Detection of selective sweeps in structured populations: a comparison of recent methods

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keywords: positive selection, haplotype structure, genome scan methods, accuracy

Abstract

Identifying genomic regions targeted by positive selection has been a longstanding interest of evolutionary biologists. This objective was difficult to achieve until the recent emergence of Next Generation Sequencing, which is fostering the development of large-scale catalogs of genetic variation for increasing number of species. Several statistical methods have been recently developed to analyze these rich datasets but there is still a poor understanding of the conditions under which these methods produce reliable results. This study aims at filling this gap by assessing the performance of genome-scan methods that consider explicitly the physical linkage among SNPs surrounding a selected variant. Our study compares the performance of seven recent methods for the detection of selective sweeps (iHS, nSL, EHHST, xp-EHH, XP-EHHST, XPCLR and hapFLK). We use an individual-based simulation approach to investigate the power and accuracy of these methods under a wide range of population models under both hard and soft sweeps. Our results indicate that XPCLR and hapFLK perform best and can detect soft sweeps under simple population structure scenarios if migration rate is low. All methods perform poorly with moderate to high migration rates, or with weak selection and very poorly under a hierarchical population structure. Finally, no single method is able to detect both starting and nearly completed selective sweeps. However, combining several methods (XPCLR or hapFLK with iHS or nSL) can greatly increase the power to pinpoint the selected region.

Introduction

Population geneticists and evolutionary biologists have a longstanding interest in understanding the ecological and genetic mechanisms that allow species to adapt to local environmental conditions. The recent advent of Next Generation Sequencing (NGS) (Shendure & Ji 2008) and the high density SNP arrays it generates has allowed rapid advances in this field and has fostered the emergence of the population genomics approach (Luikart *et al.* 2003). This new paradigm is focused on the use of genome-wide data to distinguish between locus-specific effects (mainly selection but also mutation, and recombination) and genome-wide effects such as genetic drift. It has proven particularly useful to detect signatures of selection, and has been used to uncover genes involved in local adaptation, disease susceptibility, resistance to pathogens, and other phenotypic traits of interest to plant and animal breeders.

At the genetic level, local adaptation involves a process whereby directional selection induced by local environmental conditions will favor the spread of genetic variants associated with beneficial phenotypic traits. If selection is strong at the level of an individual locus the selected variant will increase in frequency. Additionally, selection will modify the pattern of diversity around the selected locus through genetic hitchhiking (Barton 2000; Smith & Haigh 1974). This process, known as a selective sweep, has been extensively studied using models of isolated populations (Hermisson & Pennings 2005; Pennings & Hermisson 2006a, b; Kim & Nielsen 2004; Sabeti *et al.* 2002; Smith & Haigh 1974; Voight *et al.* 2006) but much less studied under structured population scenarios. In this latter case, analyses focused on either, an universally favoured mutation that spreads from its deme of origin to other demes (Barton 2000; Bierne 2010; Slatkin & Wiehe 1998) or on a scenario where the new selected variant is favoured

in one part of the species range but counter selected in the other half (Bierne 2010). However, there is a third scenario still poorly understood but frequently assumed by studies of local adaptation, particularly in humans. Under this scenario, a selected variant is favoured in one part of the species range and is neutral elsewhere (e.g. lactase persistence, skin pigmentation, high altitude adaptation; Jeong & Di Rienzo 2014).

Several so-called "genome-scan methods' have been proposed for the detection of positive selection from dense SNP maps. The most widely used and thoroughly evaluated type of methods is based on Lewontin and Krakauer (1973) approach and is focused on single-locus F_{ST} (Beaumont & Balding 2004; Beaumont & Nichols 1996; Foll & Gaggiotti 2008). These methods implicitly or explicitly assume that SNPs are physically unlinked and are most effective when neutral genetic differentiation is low (Price *et al.* 2008) and/or when the selective sweep is close to fixation (Pickrell *et al.* 2009). Other methods are specifically aimed at detecting selective sweeps by focusing on the distribution of genetic variation along a chromosome within a population when selection is acting, as predicted by the theory of genetic hitchhiking (Fay & Wu 2000; Kim & Stephan 2002; Nielsen *et al.* 2005). These methods are applicable to isolated populations and their behavior has been extensively studied (Jensen *et al.* 2005, Zang *et al.* 2005, Zeng *et al.* 2007).

A third type of genome scan methods considers explicitly the physical linkage among SNPs surrounding a selected variant, either by focusing on patterns of long-range haplotype homozygosity (Sabeti *et al.* 2002; Voight *et al.* 2006) or by modelling the effect of linkage on multilocus genetic differentiation (Chen *et al.* 2010). These methods are more recent and their properties have not been extensively investigated. Moreover, although they are focused on either a single population (Ferrer-Admetlla *et al.* 2014; Sabeti *et al.* 2002; Voight *et al.* 2006) or on

pairs of populations (Chen *et al.* 2010; Fariello *et al.* 2013; Sabeti *et al.* 2007), they are being used to study structured populations consisting of many subpopulations without a clear understanding of how migration and complex population structure may affect their power and error rates. Thus, the objective of the present study is to carry out a thorough evaluation of the performance of these methods under various scenarios of population structure. We focus mainly on the case where the selected variant is beneficial in part of the species range and neutral elsewhere, as it is the underlying scenario envisaged by many recent studies of adaptation (Foll *et al.* 2014; Hancock *et al.* 2008; Lao *et al.* 2007). Additionally we consider both hard and soft selective sweeps. These two scenarios differ in the origin of the selected variant. In a hard selective sweep the favoured allele appears through *de novo* mutation while in a soft sweep it is already segregating at low frequency in the population (standing genetic variation) or it arises from recurrent mutations (Hermisson & Pennings 2005; Pennings & Hermisson 2006a, b; Pritchard *et al.* 2010).

