An Introduction to the *REMP* Package

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Contents

1 Introduction

REMP predicts DNA methylation of locus-specific repetitive elements (RE) by learning surrounding genetic and epigenetic information. *REMP* provides genomewide single-base resolution of DNA methylation on RE that are difficult to measure directly using array-based or sequencing-based platforms, which enables epigenome-wide association study (EWAS) and differentially methylated region (DMR) analysis on RE.

REMP supports both Illumina methylation BeadChip array platforms (450k and EPIC) and sequencing platforms (e.g. TruSeq Methyl Capture EPIC).

2 Installation

Install *REMP* (release version):

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

To install devel version:

```
> library(devtools)
> install_github("YinanZheng/REMP")
```

Load *REMP* into the workspace:

```
> library(REMP)
```

3 REMP: Repetitive Element Methylation Prediction

Currently *REMP* supports Human (hg19, build 37) Alu and LINE-1 (L1) repetitive element (RE) methylation prediction using Illumina 450k or EPIC array.

3.1 Groom methylation data

Appropriate data preprocessing including quality control and normalization of methylation data are recommended before running *REMP*. Many packages are available to carry out these data preprocessing steps, for example, *minfi*, *wateRmelon*, and *methylumi*.

REMP is trying to minimize the requirement of the methylation data format. User can maintain the methylation data in *RatioSet* or *GenomicRatioSet* object offered by *minfi*, *data.table*, *data.frame*, *DataFrame*, or *matrix*. User can input either beta value or M-value. There are only two basic requirements of the methylation data:

1. Each row should represent CpG probe and each column should represent sample.
2. The row names should indicate Illumina probe ID (i.e. cg00000029).

However, there are some other common data issues that may prevent *REMP* from running correctly. For example, if the methylation data are in beta value and contain zero methylation values, logit transformation (to create M-value) will create negative infinite value; or the methylation data contain `NA`, `Inf`, or `NaN` data. To tackle these potential issues, *REMP* includes a handy function `grooMethy` which can help detect and fix these issues. We highly recommend to take advantage of this function:

```
> # Get GM12878 methylation data (450k array)
> GM12878_450k <- getGM12878('450k')
> GM12878_450k <- grooMethy(GM12878_450k, verbose = TRUE)
> GM12878_450k
```

```
class: RatioSet
dim: 482421 1
metadata(0):
assays(2): Beta M
rownames(482421): cg00000029 cg00000108 ...
  cg27666046 cg27666123
rowData names(0):
colnames(1): GM12878
colData names(0):
Annotation
  array: IlluminaHumanMethylation450k
  annotation: ilmn12.hg19
Preprocessing
  Method: NA
  minfi version: NA
  Manifest version: NA
```

For zero beta values, `grooMethy` will replace them with smallest non-zero beta value. For one beta values, `grooMethy` will replace them with largest non-one beta value. For `NA`/`NaN`/`Inf` values, `grooMethy` will treat them as missing values and then apply KNN-imputation to complete the dataset. If the imputed value is out of the original range (which is possible when `imputebyrow = FALSE`), mean value will be used instead. Warning: imputed values for multimodal distributed CpGs (across samples) may not be correct. Please check package *ENmix* to identify the CpGs with multimodal distribution.

3.2 Prepare annotation data

To run *REMP* for RE methylation prediction, user first needs to prepare some annotation datasets. The function `initREMP` is designed to do the job.

Suppose user will predict Alu methylation using Illumina 450k array data:

```
> data(Alu.demo)
> remparcel <- initREMP(arrayType = "450k", REtype = "Alu",
+                       RE = Alu.demo, ncore = 1)
> remparcel
```

```
REMParcel object
RE type: Alu
Illumina platform: 450k
Valid (max) Alu-CpG flanking window size: 1200
Number of RE: 500
Number of Alu-CpG: 5039
```

For demonstration, we only use 500 selected Alu sequence dataset which comes along with the package (`Alu.demo`). We specify `RE = Alu.demo`, so that the annotation dataset will be generated for the 500 selected Alu sequences. Most of the time, specifying `RE` is not necessary, as the function will fetch the complete RE sequence dataset from package *AnnotationHub* using `fetchRMSK`. User can also use this argument `RE` to provide customized RE dataset.

