

# semisup: detecting SNPs with interactive effects on a quantitative trait

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This vignette explains how to use the R package **semisup**. Use the function [mixture](#) for model fitting, and the function [scrutor](#) for hypothesis testing.

## 1 Initialisation

Start with installing **semisup** from Bioconductor<sup>1</sup>:

```
if (!requireNamespace("BiocManager", quietly=TRUE))  
  install.packages("BiocManager")  
BiocManager::install("semisup")
```

Then load and attach the package:

```
library(semisup)
```

If you want to reproduce the examples, you should attach the toy database:

```
attach(toydata)
```

The following commands access the reference manual:

```
help(semisup)  
?semisup
```

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<sup>1</sup>[devtools](#) and [GitHub](#): `devtools::install_github("rauschenberger/semisup")`

## 2 Scope

Data is available for  $n$  samples. Let  $\mathbf{y} = (y_1, \dots, y_n)^T$  represent the observations,  $\mathbf{x} = (x_1, \dots, x_n)^T$  the groups, and  $\mathbf{z} = (z_1, \dots, z_n)^T$  the classes. We assume all observations from the *labelled* group are in class **A**, and those from the *unlabelled* group are in class **A** or in class **B**.

|              | 1        | ... | $s$      | $s+1$      | ... | $n = s+u$  |
|--------------|----------|-----|----------|------------|-----|------------|
| $\mathbf{y}$ | $y_1$    | ... | $y_s$    | $y_{s+1}$  | ... | $y_{s+u}$  |
| $\mathbf{x}$ | 0        | ... | 0        | 1          | ... | 1          |
| $\mathbf{z}$ | <b>A</b> | ... | <b>A</b> | <b>A/B</b> | ... | <b>A/B</b> |

Table 1: Observations  $\mathbf{y}$ , groups  $\mathbf{x}$ , and classes  $\mathbf{z}$ . Here, the first  $s$  observations are *labelled* (class **A**), and the last  $u$  observations are *unlabelled* (class **A** or **B**).

We assume all observations come from the same probability distribution, but with different parameters for the two classes:

$$\begin{aligned} Y_i | (Z_i = \text{A}) &\sim F(\cdot, \boldsymbol{\theta}_a), \\ Y_i | (Z_i = \text{B}) &\sim F(\cdot, \boldsymbol{\theta}_b). \end{aligned}$$

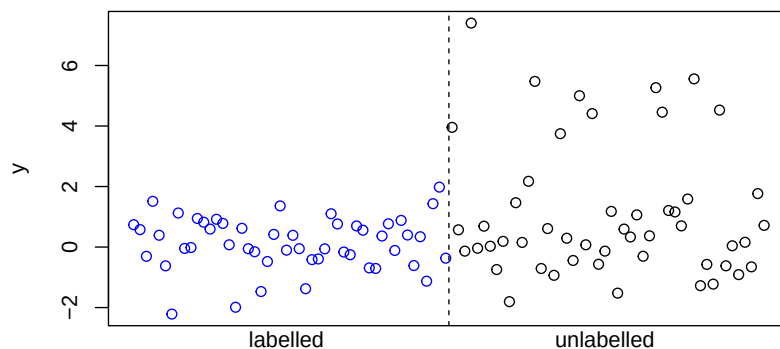
The mixing proportion  $\tau$  is the probability that a random *unlabelled* observation is in class **B**. It is of interest to test whether  $\tau$  is significantly larger than zero.

$$\begin{aligned} \tau &= \mathbb{P}[Z_i = \text{B} | X_i = 1], \\ H_0 &: \tau = 0, \\ H_1 &: \tau > 0. \end{aligned}$$

The function `mixture` estimates the unknown parameters  $(\boldsymbol{\theta}_a, \boldsymbol{\theta}_b, \tau)$  and predicts the missing class labels in  $\mathbf{z} = (z_1, \dots, z_n)^T$ . The function `scrutor` tests homogeneity ( $\tau = 0$ ) against heterogeneity ( $\tau > 0$ ).

### 3 Model fitting

Observing two groups of observations, we assume the *labelled* observations are in class **A**, and the *unlabelled* observations are in class **A** or in class **B**.