In the present analysis we compare the performance of seven recent methods to detect selective sweeps. We incorporate in the analysis, methods that were developed to study a single population, a pair of populations or multiple populations. We explain in detail the ability of each method to capture the signal of selection left by both hard and soft sweeps under different scenarios of structured populations and a range of parameter values (migration and selection). The principle is to examine these methods on the same simulated datasets and draw conclusions about how the different model parameters affect their performance as described by power and false discovery rate. The goal of this analysis is to guide scientists in the choice of the methods that is better suited for their biological model.

Material and Methods

Genome Scan Methods

We focus our study on seven methods for which software is readily available: Integrated Haplotype Score (iHS) (Voight *et al.* 2006), Number of Segregating sites by Length (nSL) (Ferrer-Admetlla *et al.* 2014), Extended Haplotype-based Homozygosity Score Test (EHHST) (Zhong *et al.* 2010), Cross Population Extended Haplotype Homozygosity (xp-EHH) (Sabeti *et al.* 2007), Cross-population extended haplotype-based homozygosity score test (xp-EHHST) (Zhong *et al.* 2011), Cross population Composite Likelihood Ratio (XPCLR) (Chen *et al.* 2010) and hapFLK (Fariello *et al.* 2013). They all use SNP data but propose different statistics to detect selection. In what follows we will highlight their main differences but we also include more technical details about all these methods in SI.

The methods we evaluate use different summary statistics that try to capture different genetic patterns consistent with the action of positive selection. We can distinguish three groups of methods:

(i) Methods based on the decay of *haplotype* homozygosity as a function of recombination distance (iHS, nSL and xp-EHH): the underlying rationale of these methods is that selected alleles will have unusually long range linkage disequilibrium given their frequency in the population.

(ii) Methods based on the decay of *genotype* homozygosity around a target SNP (EHHST and xp-EHHST): the underlying rationale is similar to that of the previous group but in this case homozygosity is measured in terms of mean homozygosity across all individuals in the sample

instead of homozygosity of a region with respect to all chromosomes in the sample as in the previous group.

(iii) Methods based on the extent of multilocus genetic differentiation among populations around a target SNP (XPCLR and hapFLK): the underlying rationale is that genetic differentiation around a selected variant will be much larger than expected under drift but instead of using single-locus measures of differentiation it calculates differentiation for all SNPs within a window centered around the target SNP.

Another important difference between methods lies in whether or not they require phased data and information on the ancestral/derived status at each segregating site. XPCLR is the only method that does not have these requirements. Finally, one last difference among methods that needs to be highlighted refers to the number of populations they consider. iHS, nSL and EHHST are focused on a single population, xp-EHH, xp-EHHST, XPCLR consider two populations, while hapFLK considers an arbitrary number of populations.

Calculation of p values

The first step in the comparison of several methods is to define a common framework for assessing significance, which then allows us to calculate false positive and false negative rates as well as power. We used two alternative approaches:

(a) From the empirical distribution of test scores: in this case, we calculate the test statistic for all SNPs in the sample. Then using the empirical distribution of test scores, we consider as potentially adaptive all the loci with scores falling in the outlying 5% of the distribution. In the context of a simulation study, we know the truth and, therefore, we can readily identify true

148 and false positives across all synthetic samples so as to calculate error rates and power of each
149 method.
150 (b) From a distribution of tests scores generated by neutral simulations: in this case, we generate a
151 large number of synthetic datasets assuming a particular demographic history (deemed
152 appropriate for the species under study) and calculate the statistic scores for a target SNP. The
153 distribution of test scores is then used as the null distribution and any loci with a test score
154 falling in the outlying 5% of the distribution is considered potentially selected. In order to
155 compare he performance of the different methods, we also carried out simulations under
156 different selection scenarios and then pooled neutral and selected replicates to estimate power
157 at various false positive rates. These results are then presented as ROC curves obtained using
158 the R package "ROCR" (Sing et *al.* 2005).
159 The most widespread approach to assess significance when analysing real data is based on
160 the empirical distribution (approach a). The reason for this is that in most cases we do not know
161 with certainty the true demographic history of the species under study. Thus, we present the
162 results of this procedure in the main text and the results of the second procedure in the
163 supplementary information.
164

165 ## Simulations

166 We generated synthetic data using SimuPOP (Peng & Amos 2008; Peng *et al.* 2011), a general-
167 purpose, individual-based simulation platform for forward-in-time population genetics modelling.
168 The Python scripts used to carry out the simulations are available at GitHub
169 (https://github.com/alexvat/simulations).

