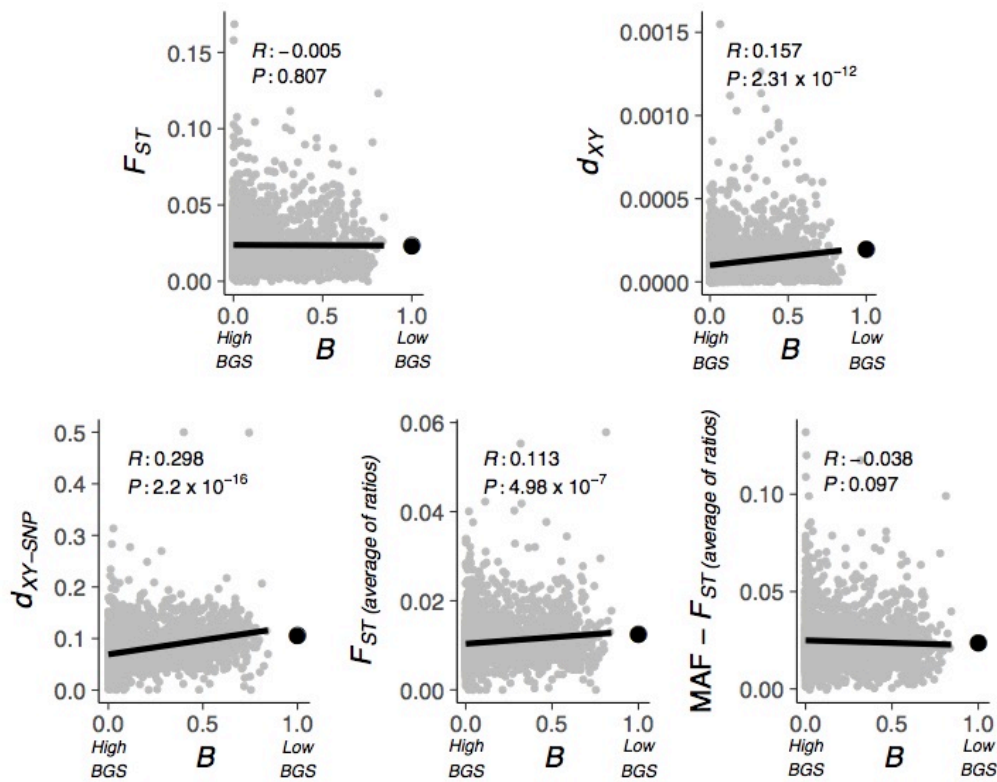35
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39   Figure S5: Relationship between total heterozygosity H_T and F_{ST} on a site per site
40   basis. Each dot represents a single site. The black line is a Local Polynomial
41   Regression (LOESS). Data is a random subset from the *Default* treatment at the last
42   generation.

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