

# SeleDiff Manual

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# 1 Introduction

**SeleDiff** is implemented with a probabilistic method for testing and estimating selection coefficient differences between populations<sup>1</sup>.

## 1.1 Basic Model

Let  $\Phi$  denote the difference of selection between population  $A$  and  $B$ , i.e.,  $\Phi = s_A - s_B$ , then

$$\hat{\Phi} = E(s_A - s_B) = \frac{\log(\text{Odds})}{t}$$

where  $s_A$  and  $s_B$  are the selection coefficients in population  $A$  and  $B$  respectively,  $t$  is the divergence time between  $A$  and  $B$ , and  $\text{Odds} = \frac{C_{A,m}C_{B,w}}{C_{A,w}C_{B,m}}$  (For more details, please see [1]),  $C_{A,m}$  denotes the count of derived allele in population  $A$ ,  $C_{A,w}$  denotes the count of ancestral allele in population  $A$ ,  $C_{B,m}$  denotes the count of derived allele in population  $B$ ,  $C_{B,w}$  denotes the count of ancestral allele in population  $B$ .

The variance of  $\Phi$  could be calculated as

$$\text{Var}(\Phi) = \frac{\text{Var}[\log(\text{Odds})]}{t^2} + \text{Var}(\Omega)$$

where  $\Omega$  is the general effect of genetic drift between population  $A$  and  $B$ .

Therefore, when a sample has  $n$  neutral loci and  $n$  is large, the variance of  $\Omega$  can be estimated as

$$\hat{\text{Var}}(\Omega) = \text{median} \left( \frac{\hat{\Phi}^2(i)}{0.455} - \frac{\text{Var}[\log(\text{Odds}_i)]}{t^2} \right), n \geq i \geq 1$$

where the variance of log-odds ratio could be effectively approximated as

$$\text{Var}[\log(\text{Odds})] = \frac{1}{C_{A,m}} + \frac{1}{C_{A,w}} + \frac{1}{C_{B,m}} + \frac{1}{C_{B,w}}$$

.

When  $C < 5$ , we do corrections as  $C' = C + 0.5$ .

The statistic for natural selection of a candidate locus is

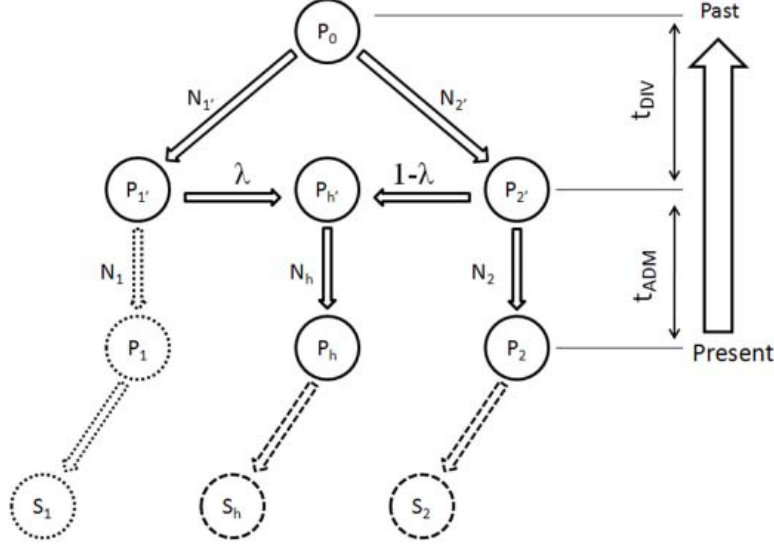
$$\delta = \frac{\hat{\Phi}^2}{\text{Var}(\hat{\Phi})}$$

Under the null hypothesis that differences in natural selection are absent, the statistics  $\delta$  follows a central chi-square distribution with a degree of freedom = 1. Under the alternative hypothesis with a selection difference the statistic  $\delta$  has a noncentral chi-square distribution with non-centrality parameter  $\hat{\Phi}^2$  and a degree of freedom = 1.

## 1.2 Correction for Admixed Populations

In the basic model, we assume no gene flow in population  $A$  and  $B$ . When at least one population is admixed, we have to estimate the admixture proportion and use its parental populations instead.