Initially, we simulated three different population structure scenarios, an island model (Wright 1990), a stepping stone model (Kimura 1953) and a dichotomous population fission model that leads to a hierarchical island structure (Figure S1). In these cases, we considered four diploid demes, each of constant effective population size N_e = 2500. Thus, total population size was 10,000. Table 1 presents a summary of the parameters that were used in the simulations. In the case of the island and the stepping-stone models, every individual migrates to another deme with probability m (0.05, 0.01 or 0.008). In the case of the hierarchical model, migration between demes within the same group (continent) was higher than migration between demes in different groups (see Figure S1c). In this latter scenario, we start at t = 0 with a single population (Z with 10,000 individuals). At t = 100 generations, it splits into two subpopulations (Y, Z of size 5,000 individuals each) and at t = 300 each of the 2 subpopulations (Y, Z) split into two other subpopulations ((X, Y) and (W, Z) respectively), resulting in four subpopulations at $t > 300$.

Following previous analyses (Hanchard *et al.* 2006; Zhong *et al.* 2010; Zhong *et al.* 2011), we considered L=101 bi-allelic SNPs located in the same chromosome. The recombination rate was $\rho = 1.5$ ($= 4N_e r$) so that r = 0.00375 cM/kb leading to a fixed distance of 4kb between loci. For all the scenarios, neutral loci shared the same mutation rate (10^{-8} per generation).

For each demographic model, we considered two selection scenarios, a hard sweep and a soft sweep. Under a hard sweep, new mutations are easily lost due to genetic drift so that large selection coefficients are needed to minimize stochastic loss. In our case we used s =0.1 ($2N_e s$ = 500), 0.08 ($2N_e s$ =400) and 0.01 ($2N_e s$ =50). On the other hand, a soft sweep acts upon standing genetic variation so selection does not need to be very strong to overcome stochastic loss in most simulations. In our case, we used s = 0.05 ($2N_e s$=250). For the simple structured population cases (island, stepping-stone and hierarchical model with a total of four subpopulations each), we

193 assumed that a selected variant at locus 50 (i.e. the middle of the genomic region) was favoured
194 in only one deme and that it was neutral in all other demes. We assumed a co-dominant selection
195 model where fitness of the homozygotes for the ancestral allele is 1, fitness of heterozygotes is (1
196 + s/2), and fitness of homozygotes for the derived allele is (1 + s).

197 For all scenarios, we used an initialization procedure that samples allele frequencies from
198 an island model at migration-mutation-drift equilibrium. More precisely, all loci were initialized
199 at the beginning of the simulations, $t_0 = 0$, by sampling the allele frequencies of each locus from a
200 Beta distribution with parameters $a = 4N_e m^* p$ and $b = 4N_e m^*(1-p)$, where p is the frequency in a
201 migrant pool, which was derived from real human SNP data from non-coding regions, m is the
202 migration rate and N_e the effective population size (Wright 1931). We started selection after a
203 burn-in (t_1) that allowed the system to reach migration-mutation-drift equilibrium. In the case of
204 the island model the burn-in period was very short (50 generations) compared to the stepping
205 stone model (100 generations) and the hierarchical model (500 generations). Figures S2-S4 in
206 supplementary information show the steady state reached in terms of equilibrium allele
207 frequencies and LD under each scenario. In the case of hard sweeps, locus 50 was monomorphic
208 at t_0 and all throughout the burn-in period. At t_1, once populations were at equilibrium, a single
209 copy of a new advantageous mutation (the derived allele) was introduced at this locus in deme Y
210 only. All the simulations were carried out until the selected locus was nearly fixed in the selected
211 population. We took samples of populations at different times points where the selected allele
212 frequency exceed a given threshold (0.1, 0.2, ..., ~1) in order to study its influence on the
213 performance of the methods.

214 In the case of the soft sweep from standing variation, the selected variant was already
215 segregating in the population before the onset of selection. More precisely, we assume that the

allele became beneficial after an environmental change, but was neutral under the previous conditions. At $t = t_0$, we set the frequency of the selected allele at locus 50 in the migrant pool to 0.02, 0.1, 0.2 or 0.4. At $t = t1$, when selection started, the average allele frequency of the selected variant over the replicates remained unchanged at these respective values. We generated 1000 replicates for each of these scenarios.

Statistical analysis

Performance of each method was evaluated using the two methods described above which henceforth are referred to as the *empirical distribution* (method a) and *simulated distribution* (method b) approaches. The results are similar for both approaches so here we focus on the empirical distribution approach while the simulated distribution approach is further described in supplementary information.