All data are stored in the *REMParcel* object:

```
> saveParcel(remparcel)
```

It is recommended to specify a working directory using argument `work.dir` so that the data generated can be preserved for later use. Without specifying working directory , the annotation dataset will be created under the temporal directory `tempdir()` by default. User can also turn on the `export` parameter in `initREMP` to save the data automatically.

3.3 Run prediction

Once the annotation data are ready, user can pass the annotation data parcel to `remp` for prediction:

```
> remp.res <- remp(GM12878_450k, REtype = 'Alu',
+                  parcel = remparcel, ncore = 1, seed = 777)
```

If `parcel` is missing, `remp` will then try to search the REMParcel data file in the directory indicated by `work.dir`. If `work.dir` is also missing, `remp` will try to search the REMParcel data file in the temporal directory `tempdir()`.

By default, `remp` uses Random Forest (`method = 'rf'`) model (package *randomForest*) for prediction. Random Forest model is recommended because it offers more accurate prediction results and it automatically enables Quantile Regression Forest (Nicolai Meinshausen, 2006) for prediction reliability evaluation. `remp` constructs predictors to carry out the prediction. For Random Forest model, the tuning parameter `param = 6` (i.e. `mtry` in *randomForest*) indicates how many predictors will be randomly selected for building the individual trees. The performance of random forest model is often relatively insensitive to the choice of `mtry`. Therefore, auto-tune will be turned off using random forest and `mtry` will be set to one third of the total number of predictors. It is recommended to specify a seed for reproducible prediction results.

`remp` will return a *REMPset* object, which inherits Bioconductor's *RangedSummarizedExperiment* class:

```
> remp.res
```

```
class: REMProduct
dim: 4808 1
metadata(8): REannotation RECpG ... GeneStats Seed
assays(3): rempB rempM rempQC
rownames: NULL
rowData names(1): RE.Index
colnames(1): GM12878
colData names(1): mtry
```

```
> # Display more detailed information
> details(remp.res)
```

```
RE type: Alu
Methylation profiling platform: 450k
Flanking window size: 1000
Prediction model: Random Forest
QC model: Quantile Regression Forest
Seed: 777
Covered 4808 CpG sites in 500 Alu

Number of Alu-CpGs by chromosome:
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
 449  276  293  131  179  397  292  102

 chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
   98   148   254   310    66   127   133   333

chr17 chr18 chr19 chr20 chr21 chr22
  295    81   674    66    37    67

Training information:
  500 profiled Alu are used for model training.
  481 Alu-CpGs that have at least 2 neighboring profiled CpGs are used for model training.

Coverage information:
  The data cover 500 Alu (4808 Alu-CpG).
  Gene coverage by Alu (out of total refSeq Gene):
    491 (1.97%) total genes;
    412 (2.15%) protein-coding genes;
    117 (1.61%) non-coding RNA genes.

Distribution of methylation value (beta value):
      Min.    1st Qu.     Median       Mean    3rd Qu.
0.03481766 0.45999624 0.65474244 0.59260625 0.75666480
      Max.
0.91885158

Distribution of reliability score:
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
0.7251337 1.4865521 1.7800897 1.8261698 2.0955836 5.6598652
```

