

Package ‘aCGH.Spline’

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R topics documented:

aCGH.Spline-package	2
batch.spline	2
dLRs	4
f.Noise	5
fe.extract	6
fe.read	7
fe.write	8
GenomePlot	9
Jspline	10
MakePDF	12
MAPlot1	13
MAPlot2	14
nim.read	15
ProPlot	17
run.spline	18

segN	19
SetJ	20
WriteGFF	21
WriteQC	22

Index	23
--------------	-----------

aCGH.Spline-package

Package for robust spline interpolation normalisation on dual color aCGH data.

Description

Carries out a robust spline interpolation method on aCGH dual color microarray data.

Contains some functions for reading and writing of standard aCGH data formats along with the generation QC statistics.

Details

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LazyLoad:	yes

Author(s)

Tomas William Fitzgerald

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batch.spline *Function for batch processing.*

Description

Function for batch processing aCGH data though the "Jspline" method.

Usage

```
batch.spline(dir, format = "FE", robust = TRUE, offset=5, knots=1000,  
            ntyp = "percentile", p = 0.68, fact = 4.5, segN = FALSE,  
            sn = 0.75, writeFE = FALSE, QC = FALSE, GFF = FALSE, PDF = FALSE)
```

Arguments

dir	- the directory to process.
format	- the type of file format - c("FE", "NIM").
robust	- make the method robust to outliers (TRUE or FALSE).
offset	- parameters to set the number of time the knot point will be offset.
knots	- the number of knot points to use for spline fitting.
ntyp	- type of noise calculation to perform - c("percentile", "derivative", "combined").
p	- value between 0 and 1 (the percentile value).
fact	- numeric value (the factor by which the noise value will be rised).
segN	- option for robust noise calculation (recommended when data contains many outliers e.g. cancer sample) TRUE or FALSE.
sn	- value between 0 and 1 - threshold for segmentation (segN).
writeFE	- Output a Feature Extraction formatted file (only to be used when processing Agilent FE files).
QC	- produce a QC report TRUE or FALSE.
GFF	- produce a GFF formatted file TRUE or FALSE.
PDF	- produce a PDF containing normalisation figures TRUE or FALSE.

Details

Running this function using default parameters (just providing the directory argument) will perform consistently across a wide range of data qualities.

If method optimisation is required, the number of knot points and offsets can be adjusted along with the various noise estimation parameters.

Value

As default this function outputs one ".temp" formatted file per file processed.

The ".temp" format consists of seven columns:

- Cy5 intensity values.
- Cy3 intensity values.
- Chromosome number.
- Start position.

- Stop position.
- An index.
- A flag.

Note

This function assumes that all "*.txt" files within the target directory are in the specified format. (Agilent "FeatureExtraction.txt" or Nimblegen "SEG_MNT.txt" files)

Author(s)

Tomas William Fitzgerald

Examples

```
# batch.spline(".")  
# This would run batch processing on the current directory using default settings.
```

dLRs

Calculate the DLR Spread.

Description

Calculates the "DLR spread" - derivative log₂ ratio spread.

Usage

dLRs (x)

Arguments

x - vector of log ratio values.

Details

Calculates the probe-to-probe log ratio difference of an array. This is a noise estimation which is robust to outliers.

Value

The derivative log₂ ratio spread.

Note

A value used to compute the minimum log ratio difference needed to detect an outlier.

Author(s)

Tomas William Fitzgerald

References

Agilent

See Also

<http://www.home.agilent.com/agilent/home.jspx>

Examples

```
r1 = rnorm(100, 0, 3)
dLRs(r1)
r2 = rnorm(100, 0, 5)
dLRs(r2)
```

f.Noise

Noise calculating function.

Description

Noise estimation function.

Usage

```
f.Noise(r1, fact = 4.5, p = 0.68, typ = "percentile")
```

Arguments

r1	- numeric vector of log ratio values.
fact	- numeric value (factor by which to rise the noise value).
p	- value from 0 to 1, the percentile to evaluate.
typ	- noise estimation type c("percentile", "difference", "combined").

Value

An estimation of noise.

Author(s)

Tomas William Fitzgerald

Examples

```
r = rnorm(100, 0, 3)
f.Noise(r, fact=4.5, p=0.68, typ="percentile")
f.Noise(r, fact=4.5, typ="derivative")
```

fe.extract

Function to extract Feature Extraction data.