We assume an admixture model as shown in the figure in below. An ancestral population  $P_0$  is split into two parental populations,  $P_{1'}$  and  $P_{2'}$  (with effective sizes  $N_{1'}$  and  $N_{2'}$ , respectively), which evolve independently for  $t_{\text{DIV}}$  generations before they contribute genes of proportion  $\lambda$  and  $1 - \lambda$  to form the hybrid population,  $P_h$ , with effective sizes  $N_1$ ,  $N_2$  and  $N_h$ , respectively, and evolve independently for  $t_{\text{ADM}}$  generations before a sample ( $S_j, j = 2, h$ ) is taken from each of them.<sup>2</sup>



### 1.2.1 Estimate Admixed Proportion

We estimate admixed proportion for neutral locus  $i$  in the admixed population  $P_h$  with  $n$  loci as

$$\lambda_i = \frac{f_{ih} - f_{i2}}{f_{i1} - f_{i2}}$$

where  $f_{ij}$  ( $j = 1, 2, h$ ) is the allele frequency of locus  $i$  in population  $j$ .

The overall admixed proportion from population  $P_1$  is estimated as

$$\hat{\lambda} = \text{mean}(\lambda_i)$$

### 1.2.2 Estimate Allele Frequencies in Missing Parental Populations

When population  $P_1$  is missing, we estimated allele frequency of each SNP in admixed population using an maximum likelihood method. Given a genetic contribution  $\lambda$  and current observation  $C_{j2}$  and  $C_{jh}$  on locus  $j$  for population  $P_2$  and  $P_h$ , allele frequency  $f_{j1'}$  in the missing ancestral population  $P_{1'}$  could be estimated when the recent effective population sizes ( $N_h$  and  $N_2$ ) are large and the admixture event is relatively young.<sup>3</sup>

Given the current observation  $C_j(C_{j2}, C_{jh})$  and sample size  $S(S_2, S_h)$ , we have the probability of observation

$$P(C_{j2}, C_{jh} | f_{j2}, f_{jh}, S_2, S_h) \approx \binom{S_h}{C_{jh}} f_{jh'}(1 - f_{jh'}) \binom{S_2}{C_{j2}} f_{j2'}(1 - f_{j2'})$$

Maximize the probability  $P(C_{j2}, C_{jh} | f_{j2}, f_{jh}, S_2, S_h)$ , we have estimation for the allele frequency in missing parental population  $f_{j1}$  by

$$\hat{f}_{j1} = \max \left( 0, \min \left( \frac{C_{jh}/S_h - (1-\lambda)C_{j2}/S_2}{\lambda}, 1 \right) \right)$$

Suppose we want to compare population  $P_1$  with another population  $P_3$  that is without admixture. Then

$$\text{Var}[\log(\text{Odds})] = \text{Var} \left[ \log \left( \frac{f_{j1}}{1-f_{j1}} \right) \right] + \text{Var} \left[ \log \left( \frac{f_{j3}}{1-f_{j3}} \right) \right]$$

Use  $\Delta$ -method<sup>4</sup>,

$$\begin{aligned} \text{Var} \left[ \log \left( \frac{f_{j1}}{1-f_{j1}} \right) \right] &\approx \text{Var} \left( \frac{f_{j1}}{1-f_{j1}} \right) \left[ 1/\text{E} \left( \frac{f_{j1}}{1-f_{j1}} \right) \right]^2 \\ &\approx \frac{\text{E}^2(f_{j1})}{\text{E}^2(1-f_{j1})} \left[ \frac{\text{Var}(f_{j1})}{\text{E}^2(1-f_{j1})} - 2 \frac{\text{Cov}(f_{j1}, 1-f_{j1})}{\text{E}(f_{j1})\text{E}(1-f_{j1})} + \frac{\text{Var}(1-f_{j1})}{\text{E}^2(1-f_{j1})} \right] \left[ 1/\text{E} \left( \frac{f_{j1}}{1-f_{j1}} \right) \right]^2 \\ &= \left( \frac{1}{\text{E}(f_{j1})} + \frac{1}{\text{E}(1-f_{j1})} \right)^2 \text{Var}(f_{j1}) \\ &= \frac{\text{Var}(f_{j1})}{\text{E}^2(f_{j1})\text{E}^2(1-f_{j1})} \end{aligned}$$

where

$$\begin{aligned} \text{E}(f_{j1}) &= \hat{f}_{j1} \\ \text{Var}(f_{j1}) &= \frac{1}{\lambda^2} \left[ \frac{C_{jh}(S_h - C_{jh})}{S_h^3} + (1-\lambda)^2 \frac{C_{j2}(S_2 - C_{j2})}{S_2^3} \right] \end{aligned}$$