Prediction results can be obtained by accessors:

```
> # Predicted RE-CpG methylation value (Beta value)
> rempB(remp.res)

DataFrame with 4808 rows and 1 column
              GM12878
            <numeric>
1    0.768885549752794
2    0.799963566842138
3      0.8082617002297
4    0.812220385522142
5    0.815500857759039
...                ...
4804 0.456434392295061
4805 0.452531714325116
```

```
4806 0.448370644949496
4807 0.451134860306801
4808 0.453391424438599

> # Predicted RE-CpG methylation value (M value)
> rempM(remp.res)

DataFrame with 4808 rows and 1 column
                GM12878
              <numeric>
1      1.73416139996151
2      1.99967151033736
3      2.07568394219424
4      2.11283078597944
5      2.14407228535569
...                 ...
4804 -0.252046674612878
4805 -0.274756490476862
4806 -0.299007404889258
4807 -0.282892940734084
4808 -0.269750990171014

> # Genomic location information of the predicted RE-CpG
> # Function inherit from class 'RangedSummarizedExperiment'
> rowRanges(remp.res)

GRanges object with 4808 ranges and 1 metadata column:
         seqnames            ranges strand |    RE.Index
            <Rle>         <IRanges>  <Rle> |       <Rle>
     [1]     chr1     943927-943928      - | Alu_0000527
     [2]     chr1     943935-943936      - | Alu_0000527
     [3]     chr1     943968-943969      - | Alu_0000527
     [4]     chr1     943974-943975      - | Alu_0000527
     [5]     chr1     943991-943992      - | Alu_0000527
     ...      ...               ...    ... .         ...
  [4804]    chr22 42095154-42095155      - | Alu_1170175
  [4805]    chr22 42095161-42095162      - | Alu_1170175
  [4806]    chr22 42095170-42095171      - | Alu_1170175
  [4807]    chr22 42095198-42095199      - | Alu_1170175
  [4808]    chr22 42095214-42095215      - | Alu_1170175
  -------
  seqinfo: 93 sequences from an unspecified genome; no seqlengths

> # Standard error-scaled permutation importance of predictors
> rempImp(remp.res)

DataFrame with 15 rows and 1 column
                       GM12878
                     <numeric>
RE.score       6.13059362426789
RE.Length      6.91960534441026
RE.CpG.density 5.23214258656752
RE.InTSS       2.47383626459844
RE.In5UTR      4.79381513664218
...                         ...
```

```
distance.min2  13.2878985734492
Methy.min      28.8720204839864
Methy.min2     11.5198782664128
Methy.mean      11.285577243543
Methy.std      3.47582843597306
```

```
> # Retrive seed number used for the reesults
> metadata(remp.res)$Seed
```

```
[1] 777
```

Trim off less reliable predicted results:

```
> # Any predicted CpG values with quality score less than
> # threshold (default = 1.7) will be replaced with NA.
> # CpGs contain more than missingRate * 100% (default = 20%)
> # missing rate across samples will be discarded.
> remp.res <- rempTrim(remp.res, threshold = 1.7, missingRate = 0.2)
> details(remp.res)
```

```
RE type: Alu
Methylation profiling platform: 450k
Flanking window size: 1000
Prediction model: Random Forest - trimmed (1.7)
QC model: Quantile Regression Forest
Seed: 777
Covered 2068 CpG sites in 388 Alu

Number of Alu-CpGs by chromosome:
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
 197  118  140   63   79  201  128   58

 chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
   40    76    74   112    15    89    17   156

chr17 chr18 chr19 chr20 chr21 chr22
  142    30   267    38     5    23

Coverage information:
  The data cover 388 Alu (2068 Alu-CpG).
  Gene coverage by Alu (out of total refSeq Gene):
    376 (1.51%) total genes;
    312 (1.63%) protein-coding genes;
    88 (1.21%) non-coding RNA genes.

Distribution of methylation value (beta value):
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
0.0689806 0.6696456 0.7515249 0.7072482 0.7966527 0.9169446

Distribution of reliability score:
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
0.7251337 1.3036668 1.4502028 1.4293100 1.5798642 1.6993111
```