Given that the aim of all methods is to identify genomic regions under selection and not necessarily to uncover a specific advantageous mutation, we considered that a method succeeded at detecting selection if at least one of the SNPs in a window bounded between SNP 45 and SNP 55 was identified as selected (*i.e.* a window spanning 20kb upstream and 20kb downstream the selected locus). Outlier SNPs outside of this window were considered as False Positives. The choice of a 40kb window (10 SNPs) was decided after investigating the distribution of the scores produced by each method around the selected variant (see Fig. S5) and ensures that the signature of selection is restricted to the window, and, therefore, does not lead to wrong estimations of power and FDR. The statistical significance threshold for all tests was defined as the 5% outliers considering the whole region of 101 loci. FDR is rarely measured. Indeed, most previous studies

238 assess performance based on neutral simulations that only allow for the calculation of power and
239 FPR. However, the application of these methods involve multiple testing and, therefore, we
240 measure error rates in terms of FDR at several time points to better characterize the stage of the
241 selective sweep (i.e. initial, intermediate or nearly completed) at which each method performs
242 best.
243

244 Results

245 We first compared the performance of six methods (iHS (Voight *et al.* 2006), nSL (Ferrer-
246 Admetlla *et al.* 2014), EHHST (Zhong *et al.* 2010), xp-EHH (Sabeti *et al.* 2007), xp-EHHST
247 (Zhong *et al.* 2011) and XPCLR (Chen *et al.* 2010)) for the hard sweep scenario under the island
248 (Wright 1990) and stepping-stone (Kimura 1953) models, the two most well known population
249 models. We then selected the methods that were the most efficient under these conditions and we
250 compared them under the hierarchical island model. In this case, we also included hapFLK
251 (Fariello *et al.* 2013) in the comparison because it is specifically developed for this scenario.
252 Next, we selected the methods that were the most efficient under this latter scenario and subjected
253 them to further scrutiny, using data generated from soft sweep scenarios and more complex
254 stepping stone models. The results are similar for the two approaches used to compare methods,
255 therefore, we present the results of the *empirical distribution* approach here and those of the
256 *simulated distribution* approach in the supplementary information.
257

258 Hard Sweep

259 Local selective sweeps under simple population structure models

Figure 1 presents the results for a hard sweep under the island model for five different scenarios: i) m=0.008, s=0.01 ($2N_es=50$), ii) m=0.008, s=0.08 ($2N_es=400$), iii) m=0.008, s=0.1 ($2N_es=500$), iv) m=0.01, s=0.1 ($2N_es=500$) and v) m=0.05, s=0.1 ($2N_es=500$). Both EHHST and XP-EHHST performed poorly under all scenarios (Fig. 1e,g), exhibiting very low power and high FDR (Fig. S6c,e) regardless of the allele frequency of the selected variant. The performance of the four other methods (iHS, nSL, xp-EHH and XPCLR) varies depending on the allele frequency of the favoured variant in the selected population (Y) and the different parameters tested (migration rate and selection coefficient).

As expected, when selection is strong ($2N_es=500$ or 400) and migration is low (m=0.008 or $2N_es=50$), the four above-mentioned methods performed quite well at least at one stage of the selective sweep (initial, intermediate or nearly completed; Figure 1). More precisely, iHS and nSL detected sweeps for which the selected variant was still at low frequency (~0.1 to ~0.3). The performance of xp-EHH increased slowly as the frequency of the selected allele in the selected population increases and it has a power of ~ 100% when the selected locus is close to fixation (Allele Frequency: AF = ~0.9). XPCLR behaved in a similar way but the performance increased sharply first and remained high until the selected locus approached fixation. The performance of XPCLR was the highest of all methods when the allele frequency was intermediate to high (AF = 0.3, 0.9) but extremely poor when it was low (AF = 0.1,0.2), in which case iHS and nSL were better methods.

Migration has a strong detrimental effect on the performance of all methods (Fig. 1). Indeed, when migration was high (m=0.05 per generation), the performance of iHS, nSL, xp-EHH and XPCLR was poor. When the selected variant is favoured in one population but neutral elsewhere, migration has a strong homogenizing effect. Therefore, the performance of iHS and

283 nSL decreased because the selected population was swamped by haplotypes carrying the counter
284 selected variants. Thus, the frequency of the haplotype containing the selected variant decreased
285 and the genetic signal of selection was weakened. On the other hand, the performance of xp-EHH
286 and XPCLR decreased because the non-selected populations were swamped by the haplotype
287 containing the beneficial allele. Thus, with high migration (m=0.05) the beneficial allele spread
288 much faster (than with m=0.01) and the differentiation in frequency of the selected variant
289 between the selected and non-selected populations decreased sharply (Figs. 1a, b). These results
290 hold for both the island and the stepping-stone model (Fig. S7).

291 Under an isolation-by-distance scenario the choice of the two populations to include in
292 xp-EHH and XPCLR analyses can affect their performance. To investigate this, we examined the
293 performance of XPCLR, the method with highest power in the previous scenarios, as a function
294 of the distance between the population undergoing selection and the "neutral" ones for the
295 scenario with m=0.01 and $2N_es=500$. Figure 2 shows that the larger the distance between the
296 selected and non-selected populations, the lower the power of XPCLR was for intermediate
297 values of the allele frequency of the selected variant. This may seem counterintuitive because
298 larger distance leads to reduced migration and results obtained for the island model suggest that
299 weak migration facilitates the detection of the selection signal. However, we note that XPCLR is
300 based on the multilocus genetic differentiation between a selected and a non-selected population.
301 More precisely, it compares the multilocus differentiation expected around a selected variant with
302 that expected around a neutral variant (c.f. eq. 6 in Chen *et al.* 2010). As distance between the
303 two populations increases, the neutral multilocus differentiation increases strongly and, therefore,
304 the difference in genetic differentiation between neutral and selected regions decreases. This
305 behaviour is similar to that observed for genome-scan methods based on F_{ST} (Price *et al.* 2008).