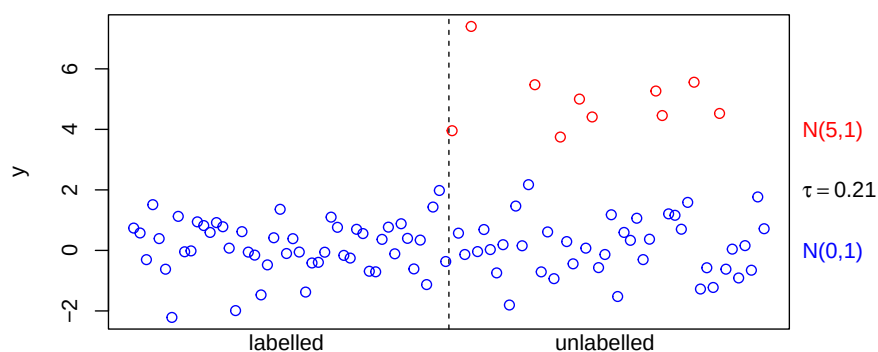


The function `mixture` estimates the unknown parameters and predicts the missing class labels:

```
fit <- mixture(y,z)
```

Here, 21% of the *unlabelled* observations are assigned to class **B**, and all other observations are assigned to class **A**:

```
class <- round(fit$posterior)
```



These are the parameter estimates:

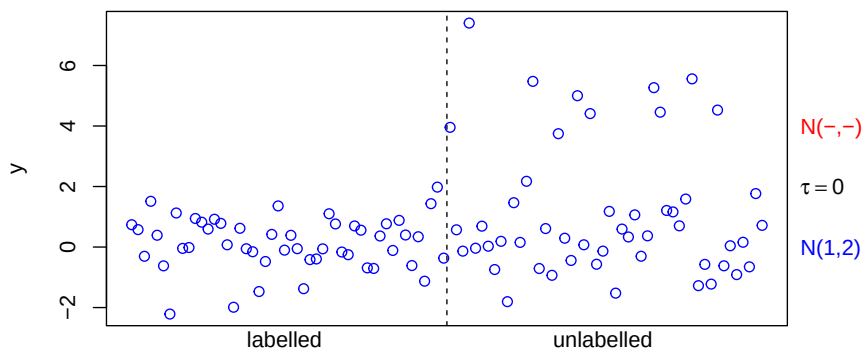
```
fit$estim1
```

## 4 Hypothesis testing

Under the null hypothesis, all observations are in class **A**. Under the alternative hypothesis, some *unlabelled* observations are in class **B**.

The function `mixture` not only fits the model under the alternative hypothesis (see above), but also under the null hypothesis:

```
fit$estim0
```



Because the null distribution of the likelihood-ratio test statistic is unknown, we compare the hypotheses by resampling. The function `scrutor` uses parametric bootstrapping or permutation:

```
scrutor(y,z)
```

If the  $p$ -value is less than or equal to the significance level, we reject the null hypothesis in favour of the alternative hypothesis.

## Options

The functions `mixture` and `scrutor` have similar arguments. Set `dist` equal to "norm" or "nbinom" to choose between the Gaussian and the negative binomial distributions. In the latter case, optionally provide a dispersion estimate `phi` or an offset `gamma`. All other arguments are technical.

## 5 Application

### 5.1 Data preparation

Let  $n$  be the sample size,  $q$  the number of quantitative traits, and  $p$  the number of single nucleotide polymorphisms (SNPs).

- Transform the quantitative trait to a vector of length  $n$ , or transform the quantitative traits to a matrix with  $n$  rows (samples) and  $q$  columns (variables).
- Transform the SNP to a vector of length  $n$ , or transform the SNPs to a matrix with  $n$  rows (samples) and  $p$  columns (variables).
- Binarise the SNP(s), indicating the *labelled* group by zero, and the *unlabelled* group by a missing value.

For example, assign observations with zero minor alleles to the *labelled* group, and those with one or two minor alleles to the *unlabelled* group:

```
n <- length(snp)
```

```
z <- rep(NA, times=n)  
z[snp==0] <- 0
```

```
n <- nrow(SNPs)
```

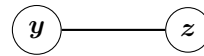
```
p <- ncol(SNPs)
```

```
Z <- matrix(NA, nrow=n, ncol=p)  
Z[SNPs==0] <- 0
```

### 5.2 Test of association

Use `scrutor` to test for association between a quantitative trait (vector) and a SNP (vector). The function returns a test statistic and a  $p$ -value.