(Optional) Aggregate the predicted methylation of CpGs in RE by averaging them to obtain the RE-specific methylation level:

```
> remp.res <- rempAggregate(remp.res, NCpG = 2)
> details(remp.res)

RE type: Alu (aggregated by mean: min # of CpGs: 2)
Methylation profiling platform: 450k
Flanking window size: 1000
Prediction model: Random Forest - trimmed (1.7)
QC model: Quantile Regression Forest
Seed: 777
Covered 291 Alu (aggregated by mean: min # of CpGs: 2)

Number of Alu (aggregated by mean: min # of CpGs: 2) by chromosome:
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
  29   13   20   12    9   30   19    8

 chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
    6    12    11    13     2    10     4    19

chr17 chr18 chr19 chr20 chr21 chr22
   18     6    39     7     1     3

Coverage information:
  The data cover 291 Alu (aggregated by mean: min # of CpGs: 2)
  Gene coverage by Alu (aggregated by mean: min # of CpGs: 2) (out of total refSeq Gene):
    274 (1.1%) total genes;
    232 (1.21%) protein-coding genes;
    57 (0.79%) non-coding RNA genes.

Distribution of methylation value (beta value):
      Min.    1st Qu.     Median       Mean    3rd Qu.
0.09429169 0.63521936 0.72732788 0.68893442 0.78857025
      Max.
0.89106795

Distribution of reliability score:
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
0.8944415 1.3379132 1.4551258 1.4383820 1.5505395 1.6959993
```

Aggregating CpGs in the same RE for RE-level methylation data is beneficial because 1) it greatly reduces the data dimension for downstream analysis and 2) it may produce more robust RE methylation estimation. Note that by default, RE with 2 or more predicted CpG sites will be aggregated. Therefore, the downside of doing this is the reduced coverage of RE. The assumption of doing this is the CpG methylation level within each RE are similar.

To add genomic regions annotation of the predicted REs:

```
> # By default gene symbol annotation will be added
> remp.res <- decodeAnnot(remp.res)
> rempAnnot(remp.res)

GRanges object with 291 ranges and 10 metadata columns:
        seqnames            ranges strand |        name
           <Rle>         <IRanges>  <Rle> | <character>
    [1]     chr1     943896-944203      - |      AluSq2
    [2]     chr1   1197026-1197260      - |        AluY
    [3]     chr1   1885941-1886230      + |       AluJb
    [4]     chr1   6265537-6265810      - |       AluSz
```

```
  [5]     chr1   7914008-7914123      + |       AluJb
  ...      ...               ...    ... .         ...
[287]    chr20 57413692-57413996      + |       AluSz
[288]    chr21 34146037-34146235      - |       AluSx
[289]    chr22 22987350-22987681      - |        AluY
[290]    chr22 24103787-24104072      + |      AluSx1
[291]    chr22 27050687-27050975      - |        AluY
         score       Index InNM.symbol
     <numeric>       <Rle> <character>
  [1]      2417 Alu_0000527        <NA>
  [2]      1697 Alu_0000636      UBE2J2
  [3]      1962 Alu_0001407      CFAP74
  [4]      2092 Alu_0002477      RNF207
  [5]      1680 Alu_0003481        UTS2
  ...       ...         ...         ...
[287]      2424 Alu_1136815        GNAS
[288]      1107 Alu_1144838      PAXBP1
[289]      2378 Alu_1156182      GGTLC2
[290]      1980 Alu_1156753    C22orf15
[291]      2468 Alu_1158731        <NA>
            InNR.symbol     InTSS.symbol In5UTR.symbol
            <character>      <character>   <character>
  [1]               <NA>             <NA>          <NA>
  [2]               <NA>             <NA>          <NA>
  [3]               <NA>             <NA>          <NA>
  [4]               <NA>           RNF207          <NA>
  [5]               <NA>             UTS2          <NA>
  ...                ...              ...           ...
[287]         GNAS-AS1             GNAS          <NA>
[288] PAXBP1|C21orf62-AS1           PAXBP1          <NA>
[289]       POM121L1P POM121L1P|GGTLC2        GGTLC2
[290]            <NA>         C22orf15          <NA>
[291]            <NA>             <NA>          <NA>
     InCDS.symbol InExon.symbol In3UTR.symbol
      <character>   <character>   <character>
  [1]         <NA>          <NA>          <NA>
  [2]       UBE2J2          <NA>          <NA>
  [3]         <NA>        CFAP74        CFAP74
  [4]         <NA>          <NA>          <NA>
  [5]         <NA>          <NA>          <NA>
  ...          ...           ...           ...
[287]         <NA>          <NA>          <NA>
[288]         <NA>          <NA>          <NA>
[289]         <NA>          <NA>          <NA>
[290]         <NA>          <NA>          <NA>
[291]         <NA>          <NA>          <NA>
-------
seqinfo: 93 sequences (1 circular) from hg19 genome
```