While

$$\text{Var} \left[ \log \left( \frac{f_{j3}}{1-f_{j3}} \right) \right] = \frac{1}{C_{j3}} + \frac{1}{S_3 - C_{j3}}$$

where  $C_{j3}$  is the observation in population  $P_3$  and  $S_3$  is the sample size of  $P_3$ .

## 2 Usages

### 2.1 Environment Setting

To use **SeleDiff**, you should install [Java SE Runtime Enviroment 8](#) first.

After the installation, you can check Java version in the command line (command starts by “>” prompt).

```
> java -version
java version "1.8.0_25"
Java(TM) SE Runtime Environment (build 1.8.0_25-b17)
Java HotSpot(TM) 64-Bit Server VM (build 25.25-b02, mixed mode)
```

Once you have installed Java SE Runtime Environment 8, you can run **SeleDiff** without any parameter in the command line to look at help information.

```

> java -jar SeleDiff.jar
Usage: SeleDiff [options]
Options:
  --admixed-population
    A file specifies admixed population.
  --all-gen
    A Oxford GEN file contains all the sample SNPs' information and genotype
    data.
  --all-gen-threshold
    A threshold specifies the confidence of genotype in all the sample data,
    if Oxford GEN/SAMPLE format is used.
    Default: 0.9
  --all-geno
    A EIGENSTRAT GENO file contains all the sample genotype data.
  --all-haps
    A HAPS file contains all the sample SNPs' information and genotype data.
  --all-ind
    A EIGENSTRAT IND file contains all the sample individuals' information.
  --all-sample
    A Oxford SAMPLE file contains all the sample individuals' information.
  --all-snp
    A EIGENSTRAT SNP file contains all the sample SNPs' information.
* --ancestral-allele
    A file specifies ancestral alleles.
  --candidate-gen
    A Oxford GEN file contains the candidate SNPs' information and genotype
    data.
  --candidate-gen-threshold
    A threshold specifies the confidence of genotypes in the candidate data,
    if Oxford GEN/SAMPLE format is used.
    Default: 0.9
  --candidate-geno
    A EIGENSTRAT GENO file contains the candidate genotype data.
  --candidate-haps
    A HAPS file contains the candidate SNPs' information and genotype data.
  --candidate-ind
    A EIGENSTRAT IND file contains the candidate individuals' information.
  --candidate-sample
    A Oxford SAMPLE file contains the candidate individuals' information.
  --candidate-snp
    A EIGENSTRAT SNP file contains the candidate SNPs' information.
* --divergence-time
    A file specifies divergence time.
  --haplotype
    A file specifies haplotypes.
  --help
    Show SeleDiff's usage.
    Default: false
  --log
    Redirect log into a file.
* --output
    The output file.

```

\* indicates required options.

## 2.2 Input Files

SeleDiff accepts 3 kinds of file formats of genetic data as inputs. They are [EIGENSTRAT](#) format, [Oxford GEN/SAMPLE](#) format and [HAPS/SAMPLE](#) format.

In order to describe each format, consider an example dataset containing 3 unrelated individuals (Ind1, Ind2 & Ind3) from 3 populations (Pop1, Pop2 & Pop3) that were typed on 3 SNPs (SNP1, SNP2 & SNP3):

|      | SNP1 | SNP2 | SNP3 |
|------|------|------|------|
| Ind1 | T/T  | A/T  | T/T  |
| Ind2 | C/G  | C/G  | C/G  |
| Ind3 | C/C  | A/A  | ?/?  |

### 2.2.1 EIGENSTRAT

For EIGENSTRAT format, there are 3 files: **SNP** file, **IND** file and **GENO** file.

