Package 'dREG'

September 24, 2018

Version 1.4.0	
Date 2018-08-28	
Title Detection of Regulatory DNA using PRO-seq, GRO-seq Data(dREG)	
Author Charles G. Danko <dankoc@gmail.com></dankoc@gmail.com>	
Maintainer Charles G. Danko <dankoc@gmail.com></dankoc@gmail.com>	
Depends R (>= 2.14), bigWig (>= 0.2-9), e1071, rphast, snowfall, data.table, rmutil, mvtnorm, methods,randomForest, stats, utils	
LinkingTo	
Suggests Rgtsvm	
Description This package is an analysis pipeline for the analysis of GRO-seq data.	
License GPL-3	
biocViews Sequencing, Analysis	
LazyLoad yes	
R topics documented:	
check_bigwig	2
combine.roc	2
eval_reg_svm	3
genomic_data_model	5
get_informative_positions	5
get_test_set	7
logreg.roc.calc	8
peak_calling	9
	12
2 7-	1315
	16
	17
	18

2 combine.roc

check_bigwig

Check bigWig data meet the dREG requirement

Description

There are 3 check points for dREG: 1) Each read should be mapped to a locus (3' for PRO-seq and 5' for GRO-seq), not a region; 2) No normalization; 3) Only positive values or negative values in one file;

Usage

```
check_bigwig(bw_path, strand = "+", out.file = "")
```

Arguments

bw_path String value, bigWig file

strand "+" or "-", strand

out.file file name, indicating detailed information will be outputted.

Value

Boolean value indicates whether it is suitable to do peak calling. If the bigWig doesn't meet the requirements of dREG, the function will return FALSE with the details outputted into console or file.

combine.roc

Combines ROC plots

Description

Combines ROC plots, interpolating and weighting by nTP.

Usage

```
combine.roc(list.roc,
    weight = rep(1, NROW(list.roc)),
    interp.corners = FALSE,
    use.max = FALSE,
    nvals = 100)
```

Arguments

list.roc List including multiple ROC data frame weight Weight vector for each ROC dataframe

 $interp.\, corners \quad Logical \ value \ indicating \ if \ the \ header(1,1) \ and \ tail \ values(0,0) \ are \ interpolated$

to each ROC data frame.

use.max Logical value indicating if maximum value of muliple ROCs at same point are

used as TPF values.

nvals Integer value indicating interval number for ROC plot.

eval_reg_svm 3

Value

A data frame with 2 columns is returned

FPR False Positive Rate
TPR True Positive Rate

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
roc.calc, logreg.roc.calc, roc.auc, roc.plot
```

Examples

```
list.roc<-list();

true <- c(rep(1, 100), rep(0, 100));
scores <- c( rnorm(100, 1, 1 ), rnorm(100, 0, 1 ) );
list.roc[[1]] <- logreg.roc.calc( true, scores );

true <- c(rep(1, 120), rep(0, 110));
scores <- c( rnorm(120, 1, 0.8 ), rnorm(110, 0, 1.2 ) );
list.roc[[2]] <- logreg.roc.calc( true, scores );

r <- combine.roc(list.roc);
roc.plot(r)</pre>
```

eval_reg_svm

Evaluates a set of genomic coordinates for regulatory potential using P/GRO-seq data

Description

Evaluates a set of genomic coordinates for regulatory potential using P/GRO-seq data

Usage

4 eval_reg_svm

Arguments

gdm	Genomic data model return by genomic_data_model.
asvm	A pre-trained SVM model from the e1071 package returned by ${\tt regulatory_svm}$.
positions	Data frame with 2 columns indicating the universe of positions to test and evaluate(chrom,chromCenter). It can be returned by get_informative_positions.
bw_plus_path	String value indicating file path to bigWig file representing the plus strand.
bw_minus_path	String value indicating file path to bigWig file representing the minus strand
batch_size	Number of positions to evaluate at once (more might be faster, but takes more memory).
ncores	Number of CPU cores in parallel computing
use_rgtsvm	Indictating whether the predict will be performed on GPU through the Rgtsvm package.
debug	Logical value indicating the process detail is outputted.

Value

Returns the value of the SVM for each genomic coordinate specified.

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
get_informative_positions, get_test_set, read_genomic_data, regulatory_svm
```

```
## The following codes cannot run without the bigWig files

# ps_plus_path <- "bigwig.plus.bw"

# ps_minus_path <- "bigwig.minus.bw"

## Now scan all positions in the genome ...

# positions <- get_informative_positions(ps_plus_path, ps_minus_path,
# depth= 0, step=50, use_ANDOR=TRUE, use_OR=FALSE);

# pred_val<- eval_reg_svm( gdm, asvm, inf_positions, ps_plus_path, ps_minus_path, batch_size=50000)
# write.table( data.frame(inf_positions, pred_val), file="eval.tab",
# row.names=FALSE, col.names=FALSE, quote=FALSE, sep="\t")</pre>
```

genomic_data_model 5

genomic_data_model

Builds a multiscale window object for feature extracting.