Seven genomic region indicators will be added to the annotation data in the input *REMProduct* object:

- InNM: in protein-coding genes (overlap with refSeq gene's "NM" transcripts + 2000 bp upstream of the transcription start site (TSS))
- InNR: in noncoding RNA genes (overlap with refSeq gene's "NR" transcripts + 2000 bp upstream of the TSS)

- InTSS: in flanking region of 2000 bp upstream of the TSS. Default upstream limit is 2000 bp, which can be modified globally using `remp_options`
- In5UTR: in 5'untranslated regions (UTRs)
- InCDS: in coding DNA sequence regions
- InExon: in exon regions
- In3UTR: in 3'UTRs

Note that intron region and intergenic region information can be derived from the above genomic region indicators: if "InNM" and/or "InNR" is not missing but "InTSS", "In5UTR", "InExon", and "In3UTR" are missing, then the RE is strictly located within intron region; if all indicators are missing, then the RE is strictly located in intergenic region.

3.4 Plot prediction

Make a density plot of the predicted methylation (beta values):

```
> remplot(remp.res, main = "Alu methylation (GM12878)", col = "blue")
```

4 Extract RE-CpG methylation profiled by Illumina BeadChip array

REMP offers a handy tool to extract methylation data of CpGs that are located in RE.

```
> # Use Alu.demo for demonstration
> remp.res <- remprofile(GM12878_450k, REtype = "Alu", RE = Alu.demo)
> details(remp.res)

RE type: Alu
Methylation profiling platform: 450k
Flanking window size: N/A
Prediction model: Profiled
QC model: N/A
Covered 594 CpG sites in 500 Alu

Number of Alu-CpGs by chromosome:
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
  51   38   39   20   21   61   39   13

 chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
   11    22    25    31     8    15    21    34

chr17 chr18 chr19 chr20 chr21 chr22
   28    11    82    11     4     9

Coverage information:
  The data cover 500 Alu (594 Alu-CpG).
  Gene coverage by Alu (out of total refSeq Gene):
    491 (1.97%) total genes;
    412 (2.15%) protein-coding genes;
    117 (1.61%) non-coding RNA genes.

Distribution of methylation value (beta value):
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
0.0010000 0.4232500 0.6695000 0.6052828 0.8280000 0.9710000

> # All accessors and utilites for REMProduct are applicable
> remp.res <- rempAggregate(remp.res)
> details(remp.res)

RE type: Alu (aggregated by mean: min # of CpGs: 2)
Methylation profiling platform: 450k
Flanking window size: N/A
Prediction model: Profiled
QC model: N/A
Covered 75 Alu (aggregated by mean: min # of CpGs: 2)

Number of Alu (aggregated by mean: min # of CpGs: 2) by chromosome:
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
   5    7    6    3    3   11    5    1

chr10 chr11 chr12 chr13 chr14 chr15 chr16 chr17
    1     1     4     1     2     4     3     1

chr18 chr19 chr20 chr22
```

```
    3    11     2     1

Coverage information:
  The data cover 75 Alu (aggregated by mean: min # of CpGs: 2)
  Gene coverage by Alu (aggregated by mean: min # of CpGs: 2) (out of total refSeq Gene):
    86 (0.34%) total genes;
    71 (0.37%) protein-coding genes;
    17 (0.23%) non-coding RNA genes.

Distribution of methylation value (beta value):
      Min.    1st Qu.     Median       Mean    3rd Qu.
0.04713393 0.42243309 0.66087749 0.59936950 0.83849455
      Max.
0.92886423
```

