

An Introduction to the *REMP* Package

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May 4, 2019

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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 `groomMethy` 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 <- groomMethy(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, `groomMethy` will replace them with smallest non-zero beta value. For one beta values, `groomMethy` will replace them with largest non-one beta value. For NA/NaN/Inf values, `groomMethy` 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

```

```

REMPParcel 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 *REMPParcel* 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 *REMPParcel* data file in the directory indicated by `work.dir`. If `work.dir` is also missing, `remp` will try to search the *REMPParcel* 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 hg19 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.
0.02874938	0.43376623	0.67667562	0.59945612	0.77309994
Max.				
0.91582549				

Distribution of reliability score:

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.5813885	1.3273597	1.6619555	1.7149902	2.0423184	5.7482651

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 0.816686857338541
2 0.821153094907731
3 0.820738668295185
4 0.823437529888668
5 0.82633793661065
...
4804 0.460901915716023
4805 0.404909947820103
```

```

4806 0.403652400896257
4807 0.381116002186071
4808 0.395271454284738

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

DataFrame with 4808 rows and 1 column
      GM12878
      <numeric>
1      2.15547278728556
2      2.19892606858779
3      2.19485860669642
4      2.22148048580896
5      2.25044927179775
...
4804 -0.226088018700757
4805 -0.555506913643792
4806 -0.563040021207817
4807 -0.699438834480699
4808 -0.613443911469568

> # 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 18 rows and 1 column
      GM12878
      <numeric>
RE.score      7.81335061184096
RE.Length     3.97239343456501
RE.CpG.density 6.08865823018943
RE.InTSS      2.45435672372131
RE.In5UTR     2.42268860968164
...

```

```
Methy.mean.mov1 15.5055800080439
Methy.mean.mov2 11.079203125388
Methy.mean.mov3 8.50757051660798
Methy.mean.mov4 5.91653364225333
Methy.std        3.6930835504382
```

```
> # Retrieve seed number used for the results
> 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 2520 CpG sites in 396 Alu
```

Number of Alu-CpGs by chromosome:

```
chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8
 250  157  168   76  100  243  138   61

chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
  46   97  101  136   23  108   27  178

chr17 chr18 chr19 chr20 chr21 chr22
 162   44  302   47   14   42
```

Coverage information:

```
The data cover 396 Alu (2520 Alu-CpG).
Gene coverage by Alu (out of total hg19 refSeq Gene):
 383 (1.53%) total genes;
 315 (1.64%) protein-coding genes;
 90 (1.24%) non-coding RNA genes.
```

Distribution of methylation value (beta value):

```
Min.      1st Qu.      Median      Mean      3rd Qu.
0.07871552 0.67721325 0.74438242 0.71226295 0.80296306
Max.
0.91582549
```

Distribution of reliability score:

```
Min.      1st Qu.      Median      Mean      3rd Qu.      Max.
0.5813885 1.2128552 1.3395243 1.3439807 1.4927728 1.6984400
```

(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 322 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
  32  20  23  11  12  32  19   7

chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16
   5   15   14   17   3   10   4   21

chr17 chr18 chr19 chr20 chr21 chr22
  19   6   39   7   2   4
```

Coverage information:

```
The data cover 322 Alu (aggregated by mean: min # of CpGs: 2)
Gene coverage by Alu (aggregated by mean: min # of CpGs: 2) (out of total hg19 refSeq Gene):
  312 (1.25%) total genes;
  259 (1.35%) protein-coding genes;
  70 (0.96%) non-coding RNA genes.
```

Distribution of methylation value (beta value):

```
Min.      1st Qu.      Median      Mean      3rd Qu.
0.09259713 0.64246956 0.72631429 0.68626391 0.79452435
Max.
0.88508196
```

Distribution of reliability score:

```
Min.      1st Qu.      Median      Mean      3rd Qu.      Max.
0.7891364 1.2400293 1.3554436 1.3600592 1.4787086 1.6943242
```