Usage

```
genomic_data_model(window_sizes, half_nWindows)
```

Arguments

window_sizes

vector of integer, indicating the genomic size (bp) for each window.

half_nWindows

vector of integer, specifying the window count for each above window. Because the windows are extended at the both sides of an observed position, here this number is considered as half number(left or right side).

Details

The total number of features including plus and strand is sum(half_nWindows)*2 sides * 2 strands. The covered region are max(window_sizes)*half_nWindows[which.max(window_sizes)]*2 bps.

Value

A S4 object including two attributes.

Examples

```
get_informative_positions
```

Gets center positions that pass a minimum depth filter

Description

Returns a data frame with center positions that pass a minimum depth filter

Usage

```
get_informative_positions(bw_path,
    bw_minus_path = NULL,
    depth = 0,
    window = 400,
    step = 50,
    use_OR = TRUE,
    use_ANDOR = TRUE,
    debug = TRUE)
```

Arguments

bw_path String indicating file path to bigwig file representing the plus strand.

bw_minus_path String indicating file path to bigwig file representing the minus strand, If speci-

fied, takes the windows that pass the step in both bigWig files.(intersection)

depth Integer value indicating minimum number of reads to return.

window Integer value indicating window distance between to search for #depth reads

[bp].

step Integer value indicating step distance for window list.

use_OR Logical value indicating if the center positions in minus bigwig file are merged

into the results. If false, the intersection operation will be performed to the

center positions of plus bigwig and from minus bigwig.

use_ANDOR Logical value indicating if the center positions will be merged from the two

results. a) Intersection operation with the conditions: window interval=1000 depth>=0. b) Union operation with with the conditions: window interval=100

depth >= 2.

debug Logical value indication the process detail is outputted.

Details

The use_ANDOR and use_OR parameter are applied to two Bigwig files as following logical:

```
if(use_ANDOR){
    v1 <- get_window_Or (window=1000, depth=0);
    v2 <- get_window_and (window=100, depth=2);
    vals <- c(v1,v2);
}
else {
    if(use_OR){
       vals <- get_window_Or( window=window, depth=depth);
    }
    else {
       vals <- get_window_and( window=window, depth=depth);
    }
}</pre>
```

Value

A BED-style data frame will be returned with 3 columns

chrom Chromosome information

chromStart Start position
chromEnds End position

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

get_test_set 7

See Also

```
get_test_set, read_genomic_data, regulatory_svm, eval_reg_svm
```

get_test_set Returns a genome loci of positive set and negative set for SVM training purpose.

Description

Returns a genome loci of positive set and negative set for SVM training purpose

Usage

```
get_test_set(positions,
    positive,
    n_samp,
    allow = NULL,
    enrich_negative_near_pos = 0.15,
    extra_enrich_bed = NULL,
    extra_enrich_frac = 0.1,
    avoid_dist = 100)
```

Arguments

positions Bed-style data frame indicating the universe of positions to test and evaluate

(chrom,chromCenter).

positive Bed-style data frame containing positive positions (chrom,chromStart,chromEnd).

n_samp Number of training examples

allow Bed-style data frame containing inverse negative set of positions (chrom,chromStart,chromEnd).

enrich_negative_near_pos

Fraction of training examples chosen to be nearby (<=5kb) a positive example

[0,1].

extra_enrich_bed

Bed-style data frame indicating extra bed file to enrich near.

extra_enrich_frac

Fraction of final positions sampled in the negative set which are in the bed file.

Unused if extra_enrich_bed is NULL.

avoid_dist Integer value indicating how long extend avoiding genomic loci.

Details

(1). The parameter of positions can be obtained by get_informative_positions.