5 Session Information

```
R version 3.6.0 (2019-04-26)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 18.04.2 LTS

Matrix products: default
BLAS:   /home/biocbuild/bbs-3.9-bioc/R/lib/libRblas.so
LAPACK: /home/biocbuild/bbs-3.9-bioc/R/lib/libRlapack.so

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=en_US.UTF-8        LC_COLLATE=C
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] parallel  stats4    stats     graphics  grDevices
[6] utils     datasets  methods   base

other attached packages:
 [1] REMP_1.8.0
 [2] IlluminaHumanMethylationEPICanno.ilm10b2.hg19_0.6.0
 [3] IlluminaHumanMethylation450kanno.ilmn12.hg19_0.6.0
 [4] minfi_1.30.0
 [5] bumphunter_1.26.0
 [6] locfit_1.5-9.1
 [7] iterators_1.0.10
 [8] foreach_1.4.4
 [9] Biostrings_2.52.0
[10] XVector_0.24.0
[11] SummarizedExperiment_1.14.0
[12] DelayedArray_0.10.0
[13] BiocParallel_1.18.0
[14] matrixStats_0.54.0
[15] Biobase_2.44.0
```

```
[16] GenomicRanges_1.36.0
[17] GenomeInfoDb_1.20.0
[18] IRanges_2.18.0
[19] S4Vectors_0.22.0
[20] BiocGenerics_0.30.0
[21] knitr_1.22

loaded via a namespace (and not attached):
  [1] AnnotationHub_2.16.0
  [2] BiocFileCache_1.8.0
  [3] plyr_1.8.4
  [4] lazyeval_0.2.2
  [5] splines_3.6.0
  [6] ggplot2_3.1.1
  [7] digest_0.6.18
  [8] htmltools_0.3.6
  [9] magrittr_1.5
 [10] memoise_1.1.0
 [11] BSgenome_1.52.0
 [12] doParallel_1.0.14
 [13] limma_3.40.0
 [14] recipes_0.1.5
 [15] readr_1.3.1
 [16] annotate_1.62.0
 [17] gower_0.2.0
 [18] askpass_1.1
 [19] siggenes_1.58.0
 [20] prettyunits_1.0.2
 [21] colorspace_1.4-1
 [22] blob_1.1.1
 [23] rappdirs_0.3.1
 [24] xfun_0.6
 [25] dplyr_0.8.0.1
 [26] settings_0.2.4
 [27] crayon_1.3.4
 [28] RCurl_1.95-4.12
 [29] genefilter_1.66.0
 [30] impute_1.58.0
 [31] GEOquery_2.52.0
 [32] survival_2.44-1.1
 [33] glue_1.3.1
 [34] registry_0.5-1
 [35] gtable_0.3.0
 [36] ipred_0.9-9
 [37] zlibbioc_1.30.0
 [38] kernlab_0.9-27
 [39] Rhdf5lib_1.6.0
 [40] HDF5Array_1.12.0
 [41] scales_1.0.0
 [42] DBI_1.0.0
 [43] rngtools_1.3.1.1
 [44] bibtex_0.4.2
 [45] Rcpp_1.0.1
 [46] xtable_1.8-4
```

```
 [47] progress_1.2.0
 [48] bit_1.1-14
 [49] mclust_5.4.3
 [50] preprocessCore_1.46.0
 [51] lava_1.6.5
 [52] prodlim_2018.04.18
 [53] httr_1.4.0
 [54] RColorBrewer_1.1-2
 [55] pkgconfig_2.0.2
 [56] reshape_0.8.8
 [57] XML_3.98-1.19
 [58] nnet_7.3-12
 [59] dbplyr_1.4.0
 [60] caret_6.0-84
 [61] tidyselect_0.2.5
 [62] rlang_0.3.4
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