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`selscan`: an efficient multi-threaded program to perform EHH-based scans for positive selection

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Abstract

Haplotype-based scans to detect natural selection are useful to identify recent or ongoing positive selection in genomes. As both real and simulated genomic datasets grow larger, spanning thousands of samples and millions of markers, there is a need for a fast and efficient implementation of these scans for general use. Here we present `selscan`, an efficient multi-threaded application that implements Extended Haplotype Homozygosity (EHH), Integrated Haplotype Score (iHS), and Cross-population Extended Haplotype Homozygosity (XPEHH). `selscan` accepts phased genotypes in multiple formats, including TPED, and performs extremely well on both simulated and real data and over an order of magnitude faster than existing available implementations. It calculates iHS on chromosome 22 (22,147 loci) across 204 CEU haplotypes in 353s on one thread (33s on 16 threads) and calculates XPEHH for the same data relative to 210 YRI haplotypes in 578s on one thread (52s on 16 threads). Source code and binaries (Windows, OSX and Linux) are available at `https://github.com/szpiech/selscan`.

1 Introduction

Extended Haplotype Homozygosity (EHH) (Sabeti *et al.*, 2002), Integrated Haplotype Score (iHS) (Voight *et al.*, 2006), and Cross-population Extended Haplotype Homozygosity (XPEHH) (Sabeti *et al.*, 2007) are statistics designed to use phased genotypes to identify putative regions of recent or ongoing positive selection in genomes. They are all based on the model of a hard selective sweep, where a *de novo* adaptive mutation arises on a haplotype that quickly sweeps toward fixation, reducing diversity around the locus. If selection is strong enough, this occurs faster than recombination or mutation can act to break up the haplotype, and thus a signal of high haplotype homozygosity can be observed extending from an adaptive locus.

As genetics data sets grow larger both in number of individuals and number of loci, there is a need for a fast and efficient publicly available implementation of these statistics. Below we introduce these statistics and provide concise definitions for their calculations. We then evaluate the performance of our implementation, `selscan`.

1.1 Extended Haplotype Homozygosity

In a sample of n chromosomes, let $\mathcal{C}$ denote the set of all possible distinct haplotypes at a locus of interest (named x_0), and let $\mathcal{C}(x_i)$ denote the set of all possible distinct haplotypes extending from the locus x_0 to the i^{th} marker either upstream or downstream from x_0. For example, if the locus of interest x_0 is a biallelic SNP where 0 represents the ancestral allele and 1 represents the derived allele, then $\mathcal{C} := \{0, 1\}$. If x_1 is an immediately adjacent marker, then the set of all possible haplotypes is $\mathcal{C}(x_1) := \{11, 10, 00, 01\}$.

EHH of the entire sample, extending from the locus x_0 out to marker x_i, is calculated as

$$EHH(x_i) = \sum_{h \in \mathcal{C}(x_i)} \frac{\binom{n_h}{2}}{\binom{n}{2}}, \quad (1)$$

where n_h is the number of observed haplotypes of type $h \in \mathcal{C}(x_i)$.

In some cases, we may want to calculate the haplotype homozygosity of a sub-sample of chromosomes all carrying a 'core' haplotype at locus x_0. Let $\mathcal{H}_c(x_i)$ be a partition of $\mathcal{C}(x_i)$ containing all distinct haplotypes carrying the core haplotype, $c \in \mathcal{C}$, at x_0 and extending to marker x_i. Note that

$$\mathcal{C}(x_i) = \bigcup_{c \in \mathcal{C}} \mathcal{H}_c(x_i). \quad (2)$$

Following the example above, if the derived allele (1) is chosen as the core haplotype, then $\mathcal{H}_1(x_1) := \{11, 10\}$. Similarly, if the ancestral allele is the core haplotype, then $\mathcal{H}_0(x_1) := \{00, 01\}$

We calculate the EHH of the chromosomes carrying the core haplotype c to marker x_i as

$$EHH_c(x_i) = \sum_{h \in \mathcal{H}_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}, \quad (3)$$

where n_h is the number of observed haplotypes of type $h \in \mathcal{H}_c(x_i)$ and n_c is the number of observed haplotypes carrying the core haplotype ($c \in \mathcal{C}$).