306 We further studied whether or not selection could be detected when the selected population was
307 not included in the analysis. Interestingly, the selected region is detected when the selected
308 variant has reached intermediate to high frequencies in the population right next to a selected one.
309 Thus, in the case of a nearly completed selective sweep, it is possible to wrongly conclude that
310 selection is acting upon one of the two populations when this is not really the case. However, the
311 power of the method decreases sharply when the selected population is not adjacent to one of the
312 two populations included in the analysis.

313 In the case of the hierarchical island model (Fig. 3), we focus on five methods (iHS, nSL,
314 xp-EHH, XPCLR and hapFLK) discarding EHHST and XP-EHHST because they performed very
315 poorly under the simple population structure scenarios considered above (island and stepping
316 stone model with four populations). For the two-populations tests (xp-EHH and XPCLR), we
317 investigated the power of the methods both when the selected and non-selected sampled
318 populations were in the same group (continent) and when they were in different groups. Note that
319 migration between populations in the same group is higher (m = 0.02) than between those in
320 different groups (m = 0.01). The overall pattern of performance as a function of allele frequency
321 of the selected variant is similar to that observed under the simpler spatial structure scenarios.
322 However, the baseline power of all methods is largely reduced. More specifically, the power of
323 iHS and xp-EHH was decreased to ~70%, with an FDR ~30% for the allele frequencies at which
324 they performed optimally under the simpler spatial scenarios. On the other hand, the performance
325 of XPCLR remained high with power ~90% and FDR lower than 20%. Nevertheless, such high
326 performance is achieved for a narrower range of allele frequencies (0.6, 0.7) than for the simple
327 spatial structure scenarios tested before (AF: 0.3-0.9). As it was expected, when comparing
328 populations from the same geographic group (Y-X), the power of the methods was more strongly

329 reduced (~10% for xp-EHH and ~20% for XPCLR) than when populations belonged to different
330 groups. HapFLK exhibited the best performance for a wide range of allele frequencies but was
331 outperformed by xp-EHH and XPCLR for very high allele frequencies.
332
333 **Local selective sweeps in a heterogeneous environment**
334 We explore a scenario akin to that considered by previous studies of genetic sweeps in
335 structured populations (e.g. Bierne 2010). More precisely, we simulated a stepping-stone scenario
336 with a large number of populations (52) undergoing a hard selective sweep in a heterogeneous
337 environment where the new mutation is beneficial in half of the species range and detrimental in
338 the other half. We simulated 52 populations with 500 individuals each, a genomic region
339 comprising 101 loci with a recombination rate of 0.00375cM/kb per generation, a selection
340 coefficient of 0.05 ($2N_e s=50$) and a migration rate of 0.05 per generation. Locus 50 was initially
341 fixed for allele 0 in all populations and after equilibrium a *de novo* advantageous mutation was
342 introduced in the far left deme. The new mutant was favoured in habitat 1 (populations 1 to 25)
343 and was counter selected in habitat 2 (populations 26 to 50) (Fig. 4b). To avoid computational
344 burden due to the very large number of populations studied here, we evaluated performance using
345 100 simulations instead of the 1000 used for the simpler scenarios. However, as shown in Figure
346 S5, this reduced number of replicates does not have an impact on the outcome of the analysis. All
347 methods were tested but we only present results for XPCLR and hapFLK because all other
348 methods have negligible power under this scenario.
349 The power of hapFLK was almost maximal (99.9%) but its error rate was very high too
350 (FDR 43.3%). All 50 populations except the boundary ones were included in the hapFLK
351 analysis. However, in the case of XPCLR, which can only analyse two populations at a time, we

352 focused on pairs of populations and evaluated the effect of distance between them on the
353 performance of the test. Figure 4a shows the XPCLR results for analyses using population 1 (*i.e.*
354 the far left population) as objective and each one of the other populations as reference. Results
355 were obtained after 40,000 generations since the appearance of the mutation. The results show
356 that XPCLR can detect selection only when the reference population is near the boundary
357 between the two habitats (a similar pattern is observed when using demes 13 or 25 as objective
358 populations; Fig. S8). The FDR follows the inverse pattern of the power and this holds true for all
359 the populations in habitat 1 (Fig. S8). XPCLR does not perform well when populations from the
360 same habitat are compared because after 40,000 generations the sweep is complete in all demes
361 belonging to habitat 1 (Fig. 4b) and multilocus differentiation around the selected allele has
362 disappeared (Fig. 4c). When the reference population is in habitat 2 and far from the boundary
363 with habitat 1, XPCLR does not perform well either, as the genetic differentiation of the neutral
364 background increases strongly with distance from the objective population (Fig. 4d) and this
365 decreases the power to detect selection using multilocus differentiation. Thus, we conclude that
366 caution is needed when using XPCLR to study scenarios involving genetic clines or secondary
367 contact zones. Nevertheless, it is worth mentioning that this method may be useful to identify the
368 transition zone were the change in selection regime is observed.
369