The **SNP** file describes the information of each SNP. The SNP file corresponding to the example dataset is:

```
SNP1 1 0.1 100 A T
SNP2 1 0.2 101 C G
SNP3 1 0.3 103 C A
```

Each row corresponds to a SNP. The 6 columns are:

1. SNP ID
2. Chromosome number
3. SNP genetic position
4. SNP physical position
5. Reference allele
6. Alternative allele

The **IND** file describes the information of each individual. The IND file corresponding to the example dataset is:

```
Ind1 M pop1
Ind2 F pop2
Ind3 U pop3
```

Each row corresponds to an individual. The 3 columns are:

1. Individual ID
2. Sex: M for male, F for female and U for unknown
3. Population ID

The **GENO** file contains genetic data. The GENO file corresponding to the example dataset is:

```
010
111
209
```

Each row corresponds to a SNP, and each column corresponds to an individual. The characters, 0, 1, 2, 9, correspond to an individual's genotype:

- 0 means zero copies of reference allele.
- 1 means one copy of reference allele.
- 2 means two copies of reference allele.
- 9 means missing data.

### 2.2.2 Oxford GEN/SAMPLE

For Oxford GEN/SAMPLE format, there are 2 files: **GEN** file and **SAMPLE** file.

The **GEN** file describes the information of each SNPs and its genotypes. The GEN file corresponding to the example dataset is:

```
1 SNP1 100 A T 0 0 1 0 1 0 0 0 1
1 SNP2 101 C G 0 1 0 0 1 0 0 1 0
1 SNP3 103 C A 1 0 0 0 0 1 0 0 0
```

Each row corresponds to a SNP. The first 5 columns are:

1. Chromosome number
2. SNP ID
3. SNP physical position
4. Reference allele
5. Alternative allele

From the 6th column, every 3 columns correspond to 3 probabilities of an individual's genotype (AA, AB, BB). If the largest of the probabilities is over the threshold specified by `--all-gen-threshold` or `--candidate-gen-threshold`, then the genotype corresponding to the largest probability is used for `SeleDiff`.

The **SAMPLE** file describes the information of each individuals. The SAMPLE file corresponding to the example dataset is:

```
ID_1 ID_2 missing sex phenotype
0 0 0 D P
Pop1 Ind1 0 M -9
Pop2 Ind2 0 F -9
Pop3 Ind3 0.33 U -9
```

The 1st and 2nd rows are headers. From the 3rd row, each row corresponds to an individual. The 5 columns are:

1. Population ID
2. Individual ID
3. Missing data rate
4. Sex
5. Phenotype



### 2.2.3 HAPS/SAMPLE

For HAPS/SAMPLE format, there are 2 files: **HAPS** file and **SAMPLE** file.

The **HAPS** file describes the information of each SNPs and its genotypes. The HAPS file corresponding to the example dataset is:

```
1 SNP1 100 A T 1 1 0 1 1 1
1 SNP2 101 C G 0 1 0 1 0 1
1 SNP3 103 C A 0 0 1 1 9 9
```

Each row corresponds to a SNP. The first 5 columns are the same as those in Oxford GEN file.

From the 6th column, every two columns correspond to an individual's genotype. The characters, 0, 1, 9, correspond to alleles of a SNP:

- 0 means reference allele
- 1 means alternative allele
- 9 means missing data

The **SAMPLE** file is the same as the Oxford SAMPLE file.

### 2.2.4 Ancestral Allele File

SeleDiff uses `--ancestral-allele` option (required) to accept a *TAB* delimited file that specifies the ancestral allele of each SNP in the data. The content of the file looks like:

```
rsID    Ancestral Allele
rs001    A
rs002    G
...
```

The first line is a header which will be skipped by SeleDiff.

### 2.2.5 Divergence Time File

SeleDiff uses `--divergence-time` option (required) to accept a *TAB* delimited file that specifies divergence time between two populations.

```
Population1 Population2 Time(generations)
EastAfrica  WesAfrica    2000
EastAfrica  EastSouthasia(EastAsia) 3600
...
```

The first line is a header which will be skipped by SeleDiff. Here, EastSouthasia is a admixed population. We estimate and use its missing parental population in East Asia instead.