1.2 Integrated Haplotype Score

iHS is calculated by using Equation 3 to track the decay of haplotype homozygosity for both the ancestral and derived haplotypes extending from a query site. To calculate iHS at a site, we first calculate the integrated haplotype homozygosity (iHH) for the ancestral (0) and derived (1) haplotypes ($\mathcal{C} := \{0, 1\}$) via trapezoidal quadrature.

$$iHH_c = \sum_{i=1}^{|\mathcal{D}|} \frac{1}{2} \left(EHH_c(x_{i-1}) + EHH_c(x_i) \right) g(x_{i-1}, x_i) + \sum_{i=1}^{|\mathcal{U}|} \frac{1}{2} \left(EHH_c(x_{i-1}) + EHH_c(x_i) \right) g(x_{i-1}, x_i), \quad (4)$$

where $\mathcal{D}$ is the set of markers downstream from the current locus such that $x_i \in \mathcal{D}$ denotes the i^{th} closest downstream marker from the locus of interest (x_0). $\mathcal{U}$ and $x_i \in \mathcal{U}$ are defined similarly for upstream markers. $g(x_{i-1}, x_i)$ gives the genetic distance between two markers. The (unstandardized) iHS is then calculated as

$$\ln\left(\frac{iHH_1}{iHH_0}\right). \quad (5)$$

Note that this definition differs slightly from that in Voight *et al.* (2006), where unstandardized iHS is defined with iHH_1 and iHH_0 swapped.

Finally, the unstandardized scores are normalized in frequency bins across the entire genome.

$$iHS = \frac{\ln\left(\frac{iHH_1}{iHH_0}\right) - E_p\left[\ln\left(\frac{iHH_1}{iHH_0}\right)\right]}{SD_p\left[\ln\left(\frac{iHH_1}{iHH_0}\right)\right]}, \quad (6)$$

where $E_p\left[\ln\left(\frac{iHH_1}{iHH_0}\right)\right]$ and $SD_p\left[\ln\left(\frac{iHH_1}{iHH_0}\right)\right]$ are the expectation and standard deviation in frequency bin p.

In practice, the summations in Equation 4 are truncated once $EHH_c(x_i) < 0.05$. Additionally with low density SNP data, if the physical distance b (in kbp) between two markers is > 20, then $g(x_{i-1}, x_i)$ is scaled by a factor of $20/b$ in order to reduce possible spurious signals induced by lengthy gaps. During computation if the start/end of a chromosome arm is reached before $EHH_c(x_i) < 0.05$ or if a gap of $b > 200$ is encountered, the iHS calculation is aborted for that locus. iHS is not reported at core sites with minor allele frequency < 0.05. In `selscan`, the EHH truncation value, gap scaling factor, and core site MAF cutoff value are all flexible parameters definable on the command line.

1.3 Cross-population Extended Haplotype Homozygosity

To calculate XPEHH between populations A and B at a marker x_0, we first calculate iHH for each population separately, integrating the EHH of the entire sample in the population (Equation 1).

$$iHH = \sum_{i=1}^{|\mathcal{D}|} \frac{1}{2} \left(EHH(x_{i-1}) + EHH(x_i) \right) g(x_{i-1}, x_i) + \sum_{i=1}^{|\mathcal{U}|} \frac{1}{2} \left(EHH(x_{i-1}) + EHH(x_i) \right) g(x_{i-1}, x_i) \quad (7)$$

If iHH_A and iHH_B are the iHHs for populations A and B, then the (unstandardized) XPEHH is

$$\ln\left(\frac{iHH_A}{iHH_B}\right), \quad (8)$$

and after genome-wide normalization we have

$$XPEHH = \frac{\ln\left(\frac{iHH_A}{iHH_B}\right) - E\left[\ln\left(\frac{iHH_A}{iHH_B}\right)\right]}{SD\left[\ln\left(\frac{iHH_A}{iHH_B}\right)\right]}. \quad (9)$$

In practice, the sums in each of iHH_A and iHH_B (Equation 7) are truncated at x_i—the marker at which the EHH of the haplotypes *pooled across populations* is $EHH(x_i) < 0.05$. Scaling of $g(x_{i-1}, x_i)$ and handling of gaps is done as for iHS, and these parameters are definable on the `selscan` command line.