370 ## Soft Sweep

371 In the case of soft sweeps from standing variation, the most crucial parameter influencing the
372 power of the methods is expected to be the Initial Allele Frequency (IAF) of the selected variant.
373 To investigate this, we examined the power of the methods at the following IAF of the selected

374 variant: 0.4, 0.2, 0.1 and 0.02. Given that the methods did not show sufficient performance with a
375 high migration rate (*m*=0.05) under the hard sweep scenario, we examined their behaviour for the
376 soft sweep with a migration rate of 0.01. The results for the island model are presented in Figure
377 5 and are identical to those of the stepping stone model, which are presented in Figure S9. The
378 power of iHS and nSL was dramatically reduced (to less than 50%) under all three scenarios
379 tested. The performance of xp-EHH was good at high allele frequencies (AF=0.9) before fixation,
380 as in the case of the hard sweep. This holds true for all the different initial allele frequencies that
381 were tested. The performance of XPCLR was good for intermediate and high allele frequencies of
382 the selected locus before fixation, particularly for IAF: 0.2, 0.1 and 0.02.

383 Next we investigated the performance of xp-EHH, XPCLR and hapFLK under a
384 hierarchical island model undergoing a soft sweep. The power of all methods drops substantially,
385 being in general below ≈40%, while their FDR is very high (Fig. S10). As opposed to iHS and
386 xp-EHH that are based on long range haplotype homozygosity, XPCLR and hapFLK are based on
387 multilocus genetic differentiation and, therefore, their performance under this scenario might be
388 improved in the absence of migration. To investigate this possibility, we carried out simulations
389 of this same scenario without migration. The results show that performance of both methods, but
390 especially of hapFLK, improves particularly for high frequencies of the selected variant (Fig.
391 S11).

392

393 Discussion

394 This study aimed at assessing the performance of recent statistical methods that are being used to
395 detect selective sweeps in structured populations. These methods focus on multi-locus signatures

of selection that include information on linkage disequilibrium. Although they were originally developed to study isolated populations or two population scenarios, they are being applied to all kinds of structured populations (*e.g.*. island, stepping-stone, hierarchical). Thus, our objective was to investigate how violations to the underlying model influences their power and error rates.

We compared the performance of seven genome-scan methods (iHS, nSL, EHHST, XP-EHHST, xp-EHH, XPCLR and hapFLK) under subdivided population structures. Some of them such as iHS and xp-EHH have already been widely used (Andersen *et al.* 2012; Park *et al.* 2012; Qanbari *et al.* 2011) while the others, such as XPCLR, nSL and hapFLK, are quite popular but fairly recent and have not yet been extensively scrutinized (Peng *et al.* 2011). We evaluated these methods under a wide range of population structure scenarios undergoing either a hard or a soft selective sweep. Furthermore, we investigated how the power and false discovery rate of the methods are influenced by the allele frequency of the selected variant at the time of sampling.

We mainly focus on a local selective sweep scenario where the sweeping allele is beneficial in one deme and neutral in all the others; a selection scenario that has been frequently used in studies of human populations (Fournier-Level *et al.* 2011) but which has not yet been studied extensively. Previous analyses on subdivided populations have examined the case of global sweeps (Barton 2000; Bierne 2010; Santiago & Caballero 2005) or sweeps where a new variant is beneficial in one part of the species range but detrimental elsewhere (Bierne 2010; Le Corre & Kremer 2003). Here, we investigate in detail the scenario of an allele that is neutral in most of the range but beneficial in one population. A feature of this latter scenario that is shared with models of global sweeps is that migration will ultimately lead to the fixation of the beneficial allele in all populations (Fig. 1b).

In general, our results suggest that five (iHS, nSL, xp-EHH, XPCLR, hapFLK) out of the seven methods we evaluated are able to identify genomic regions undergoing a selective sweep in one or more of the scenarios we considered. The main difference between this group and the other two methods (EHHST and XP-EHHST) is the nature of the information they use to calculate the test statistic. The first group of five methods uses population level information (either haplotype frequencies or allele frequencies) while the two other methods are based on mean and standard deviation of homozygosity across all individuals in the sample (as opposed to homozygosity of a region with respect to all chromosomes in the sample – see Material and Methods and SI). This could explain their poor performance. More precisely, when there is no migration among populations, as in the scenarios considered by Zhong *et al.* (2010), the homozygosity is high for all individuals in the sample from the selected population and, therefore, its standard deviation is small, which increases the power of the test (Zhong *et al.* 2010). However, in our scenarios migration is present and, therefore, there is a mixture of individuals with very low and very high homozygosity in the selected population, and thus the standard deviation of homozygosity is extremely large, decreasing the power of the test. A second general result of our local selective sweep study is that XPCLR (Chen *et al.* 2010) has the best overall performance under the range of scenarios considered in this study. However, it is surpassed by iHS (Voight *et al.* 2006) and nSL (Ferrer-Admetlla *et al.* 2014), when the frequency of the selected variant is low (i.e. for starting selective sweeps ≥ 0.1 and ≤ 0.3). XP-EHH performs well for a narrow range of high allele frequencies of the selected variant, as previously shown by Sabeti *et al.* (2007).