Value

Returns a data frame including double number of the _train set(2*n_samp), each sample includes 4 items.

chrom

chromStart

chromEnd

status 1 for positive and 0 for negative.

8 logreg.roc.calc

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

get_informative_positions, read_genomic_data, regulatory_svm, eval_reg_svm

logreg.roc.calc

Calculates the TPR and FPR for a ROC plot.

Description

Calculates the TPR and FPR for a ROC plot from the status and score vector.

Usage

```
logreg.roc.calc(true, scores)
```

Arguments

true Vector indicating the two status, 1 and 0.

scores Vector indicating the scores for each status calculated by the predict function.

Details

The function of roc.calc calculates a ROC matrix for the genomic loci, whereas the function of logreg.roc.calc calculates for a status vector.

Value

A data frame with 3 columns is returned, which is same as roc.calc.

FPR False Positive Rate.

TPR True Positive Rate.

threshold Threshold based on the score parameter.

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
roc.calc, combine.roc, roc.auc,roc.plot
```

peak_calling 9

Examples

```
true <- c(rep(1, 100), rep(0, 100));
scores <- c( rnorm(100, 1, 1 ), rnorm(100, 0, 1 ) );
roc_mat <- logreg.roc.calc( true, scores );
AUC<- roc.auc(roc_mat);
roc.plot(roc_mat, main=AUC );</pre>
```

peak_calling

Peak calling based on dREG prediction

Description

This procedure calls SVR prediction for paired bigWig files using pre-trained SVM model and detects divergent peaks based on the predicted score.

Usage

```
peak_calling(asvm, gdm,
    bw_plus_path, bw_minus_path,
    infp_bed = NULL,
    use_rgtsvm = TRUE,
    min_score = NULL,
    pv_adjust="fdr",
    pv_threshold=0.05,
    smoothwidth = 4,
    cpu_cores=1,
    gpu_cores=1)
```

Arguments

asvm	SVR model pre-trained for dREG package, which can be downloaded from the dREG page in Github.
gdm	Genomic data model return by genomic_data_model. This data is binding with SVR model.
bw_plus_path	File name indicating file path to bigWig file representing the plus strand.
bw_minus_path	File name indicating file path to bigWig file representing the minus strand.
infp_bed	A BED data frame indicating informative sites and scores returned by eval_reg_svm. If NULL is specified, the peak calling starts from the informative sites finding and predicting.
use_rgtsvm	Logical value indictating whether the predict will be performed on GPU through the Rgtsvm package.
min_score	Numerical value indicating the minimum dREG score applied to the peak calling procedure. If NULL is specified, this value is calculated based on the predicted scores.
pv_adjust	String value indictating which correction method is used to do multiple comparison, see details in p.adjust, default is 'fdr'.
pv_threshold	Numerical value indicating the threshold is used to report the dREG peaks.

10 peak_calling

age.

cpu_cores Number of CPU cores in parallel computing.

gpu_cores Number of GPU cores in parallel computing if **Rgtsvm** is used.

Value

This function returns a list containing 6 items, including:

1) dREG peaks: peak_bed

chr Chromosome start Start position end End position

score Maxmimum score in the peak region

prob Probability of multivariate Laplace distribution indicating the probability of the

peak points belonging to negative set (No divergent peak)

center the center position in original peak

2) Informative sites with score infp_bed

chr Chromosome
start Start position
end End position
score predicted score

infp indicating the informative site or dense site

3) Broad peak regions peak_broad

chr Chromosome start Start position end End position

no index

min minimum score in this region
max maximum score in this region
mean score mean in this region
sum score um in this region

stdev standard deviation of scores in this region

count informative site in this region

- 4) Threshold of dREG score min_score
- 5) Raw results of peak calling raw_peak

chr Chromosome start Start position peak_calling 11

end End position score Maxmimum score in the peak region prob Probability of multivariate Laplace distribution indicating the probability of the peak points belonging to negative set (No divergent peak) smooth.mode the center position in smoothed peak original.mode the center position in original peak centroid the centroid 6) Summary of peak calling peak_sum adjust.none.0.05 The count of dREG peak withou p-value correction. adjust.fdr.0.05 The count of dREG peak adjusted by the 'fdr' method. adjust.BH.0.05 The count of dREG peak adjusted by the 'BH' method. adjust.bonferroni.0.05 The count of dREG peak adjusted by the 'bonferroni' method. adjust.holm.0.05 The count of dREG peak adjusted by the 'holm' method. adjust.hochberg.0.05 The count of dREG peak adjusted by the 'hochberg' method. adjust.BY.0.05 The count of dREG peak adjusted by the 'BY' method. peak.sig.score The score range of significant dREG peaks. peak.narrow100 The ignored narrow peaks which length are less than 100. peak.narrow100.sig The ignored narrow peaks which may be significant based on 'peak.sig.score'. peak.narrow100.score The score range of the ignored narrow peaks.