2 Performance

Here we evaluate the performance of `selscan` (`https://github.com/szpiech/selscan`) for computing the iHS and XPEHH statistics. In addition, we compare performance on these statistics with the programs `rehh` (Gautier and Vitalis, 2012, `http://cran.r-project.org/package=rehh`), `ihs` (Voight *et al.*, 2006) and `xpehh` (Pickrell *et al.*, 2009). Both `ihs` and `xpehh` are available for download at `http://hgdp.uchicago.edu/Software/`. All computations were run on a MacPro running OSX 10.8.5 with two 2.4 GHz 6−core Intel Xeon processors with hyperthreading enabled.

2.1 iHS

For runtime evaluation of iHS calculations, we simulated a 4 Mbp region of DNA with the program `ms` (Hudson, 2002) and generated four independent data sets with varying numbers of sampled haplotypes ($\theta = 1600$ and $\rho = 1600$). We sampled 250 haplotypes (9,625 SNP loci), 500 haplotypes (10,646 SNP loci), 1,000 haplotypes (11,655 SNP loci), and 2,000 haplotypes (12,724 SNP loci). We name these data sets IHS250, IHS500, IHS1000, IHS2000, respectively. These data sets represent a densely typed region similar to next-generation sequencing data. Although these data sets are generated via strictly neutral processes, they serve the purpose of runtime evaulation perfectly well. We also use data from The 1000 Genomes Project (The 1000 Genomes Project Consortium,

2012) Omni genotypes, calculating iHS scores at 22,147 SNP loci on chromosome 22 across 102 CEU individuals (204 haplotypes). We name this data set CEU22.

Table 1 summarizes the runtimes of `ihs`, `rehh`, and `selscan`. We note that `rehh` integrates haplotype homozygosity over a physical map, whereas `ihs` and `selscan` integrate over a genetic map by default. This does not affect runtimes (data not shown), which are measured using genetic maps for `ihs` and `selscan`. Even operating on a single thread, `selscan` calculates iHS scores at least an order of magnitude faster than `ihs` and up to 1.8x faster than `rehh` for large data sets.

We compare unstandardized iHS scores for the CEU22 data set using `ihs` and `selscan` and find excellent agreement (Figure 1A, Pearson's $r = 0.9946$). The slight variance in scores between the two programs is likely due to an undocumented difference in the way `ihs` calculates its scores (Sabeti *et al.* (2007) Supplemental Information), but the effect is negligible. We also calculate unstandardized iHS scores for the CEU22 data set using `rehh` and `selscan` (using a physical map) and again find excellent agreement (Pearson's $r = 0.9953$).

2.2 XPEHH

For runtime evaluation of XPEHH calculations, we simulated a 4 Mbp region of DNA with the program `ms` (Hudson, 2002) with a simple two population divergence model (time to divergence $t = 0.05$, $\theta = 1600$ and $\rho = 1600$) and generated four independent data sets with varying numbers of sampled haplotypes. We sampled 250 haplotypes (125 from each population, 12,920 SNP loci), 500 haplotypes (250 from each population, 14,989 SNP loci), 1,000 haplotypes (500 from each population, 17,142 SNP loci), and 2,000 haplotypes (1,000 from each population, 19,567 SNP loci). We name these data sets XP250, XP500, XP1000, XP2000, respectively. These data sets represent a densely typed region similar to next-generation sequencing data. Although these data sets are generated via strictly neutral processes, they serve the purpose of runtime evaulation perfectly well. We also use data from The 1000 Genomes Project (The 1000 Genomes Project Consortium, 2012) Omni genotypes, calculating XPEHH scores at 22,147 SNP loci on chromosome 22 across 102 CEU individuals (204 haplotypes) and 105 YRI individuals (210 haplotypes). We name this data set CEUYRI22.

Table 2 summarizes the runtimes of `xpehh` and `selscan`. Even operating on a single thread, `selscan` tends to calculate XPEHH scores at least an order of magnitude faster than `xpehh`. Figure 1B shows the correlation (Pearson's $r = 0.9999$) of CEUYRI22 unstandardized XPEHH scores between the two programs.