## 2.2.6 Admixed Population File

**SeleDiff** uses `--admixed-population` option to accept a TAB delimited file that specifies admixed populations in the data. The content of the file looks like:

```
Population1 Population2 Desc
EastAsia     Europe   EastSouthasia
EastAsia     Europe   CentralAsia
...
```

The first line is a header which will be skipped by **SeleDiff**. The first two columns (e.g., EastAsia and Europe) are the parental populations we can sample in the present time. The third column (e.g. CentralAsia) is the admixed population. You can find admixture proportions in the log generated by **SeleDiff**.

## 2.2.7 Haplotype File

**SeleDiff** uses `--haplotype` option to accept a TAB delimited file that specifies haplotypes in the data. The content of the file looks like:

```
rs001    rs002
rs001    rs003    rs004
```

Each row represents a haplotype.

## 2.3 Output File

The output file from **SeleDiff** is TAB delimited. The first row is a header that describes the meaning of each column.

| Column | Column Name   | Description   |
|--------|---|---|
| 1      | SNP ID/Haplotype ID   | The name of a SNP/haplotype   |
| 2      | Ancestral Allele  | The ancestral allele of a SNP/haplotype   |
| 3      | Derived Allele  | The derived allele of a SNP/haplotype   |
| 4      | Population1   | The first population's ID   |
| 5      | Ancestral Allele Count  | The count of the ancestral allele in the first population   |
| 6      | Derived Allele Count  | The count of the derived allele in the first population   |
| 7      | Population2   | The second population's ID  |
| 8      | Ancestral Allele Count  | The count of the ancestral allele in the second population  |
| 9      | Derived Allele Count  | The count of the derived allele in the second population  |
| 10     | Selection Coefficient Difference<br>(Population1 - Population2) | The selection coefficient difference between the first and second populations   |
| 11     | Std   | The standard deviation of the selection coefficient difference  |
| 12     | Divergence Time   | The divergence time between the first and second populations  |
| 13     | log(Odds Ratio)   | The logarithm of Odds Ratio   |
| 14     | Var(log(Odds Ratio))  | The variance of the logarithm of Odds Ratio   |
| 15     | Population Variance   | The drift strength $\hat{\text{Var}}(\Omega)$ between the first and second populations without dividing the square of divergence time |
| 16     | Delta   | The $\delta$ statistic for selection difference   |
| 17     | p-value   | The p-value of the $\delta$ statistic   |

Note: For a admixed population, the allele counts of its missing parental populations are estimated by their estimated allele frequencies multiply by 1000 (See Introduction section for estimating allele frequencies in missing parental populations).

### 3 Examples

Here is an example to show how **SeleDiff** tests and estimates selection coefficient differences between populations. 5 populations (YRI, CEU, CHB, CHD, ASW) from [HapMap3 \(release3\)](#) were extracted. CHB and CHD were merged into one population called CHS. Correlated individuals and SNPs which major allele frequencies are less than 0.05 were removed by [PLINK 1.07](#)(`--geno 0.01 --maf 0.05`). SNPs in strong linkage disequilibrium were removed, applying a window of 50 SNPs advanced by 5 SNPs and  $r^2$  threshold of 0.01 (`--indep-pairwise 50 5 0.01`) in PLINK. All the genetic data are stored in EIGENSTRAT format.

#### 3.1 Estimate Selection Coefficient Differences in SNPs

The SNP rs12913832 in gene *HERC2* is associated with blue/non-blue eyes. Its ancestral allele is A and its derived allele is G. The SNP rs1800407 in gene *OCA2* is also associated with blue/non-blue eyes. Its ancestral allele is C and its derived allele is T. The ancestral allele information is stored in `examples/ancestral_alleles.tsv`.

The counts of alleles in our example data were summarized in below.

| SNP ID     | Population | Ancestral Allele Count | Derived Allele Count |
|------------|------------|------------------------|----------------------|
| rs12913832 | YRI        | 294                    | 0                    |
| rs12913832 | CEU        | 47                     | 177                  |
| rs12913832 | CHS        | 491                    | 1                    |
| rs1800407  | YRI        | 290                    | 0                    |
| rs1800407  | CEU        | 207                    | 17                   |
| rs1800407  | CHS        | 486                    | 4                    |

We assume the divergence time of YRI-CEU and YRI-CHS are both 3600 generations, while the divergence time of CEU-CHS is 2000 generations. This information is stored in `examples/divergence_times.tsv`.