```
# load("../asvm.6.6M.20170828.rdata");
# gdm <- genomic_data_model(window_sizes= c(10, 25, 50, 500, 5000), half_nWindows= c(10, 10, 30, 20, 20))
# bw_plus_path <- "K562.chr21.plus.bw"
# bw_minus_path <- "K562.chr21.minus.bw"
# x <- peak_calling( svm, gdm, bw_plus_path, bw_minus_path, cpu_cores=12, use_rgtsvm=T)
# show(x$peak_bed);</pre>
```

12 read_genomic_data

read_genomic_data Gets read data from the specified genomic position.

Description

Gets read data from the specified genomic position.

Usage

Arguments

gdm Genomic data model return by genomic_data_model.

bed bed-style data frame of genomic regions.(at least 3 columns including chrom,

start, end).

file_bigwig_plus

String value indicating file path to bigwig file representing GRO-seq/ PRO-seq

reads on the plus strand.

file_bigwig_minus

String value indicating file path to bigwig file representing GRO-seq/PRO-seq

reads on the minus strand.

as_matrix Logical type,if true, returns a matrix object, otherwise returns a list() object,

where each element in the list is the zoom data.

scale.method String value indicating the normalize method of read counts. Two options are

available, "logistic" or "linear", default value is logistic. See details

batch_size Number of genomic positions to evaluate at once (more might be faster, but

takes more memory)

ncores Number of CPU cores in parallel computing

Details

Data normalize method:

(1): Logistic function: F(x) = 1/(1+exp(-a*(x-b))
(2): Linear function: F(x) = x / tootal_reads

Value

A matrix of normalized read count, the columns are windows list specified by gdm object.

regulatory_svm 13

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
get_informative_positions, get_test_set, regulatory_svm, eval_reg_svm
```

Examples

```
file_bigwig_plus <- "";
file_bigwig_minus <- "";
gdm <- genomic_data_model(20, 10);
#mat <- read_genomic_data(gdm, bed, file_bigwig_plus, file_bigwig_minus);
#summary(mat);</pre>
```

regulatory_svm

Trains a SVM to recognize a certain pattern of regulatory positions

Description

Trains a SVM to recognize a certain pattern of regulatory positions.

Usage

```
regulatory_svm(gdm,
      bw_plus_path,
      bw_minus_path,
      positions, positive,
      allow = NULL,
      n_{train} = 25000,
      n_{eval} = 1000,
      pdf_path = "roc_plot.pdf",
      plot_raw_data = TRUE,
      extra_enrich_bed = NULL,
      extra_enrich_frac = 0.1,
      enrich_negative_near_pos = 0.15,
      use_rgtsvm = FALSE,
      svm_type = "SVR",
      ncores = 1,
      debug = TRUE)
```

Arguments

gdm Genomic data model returned by genomic_data_model.

bw_plus_path String indicating file path to bigWig file representing the plus strand.

bw_minus_path String indicating file path to bigWig file representing the minus strand.

14 regulatory_svm

positions	Data frame with two columns(chrom,chromCenter), indicating the universe of positions to test and evaluate. It can be generated by get_informative_positions.		
positive	Bed-style data frame containing positive positions(chrom,chromStart,chromEnd).		
allow	$Bed-style\ data\ frame\ containing\ positions\ to\ avoid\ in\ the\ negative\ set (chrom, chromStart, chromEnd).$		
n_train	Number of training examples.		
n_eval	Number of examples on which to test performance.		
pdf_path	String value indicating a PDF file. Set to NULL if no PDF should be printed.		
plot_raw_data	If TRUE (default), and if a PDF file is specified, plots the raw data used to train the model.		
extra_enrich_b	ed		
	Bed-style data frame indicating extra bed file to enrich near. Used by get_test_set.		
extra_enrich_frac			
	Fraction of final positions sampled in the negative set which are in the bed file. Unused if extra_enrich_bed is NULL. Used by get_test_set.		
enrich_negative_near_pos			
	Fraction of training examples chosen to be nearby (<=5kb) a positive example [0,1].		
use_rgtsvm	Indictating whether the predict will be performed on GPU through the Rgtsvm package.		
svm_type	Two options, "SVR" for support vecctor regression (epsilon-regression). "P_SVM" for probabilistic SVM (C-classification).		
ncores	Integer indicating how many cores are used to improve the performance.		
• • •	The parameters for plot function		
debug	Logical value indication the process detail is outputted.		