3 Conclusions

`selscan` achieves a speed up of at least an order or magnitude over both `ihs` and `xpehh` and a speed up of nearly 2x over `rehh` for large data sets through general optimizations of the calculations. We also implement shared memory parallelism with multithreading to further speed up calculations on computers with multiple cores. Since iHS and XPEHH attempt to calculate a score for each site in the data and each score can be calculated indpendently of the others, `selscan` partitions the workload (sites at which to calculate a score) across threads, while maintaining each thread's access to the entire data set required to make the calculation.

Additional empirical testing (data not shown) suggests that `rehh`, `ihs`, and `selscan` (for both iHS and XPEHH calculations) are $O(ND^2)$, and `xpehh` is $O(N^2D^2)$, where N is the number of haploid samples and D is the SNP locus density.

Each of these statistics require phased haplotypes and a genetic or physical map as input data (TPED format) and missing genotypes must either be dropped or imputed. Because of the speed improvements we have implented, we expect that `selscan` will be a valuable tool for calculating EHH-based genome-wide scans for positive selection in very large genetic data sets, including whole genome sequencing and GWAS data, currently being generated for humans and other organisms. `selscan` will also allow for in-depth examination of the performance of these statistics under a wide range of parameters in large scale simulation studies.

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Table 1: Runtime performance (in seconds) of `ihs`, `rehh`, and `selscan` for calculating unstandardized iHS for various data sets. Calculations running over 100,000 seconds were aborted. *`rehh` integrates over a physical map instead of a genetic map. Using a physical map does not affect `selscan`'s runtime (data not shown).

Data Set	`ihs`	`rehh`*	`selscan`				
			threads = 1	2	4	8	16
IHS250	19,275	563	618	306	162	84	58
IHS500	45,547	1,652	1,554	782	399	220	150
IHS1000	> 100,000	4,834	4,018	2,019	1,040	566	380
IHS2000	> 100,000	12,652	7,054	3,633	1,869	1,046	752
CEU22	19,434	588	353	182	93	50	33

Table 2: Runtime performance (in seconds) of `xpehh` and `selscan` for calculating unstandardized XPEHH for various data sets. Calculations running over 100,000 seconds were aborted.

Data Set	`xpehh`	`selscan`				
		threads = 1	2	4	8	16
XP250	11,113	287	141	71	38	25
XP500	57,006	766	403	194	104	67
XP1000	> 100,000	2,037	1,018	515	274	180
XP2000	> 100,000	5,683	2,798	1,471	763	493
CEUYRI22	37,271	578	291	150	78	52

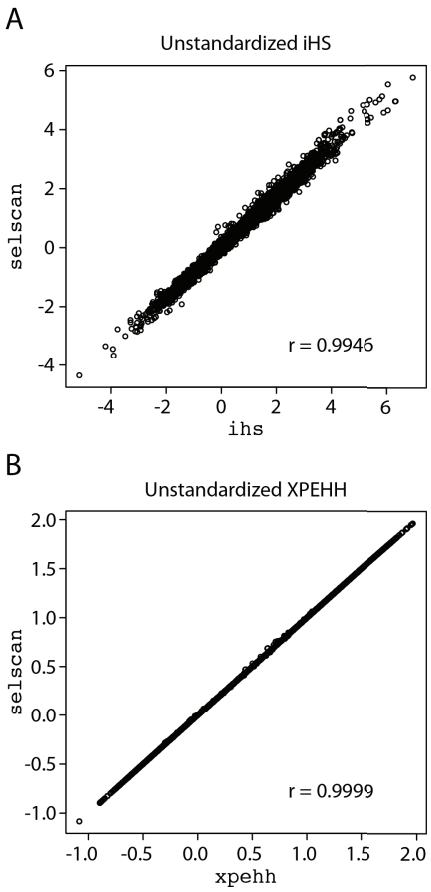

Figure 1: (A) Unstandardized iHS scores calculated on the CEU22 data set for `selscan` and `ihs` (Pearson's $r = 0.9946$) and (B) Unstandardized XPEHH scores calculated on the CEUYRI22 data set for `selscan` and `xpehh` (Pearson's $r = 0.9999$)