In the case of the more complex scenario of a hard selective sweep in heterogeneous environments, only two methods, hapFLK and XPCLR, were relatively efficient at detecting

441 sweeps but their power was still limited to some particular conditions. hapFLK had high power
442 but also a high FDR. XPCLR, on the other hand, could detect a sweep only if the reference
443 population was located near the boundary between the two habitats. Overall, these results suggest
444 that the applicability of these selection detection methods to study genetic clines and secondary
445 contact zones is limited. Nevertheless, by combining them it may be possible to identify the
446 genomic region driving the genetic cline and also the geographic region where the transition
447 between the two selective regimes occurs.

448 There is a paucity of simulation studies comparing the performance of methods aimed at
449 identifying selective sweeps. However, evaluations of individual methods are presented in the
450 publications that introduce them for the first time. Voight *et al.* (2006) indicate that iHS performs
451 best for intermediate to high allele frequencies while our results show a different pattern with best
452 performance at low frequencies (>0.1 and <0.3). We explain this difference by the homogenizing
453 effect of migration in the subdivided population structures that we investigated. In the case of a
454 local sweep where a variant is favoured in one deme and neutral elsewhere, the selected
455 population is swamped by haplotypes carrying the counter selected variant. Therefore, the
456 strength of the genetic signal used by iHS decreases. A similar pattern is observed for nSL,
457 another single-population method. The effect of migration on power is also pronounced for the
458 two-population methods (XP-EHH and XPCLR), (c.f. Fig. 1). As time goes by, and when
459 migration is low, the allele frequency of the selected variant (and linked SNPs) increases very
460 rapidly in the selected population but very slowly in the neighboring populations (Fig. 1a), so
461 power to detect the sweep is high. However, higher migration rates lead to a simultaneous and
462 rapid increase of the selected variant and linked SNPs also in neighboring populations, which
463 reduces the differentiation and the power to detect selection (Fig. 1b). A similar effect is observed

464 when the selection coefficient is low (0.01), in which case the power decreases dramatically to
465 less than 45%.

466 Fariello *et al.* (2013) compare hapFLK with several other methods (Fst, FLK, hapFST and
467 xp-EHH) and show that it performs better than all of them. However, they consider a scenario
468 where there is a single episode of migration throughout the evolutionary history of the
469 population, a scenario applicable to a limited number of species. On the other hand, our analysis
470 assumes continuous migration, a scenario that should be applicable to a wide range of species. In
471 this situation, hapFLK performs well for hard sweeps both in hierarchical and even under simpler
472 population structures (e.g. island model; Fig. S12). However, this is not the case for the soft
473 sweep scenarios. Nevertheless, a great advantage of hapFLK over the other methods is that it is
474 applicable to scenarios with arbitrary number of subpopulations, which makes results
475 independent of the choice of populations included in the analysis. Additionally, hapFLK (and
476 nSL) does not require estimates of recombination rates, and therefore it is applicable to non-
477 model species.

478 Our simulations study also systematically investigates whether or not signals produced by
479 soft selective sweeps from standing variation can be detected. Unsurprisingly, all methods are
480 less efficient under soft sweep than under hard sweep scenarios because multiple haplotypes
481 containing the selected variant segregate in the population. More specifically in the island or
482 stepping stone models, iHS has very limited power. On the other hand, xp-EHH has high power
483 only for a very small range of high allele frequencies. Interestingly, the initial frequency of the
484 selected variant before the onset of selection has a negligible effect on the performance of iHS
485 and xp-EHH. XPCLR also has high power to detect soft sweeps under simple population
486 structure scenarios, particularly for small and moderate IAF. However, none of the methods

performed satisfactorily under the hierarchical population structure with migration, not even hapFLK that was specifically designed for such scenario. Note, however, the performance of XPCLR and hapFLK is greatly increased under the hierarchical scenario in the absence of migration. Thus, XPCLR and hapFLK are the most promising methods for detecting soft sweeps under complex population structures where migration is absent or very low.

As we have shown, no single method is able to detect both starting and nearly completed selective sweeps. Combining several methods (e.g. XPCLR or hapFLK with iHS or nSL) can greatly increase power to detect a wide range of selection signatures. A first step in this direction is presented by Grossman *et al.* (2010) who propose the Composite of Multiple Signals method which combines five different approaches (Fst, xp-EHH, iHS, ΔiHH (measures the absolute integrated Haplotype Homozygosity) and ΔDAF (accounts for derived alleles at high frequency).

Although our study suggests that some of these methods are potentially useful to identify selected regions, it is important to keep in mind that the statistical properties of the test statistics they use are unknown and, therefore, assessing significance is based on *ad-hoc* methods that lack statistical rigour. The only exceptions are EHHST and xp-EHHST, which were shown to be asymptotically normal (Zhong *et al.* 2010). However, our study suggests that these two methods are not able to detect selective sweeps under most realistic scenarios. In all other cases, there are two alternative approaches (see Material and Methods). One is based on the empirical distribution of the test statistic, which includes both selected and neutral sites and, therefore, is likely to lead to high false positive rates. The second approach is based on a simulated distribution and would be preferable in principle. However, it requires very good knowledge about the demographic history of the population under study. Unfortunately, this is almost never the case even for model species. Nevertheless, it is important to note that despite their important differences, our study

suggests that both methods lead to comparable results (compare Figs. 1-3, 5 and Figs. S13-S23) giving some support for the use of the empirical distribution approach.