To estimate selection coefficient differences, in the command line, we type

```
> java -jar SeleDiff.jar --all-geno example.geno --all-ind example.ind --all-snp example.snp \
  --candidate-geno example.candidate.geno --candidate-ind example.candidate.ind \
  --candidate-snp example.candidate.snp --ancestral-allele ancestral_alleles.tsv \
  --divergence-time divergence_times.tsv --output example.result.tsv
```

The result is stored in `examples/example.result.tsv`. The main result is in below.

| SNP ID     | Population1 | Population2 | Selection Coefficient Difference | Std     | delta     | p-value  |
|------------|-------------|-------------|----------------------------------|---------|-----------|----------|
| rs12913832 | YRI         | CEU         | -0.00214                         | 3.96E-4 | 16.57374  | 4.7E-5   |
| rs12913832 | YRI         | CHS         | -1.63E-4                         | 4.54E-4 | 0.079586  | 0.777859 |
| rs12913832 | CEU         | CHS         | 0.003558                         | 4.17E-4 | 30.083597 | 0.0      |
| rs1800407  | YRI         | CEU         | -0.001073                        | 3.99E-4 | 4.127239  | 0.042198 |
| rs1800407  | YRI         | CHS         | -4.67E-4                         | 4.15E-4 | 0.730705  | 0.392655 |
| rs1800407  | CEU         | CHS         | 0.001091                         | 2.68E-4 | 3.733448  | 0.053333 |

From the result, we can see the selection coefficient of rs12913832 in CEU is significantly higher than that in YRI or CHS, which indicates rs12913832 is under positive selection in CEU. While the selection coefficient of rs1800407 in CEU is marginal significantly higher than that in YRI or CHS.

When estimating selection coefficient differences in admixed populations, we have to correct for its admixed proportions from parental populations. In our example, ASW is an admixed population. We assume its parental populations are YRI and CEU. This information is stored in `examples/admixed_populations.tsv`.

To estimate selection coefficient differences, we have to use `--admixed-population` to specify the information of admixed populations. In the command line, we type

```
> java -jar SeleDiff.jar --all-geno example.geno --all-ind example.ind --all-snp example.snp \
  --candidate-geno example.candidate.geno --candidate-ind example.candidate.ind \
  --candidate-snp example.candidate.snp --ancestral-allele ancestral_alleles.tsv \
  --divergence-time admixed_divergence_times.tsv --admixed-population admixed_populations.tsv \
  --output example.admixed.result.tsv
```

From the log information generated by `SeleDiff`, we can see the admixed proportion of ASW from YRI is approximately equal to 0.8. The result is stored in `examples/example.admixed.result.tsv`.

### 3.2 Estimate Selection Coefficient Differences in Haplotypes

It was reported that the derived allele of rs1800407 increased the penetrance of the blue eye phenotype associated with the derived allele of rs12913832.<sup>5</sup> We used [IMPUTE2](#) to phase chromosome 15 (`-phase -int 24e6 27e6 -Ne 10000 -m genetic_map_chr15_combined_b36.txt`) in our example data and stored the phased data in `examples/example.candidate.chr15.phased.haps` and `examples/example.candidate.chr15.phased.sample`. The genetic map is downloaded from [IMPUTE2](#). We specified the haplotype by the haplotype list file, which is stored in `examples/haplotype.list`.

To estimate selection coefficient differences, we have to store candidate data in HAPS/SAMPLE format and use `--haplotype` to specify the information of haplotypes. In the command line, we type

```
> java -jar SeleDiff.jar --all-geno example.geno --all-ind example.ind --all-snp example.snp \
  --candidate-geno example.candidate.geno --candidate-ind example.candidate.ind \
  --candidate-snp example.candidate.snp --ancestral-allele ancestral_alleles.tsv \
  --divergence-time divergence_times.tsv --haplotype haplotypes.list --output example.result
```

The result is stored in `examples/example.hap.result.tsv`. As the result indicates, the derived haplotypes have signature of positive selection in CEU population.

## 4 Dependencies

- [Java 1.8](#)
- [Apache Commons Math 3.5](#)
- [JCommander 1.48](#)

## 5 References

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