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 322 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
...
[318] chr21 37506146-37506436 - | AluSg
[319] chr22 18464632-18464890 + | AluJb
[320] chr22 22987350-22987681 - | AluY
[321] chr22 24103787-24104072 + | AluSx1
[322] chr22 27050687-27050975 - | AluY

```

	score	Index	InNM.symbol	InNR.symbol
	<numeric>	<Rle>	<character>	<character>
[1]	2417	Alu_0000527	<NA>	<NA>
[2]	1697	Alu_0000636	UBE2J2	<NA>
[3]	1962	Alu_0001407	CFAP74	<NA>
[4]	2092	Alu_0002477	RNF207	<NA>
[5]	1680	Alu_0003481	UTS2	<NA>
...
[318]	2311	Alu_1146404	CBR3	CBR3-AS1
[319]	1683	Alu_1152604	MICAL3	MIR648
[320]	2378	Alu_1156182	GGTLC2	POM121L1P
[321]	1980	Alu_1156753	C22orf15	<NA>
[322]	2468	Alu_1158731	<NA>	<NA>

	InTSS.symbol	In5UTR.symbol	InCDS.symbol
	<character>	<character>	<character>
[1]	<NA>	<NA>	<NA>
[2]	<NA>	<NA>	UBE2J2
[3]	<NA>	<NA>	<NA>
[4]	RNF207	<NA>	<NA>
[5]	UTS2	<NA>	<NA>
...
[318]	CBR3	<NA>	<NA>
[319]	MIR648	MICAL3	<NA>
[320]	POM121L1P GGTLC2	GGTLC2	<NA>
[321]	C22orf15	<NA>	<NA>
[322]	<NA>	<NA>	<NA>

	InExon.symbol	In3UTR.symbol
	<character>	<character>
[1]	<NA>	<NA>
[2]	<NA>	<NA>
[3]	CFAP74	CFAP74
[4]	<NA>	<NA>
[5]	<NA>	<NA>
...
[318]	<NA>	<NA>
[319]	<NA>	<NA>
[320]	<NA>	<NA>
[321]	<NA>	<NA>
[322]	<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 hg19 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 hg19 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-3.10-bioc/R/lib/libRblas.so

LAPACK: /home/biocbuild/bbs-3.10-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_1.9.1
[2]	IlluminaHumanMethylationEPICanno.ilm10b2.hg19_0.6.0
[3]	IlluminaHumanMethylation450kanno.ilmn12.hg19_0.6.0
[4]	minfi_1.31.0
[5]	bumphunter_1.27.0
[6]	locfit_1.5-9.1
[7]	iterators_1.0.10
[8]	foreach_1.4.4
[9]	Biostrings_2.53.0
[10]	XVector_0.25.0
[11]	SummarizedExperiment_1.15.0
[12]	DelayedArray_0.11.0
[13]	BiocParallel_1.19.0
[14]	matrixStats_0.54.0
[15]	Biobase_2.45.0

[16] GenomicRanges_1.37.0
[17] GenomeInfoDb_1.21.0
[18] IRanges_2.19.0
[19] S4Vectors_0.23.0
[20] BiocGenerics_0.31.0
[21] knitr_1.22

loaded via a namespace (and not attached):

[1] AnnotationHub_2.17.0
[2] BiocFileCache_1.9.0
[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_1.53.0
[12] doParallel_1.0.14
[13] limma_3.41.0
[14] recipes_0.1.5
[15] readr_1.3.1
[16] annotate_1.63.0
[17] gower_0.2.0
[18] askpass_1.1
[19] siggenes_1.59.0
[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_1.67.0
[30] impute_1.59.0
[31] GEOquery_2.53.0
[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_1.31.0
[38] kernlab_0.9-27
[39] Rhdf5lib_1.7.0
[40] HDF5Array_1.13.0
[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_1.47.0
[51] lava_1.6.5
[52] prodlim_2018.04.18
[53] httr_1.4.0
[54] RColorBrewer_1.1-2
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