Our study represents a substantial evaluation of recent genome scan methods to detect selective sweeps, and therefore it should be of broad interest. We note, however, that with the only exception of XPCLR, all these methods are applicable only to model species because they require phased data and information on the ancestral/derived status at each segregating site. However, continued developments in sequencing technology are broadening the range of species that could be studied using these methods. Our systematic comparison of genome-scan methods clarifies the conditions under which they should be applied and will help users to choose the most adequate approach for their study.

Acknowledgements

The authors thank Christelle Melodelima for helpful discussions. This work was supported by the Marie-Curie Initial Training Network INTERCROSSING (European Commission FP7). OEG was further supported by the MASTS pooling initiative (The Marine Alliance for Science and Technology for Scotland).

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"Data Accessibility:

The code, user manual of the code and an example dataset are available on https://github.com/alexvat/simulations"

Author Contributions

All authors contributed to the study design and preparation of the manuscript. AV wrote the scripts to run simuPOP and conducted the analyses; OEG was in charge of the overall supervision of the project.

Figure Legends

Figure 1: Results for the island model: a) trace of the allele frequency of the selected variant in the selected population, Y, and in a neutral population, Z with migration rate 0.01 per generation; b) likewise with m = 0.05 (the blue/green line represent the mean allele frequency over 1000 simulations and vertical lines represent the standard deviation); c-d) power for each method for the hard sweep under the island model: c) iHS; d) nSL; e) EHHST; f) xp-EHH; g) XP-EHHST; h) XPCLR. The scenario considers four demes with 2,500 individuals each, 101 loci and 0.00375cM/kb recombination rate, varying the migration rate and selection coefficient (see legend).

Figure 2: Effect of distance from selected population on XPCLR:. a) Graphical description of the stepping Stone Model with 7 populations with 2500 individuals each, 101 loci, selection coefficient 0.1 ($2N_es$ =500), migration rate 0.01 and recombination rate 0.00375cM/kb. Selection is present in population Y; b) trace of the allele frequency of the selected locus for all pairs of populations except from the boundary ones. The lines represent the mean allele frequency over the 1000 simulations and the vertical lines the standard deviation; c) power of XPCLR for the case of the hard sweep for the different pairs of populations.

Figure 3: Results for the hierarchical island model and hard sweep scenario: a) graphical representation of the population structure of the hierarchical model. Selection is present in only one of the demes (Y); b) Power for iHS (black), nSL (blue), hapFLK (grey), xp-EHH (red) and XPCLR (purple). Each of the four demes has 2500 individuals. We used 101 loci, migration rate between populations within continents 0.02 and between continent 0.01, selection coefficient 0.1 ($2N_es$ =500) and 0.00375cM/kb as recombination rate. In the case of xp-EHH and XPCLR, the comparison of demes in the same (Y-X) and different (Y-Z) continents is also shown.

Figure 4: Results of simulations of the stepping stone scenario with 52 populations. We simulated 101 loci with a recombination rate of 0.00375cM/kb. Each population had 500 individuals, the migration rate was 0.05 and the selection coefficient was 0.05 ($2N_es=50$). Allele 1 is favoured in populations 1-25 (habitat 1) and allele 0 is favoured in populations 26-50 (habitat 2). a) Power of XPCLR for analyses with population 1 as the objective population and each one of the other populations as the reference after 40,000 generations since the appearance of the mutation; b) frequency of the selected allele (at locus 50) across all populations at different times since its appearance in population 1 (number of generations indicated in the legend); c) pairwise Fst between population 1 and all the others for the selected locus (50); d) pairwise Fst between population 1 and all the others for the neutral locus (80).

Figure 5: Power of each method for the case of a soft sweep under the island model. a) iHS, b) nSL c) xp-EHH, and d) XPCLR. Results presented for different initial allele frequencies of the selected variant: 0.02 (black), 0.1 (grey), 0.2 (red), 0.4 (blue). Four demes with 2500 individuals each, 101 loci, migration rate 0.01, selection coefficient 0.05 ($2N_es=250$) and 0.00375cM/kb as recombination rate. Selection is acting only in one deme (Y).

Table 1: Parameters that were used in the simulations with simuPOP for the hard and the soft sweep. m1 is the migration rate of populations within the same group in the hierarchical model and m2 the migration rate of populations between different groups.

	Population Structure	Migration rate (m)	Selective coefficient (s)	Mutation rate	Recombination rate (r)
Hard Sweep	Island Model Stepping Stone Model	0.008 0.01 0.05	0.1 ($2N_es=500$)	10^{-8}	0.00375cM/kb
		0.008	0.08 ($2N_es=400$) 0.01 ($2N_es=50$)		
	Hierarchical Model	m1=0.02 m2=0.01	0.1 ($2N_es=500$)		
Soft Sweep	Island Model Stepping Stone Model	0.01	0.05 ($2N_es=250$)		
	Hierarchical Model	m1=0.02 m2=0.01	0.05 ($2N_es=250$)		
		m=0	0.05 ($2N_es=250$)		