BEclearCL Documentation

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Abstract

This Command-Line tool provides functions to detect and correct for batch effects in DNA methylation data. The core function for the data imputation is based on latent factor models (Candès and Recht 2009) and can also be used to predict missing values in any other matrix containing real numbers. In this documentation we guide you through the installation and usage of it. For the corresponding R-package visit *BEclear* (Akulenko, Merl, and Helms 2016).

1 Getting Started

For using the Command-Line version of BEclear, you need to have R with a version of at least 3.5 installed on your system. Furthermore you need the following R packages:

- *BEclear* (>= 2.0)
- *optparse*

To install them you can either run our provided `install.R` script or install them by typing the following in your R environment:

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

BiocManager::install("BEclear")

install.packages("optparse")
```

To make the Command-Line tool executable, you need to call:

```
chmod +x BEclearCL.R
```

2 Usage

In the following we will document the Command-Line parameters of the tool and the format of input and output.

3 Theoretical Background

In this section we explain the theoretical background behind the method.

3.1 Detection of batch effects

For the detection of batch effects we calculate the median difference between the beta values of a gene in a batch and the values of this gene in all other batches. Furthermore we use a non-parametric Kolmogorov-Smirnov test (`ks.test`) to compare the distribution of the beta value for this gene in the batch and the other batches.

If one gene in a batch has a p-value determined by the `ks.test` of less or equal 0.01 and a median difference of greater or equal 0.05 it is considered batch effected. By default the p-values are adjusted by the false discovery rate developed by Benjamini and Hochberg (1995).

3.2 Imputation of missing values

For the imputation of missing values we use a slightly modified version of the stochastic gradient descent method described by Koren, Bell, and Volinsky (2009). In this section we will describe our implementation of this method and how to use it.

We assume that our complete data matrix D_{ij} can be described by the effects of a matrix L_i, which represents the effect of the features (genes in our case) and a matrix R_j describing the effect of the samples in the following way:

$$D_{ij} = L_i^T \times R_j \tag{1}$$

The method can either be run on the complete data set or the data set can be divided into blocks on which the method is applied. This division into blocks allows for parallelisation of the method, which can be useful to speed up the process. We have found that a block-size of 60x60 works well(Akulenko, Merl, and Helms 2016).

$$errorMatrix_{ij} = Block_{ij} - L_i^T \times R_j \tag{2}$$

We try to minimalise the following loss function through a gradient descent:

$$min_{L,R} \sum_{ij \in K} (errorMatrix_{ij}^2) + \lambda \times (\|L_i\|_F^2 + \|R_j\|_F^2) \tag{3}$$

Where K is the set of tuples (i, j) for which the value is present. λ is the penalty coefficient, which controls how restrictive the selection of variables should be. The default of λ is 1.

Another coefficient γ controls the size of the step by which the two matrices L_i and R_j are modified. It is initialized by default with 0.01 and its value changes during the iterations (epochs).

For the first iteration the matrices L_i and R_j are filled with random values generated by the `rnorm` function from the *stats* package and the initial loss and error matrix are calculated.

Then for each iteration the following is done:

- L_i and R_j are modified proportional by γ through the following calculation:
  - $$L_i = L_i + 2 \times \gamma \times (errorMatrix_{ij} \times R_j - \lambda \times L_i) \tag{4}$$
  - $$R_j = R_j + 2 \times \gamma \times (errorMatrix_{ij} \times L_i - \lambda \times R_j) \tag{5}$$

- Then the new error matrix and loss are calculated.
- If the old loss is smaller than the new one:
  - $\gamma = \gamma \div 2$
- Else:
  - $\gamma = \gamma \times 1.05$

The L_i and R_j matrices at the end of the last iteration are then used to impute the missing data. The default number of iterations is 50.

References

Akulenko, Ruslan, Markus Merl, and Volkhard Helms. 2016. "BEclear: Batch effect detection and adjustment in DNA methylation data." *PLoS ONE* 11 (8): 1–17. https://doi.org/10.1371/journal.pone.0159921.

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Candès, Emmanuel J., and Benjamin Recht. 2009. "Exact Matrix Completion via Convex Optimization." *Foundations of Computational Mathematics* 9 (6): 717–72. https://doi.org/10.1007/s10208-009-9045-5.

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