Value

A sym model trained by sym function in e1071 package.

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

get_informative_positions, get_test_set, read_genomic_data, eval_reg_svm

roc.auc 15

roc.auc

Computes the AUC of a ROC plot.

Description

Computes the AUC of a ROC plot.

Usage

```
roc.auc(ROC)
```

Arguments

ROC

A matrix with 3 columns (FPR, TPR and threshold) calculated by logreg.roc.calc.

Details

The parameter of ROC is a matrix or data frame including 3 columns, FPR(False Positive Rate), TPR(True Positive Rate) and threshold.

Value

AUC value is returned.

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
roc.calc, logreg.roc.calc, combine.roc, roc.plot
```

```
roc_mat <- data.frame( FPR=c(0, 0.25, 0.5, 0.75, 1),
TPR=c(0, 0.5, 0.8, 0.95, 1),
threshold=c(1, 1, 1, 1, 1) );
AUC<- roc.auc( roc_mat );
roc.plot( roc_mat, main=AUC );</pre>
```

16 roc.calc

roc.calc

Calculates the TPR and FPR for a ROC plot.

Description

Calculates the TPR and FPR for a ROC plot.

Usage

```
roc.calc(true,
    possible,
    scores,
    filterPossible = TRUE,
    n_points = 100)
```

Arguments

true Bed-style data frame, a set of 'true' genomic intervals (e.g. ChIP-seq peaks).

possible Bed-style data frame, A set of 'possible' genomic intervals (e.g. DNAse-1

peaks).

scores Vector indicating the scores for each possibe genomic interval in parameter of

possible.

filterPossible Vector indicating indexes which be removed.

n_points Integer indicating how many points for the ROC plot.

Value

A data frame with 3 columns is returned

FPR False Positive Rate
TPR True Positive Rate

threshold Threshold based on the score parameter.

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
logreg.roc.calc, combine.roc, roc.auc, roc.plot
```

roc.plot

roc.plot

Draws a ROC figure.

Description

Draws a ROC figure.

Usage

```
roc.plot(ROC, ...)
```

Arguments

ROC Matrix or data frame with 3 columns, FPR, TPR and threshold.

... The parameters for plot function

Value

None

References

Danko, C. G., Hyland, S. L., Core, L. J., Martins, A. L., Waters, C. T., Lee, H. W., ... & Siepel, A. (2015). Identification of active transcriptional regulatory elements from GRO-seq data. Nature methods, 12(5), 433-438.

See Also

```
roc.calc, logreg.roc.calc, combine.roc, roc.auc
```

```
true <- c(rep(1, 100), rep(0, 100));
scores <- c( rnorm(100, 1, 1 ), rnorm(100, 0, 1 ) );
roc_mat <- logreg.roc.calc( true, scores );
AUC<- roc.auc(roc_mat);
roc.plot(roc_mat, main=AUC );</pre>
```

Index

```
*Topic function
    eval_reg_svm, 3
    get_informative_positions, 5
    get_test_set, 7
    peak_calling, 9
    read\_genomic\_data, 12
    regulatory_svm, 13
*Topic plot
    combine.roc, 2
    logreg.roc.calc, 8
    roc.auc, 15
    roc.calc, 16
    roc.plot, 17
check_bigwig, 2
combine.roc, 2, 8, 15–17
eval_reg_svm, 3, 7-9, 13, 14
genomic_data_model, 4, 5, 9, 12, 13
get_informative_positions, 4, 5, 7, 8, 13,
get_test_set, 4, 7, 7, 13, 14
logreg.roc.calc, 3, 8, 8, 15–17
p.adjust, 9
peak_calling, 9
read_genomic_data, 4, 7, 8, 12, 14
regulatory_svm, 4, 7, 8, 13, 13
roc.auc, 3, 8, 15, 16, 17
roc.calc, 3, 8, 15, 16, 17
roc.plot, 3, 8, 15, 16, 17
```