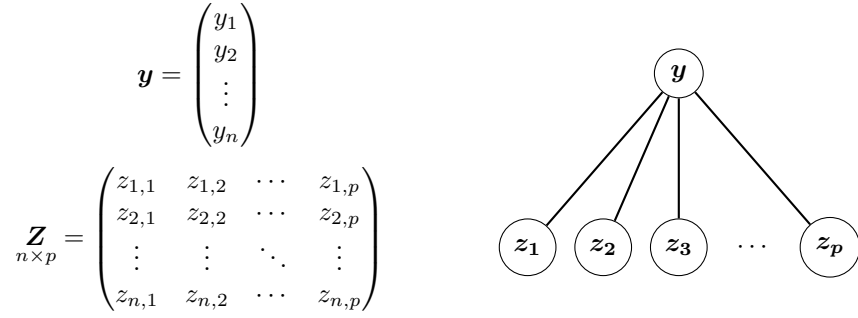
$$\mathbf{y} = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix} \quad \mathbf{z} = \begin{pmatrix} z_1 \\ z_2 \\ \vdots \\ z_n \end{pmatrix}$$



```
scrutor(y, z)
```

### 5.3 Genome-wide association study

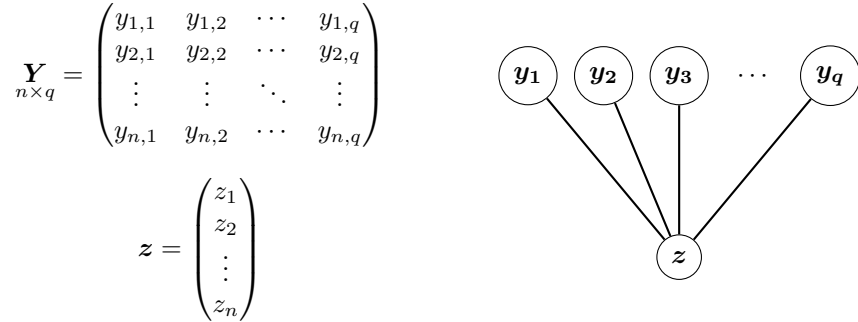
Use `scrutor` to test for association between a quantitative trait (vector) and several SNPs (matrix). For each SNP, the function returns a test statistic and a  $p$ -value.



```
scrutor(y, Z)
```

### 5.4 Differential expression analysis

Use `scrutor` to test for association between several quantitative traits (matrix) and a SNP (vector). For each quantitative trait, the function returns a test statistic and a  $p$ -value.



```
scrutor(Y, z)
```

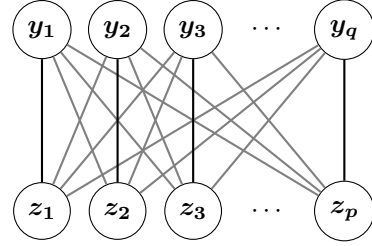
### 5.5 Expression quantitative trait loci analysis

Use `scrutor` to test for association between several quantitative traits (matrix) and several SNPs (matrix). If their numbers are different, all pairwise combinations are considered. If their numbers are equal, a one-to-one correspondence

is assumed. For each combination, the function returns a test statistic and a  $p$ -value.

$$\mathbf{Y}_{n \times q} = \begin{pmatrix} y_{1,1} & y_{1,2} & \cdots & y_{1,q} \\ y_{2,1} & y_{2,2} & \cdots & y_{2,q} \\ \vdots & \vdots & \ddots & \vdots \\ y_{n,1} & y_{n,2} & \cdots & y_{n,q} \end{pmatrix}$$

$$\mathbf{Z}_{n \times p} = \begin{pmatrix} z_{1,1} & z_{1,2} & \cdots & z_{1,p} \\ z_{2,1} & z_{2,2} & \cdots & z_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ z_{n,1} & z_{n,2} & \cdots & z_{n,p} \end{pmatrix}$$



```
scrutor(Y,Z)
```

## References

The R package **semisup** is based on Rauschenberger et al. [1], where detailed references to previous work are given. If you use **semisup** for publications, please cite Rauschenberger et al. [1].

Consider shrinkage estimation (Robinson et al. [3]) and scale normalisation (Robinson et al. [2]) to improve the negative binomial mixture model (R package **edgeR**). Use the non-parametric mixture test (van Wieringen et al. [4]) to increase robustness against outliers (R package **PDGETest**).

- [1] Armin Rauschenberger, Renée X Menezes, Mark A van de Wiel, Natasja M van Schoor, and Marianne A Jonker. Detecting SNPs with interactive effects on a quantitative trait. *Manuscript in preparation*, 0:0, 2018.
- [2] Mark D Robinson and Alicia Oshlack. A scaling normalization method for differential expression analysis of RNA-Seq data. *Genome Biology*, 11(3):R25, 2010. [link](#).
- [3] Mark D Robinson and Gordon K Smyth. Small-sample estimation of negative binomial dispersion, with applications to SAGE data. *Biostatistics*, 9(2):321–332, 2008. [link](#).
- [4] Wessel N Van Wieringen, Mark A van de Wiel, and Aad W van der Vaart. A test for partial differential expression. *Journal of the American Statistical Association*, 103(483):1039–1049, 2008. [link](#).