Description

Read Agilent Feature extraction data into R.

Usage

```
fe.extract(file, list)
```

Arguments

file - a feature extraction file to read.
list - a list of column names to extract e.g. c("rBGSubSignal", "gBGSubSignal",
"SystematicName").

Details

Function to extract data from a Feature extraction formatted file.

Value

Returns a dataframe containing all the values specified in the list argument.

Note

This function is capable of extracting any data contained within a Feature extraction file.

Author(s)

Tomas William Fitzgerald

See Also

<http://www.chem.agilent.com/en-us/products/instruments/dnamicroarrays/featureextractionsoftware/pages/default.aspx>

Examples

```
# data <- fe.extract("FEfile.txt", list = c("rBGSubSignal", "gBGSubSignal", "SystematicName")
# This would return and data frame containing background subtracted intensity values and pos
```

`fe.read`*Function to read Feature Extraction files.*

Description

Recommended feature extraction file reading function.

Usage

```
fe.read(file, raw=TRUE)
```

Arguments

`file` - the feature extraction file to read.
`raw` - the intensity values to extract (TRUE = background subtracted values, FALSE = Agilent normalised values).

Details

This function is capable of reading a FE file containing 1 million rows of data within 2 minutes.

Its also flags data points based on Feature extraction exculsion criteria and low intensity probes ($cy5 + cy3 < 100$).

Value

A dataframe containing seven columns (".temp" format):

- Cy5 intensity values.
- Cy3 intensity values.
- Chromosome number.
- Start position.
- Stop position.
- An index.
- A flag.

Note

If the flag is equal to 1 the probe should be removed from further analysis.

The index can be used as a unique identifier, it is the exact row where the data was taken from the FE file.

The function draws on methods contained within the "Jspline" class for increased speed performance.

Author(s)

Tomas William Fitzgerald

Examples

```
# data <- FeRead("FEfile.txt")
```

fe.write

Function to output a Feature extraction formatted file.

Description

Function used to replace intensity values, log ratio values and flags within a feature extraction input file.

Usage

```
fe.write(file, x)
```

Arguments

`file` - a feature extraction input file to use as a template (ideally this should be the FE file from which the data came from).

`x` - a ".temp" formatted dataframe containing the intensity values and flags to be written.

Details

Using a combination of "fe.read" and "fe.write" it is easy to modifying FE data and output results back to the original format.

Value

This outputs a new FE file having exactly the same name as the input FE file except it will start with "SS" instead of "US".

The new FE file will contain the intensity values, log ratio (calculated from the intensity values) and flags from the ".temp" format input structure(x).

Note

This function draws on methods contained within the "Jspline" class.

Author(s)

Tomas William Fitzgerald

Examples

```
# Read "FEfile.txt", flag all data points and write out in FE format.  
# data <- fe.read("FEfile.txt", raw=TRUE)  
# data[,7] = 1  
# fe.write("FEfile.txt", data)
```

GenomePlot

Produces a genome plot.

Description

Create a plot of the genome - plots each chromosome separately on the same figure.

Usage

```
GenomePlot(x, ylim=c(-3,3), axes=FALSE, pch=46, col="black")
```

Arguments

`x` - a ".temp" formatted data structure.
`ylim` - the y-axis limits defaults to c(-3,3).
`axes` - should axes be draw around each plot (TRUE or FALSE).
`pch` - the point character to use defaults to 46.
`col` - the point color defaults to "black".

Details

Plots as many chromosome as are contained within the ".temp" formatted data structure on the same figure.

Value

A plot showing each chromosome separatly.

Author(s)

Tomas William Fitzgerald

Examples

```

# Create a vector of chromosome numbers
chr = rnorm(100,1,0)
for (x in 2:24) {
  chr = c(chr, rnorm(100,x,0))
}

# Create a ".temp" data structure
mat = matrix(ncol=7, nrow=length(chr))
mat[,1] = rnorm(length(chr),1000,150)
mat[,2] = rnorm(length(chr),800,180)
mat[,3] = chr
mat[,4] = seq(1,length(chr), 1)
mat[,5] = seq(1,length(chr), 1)
mat[,6] = 0
mat[,7] = 0

# Plot the data
GenomePlot(mat)

```

Jspline

*Spline fitting and interpolation function.***Description**

Method to carry out robust spline fitting and interpolation.

Usage

```
Jspline(x, offset=5, knots=1000, ntyp="percentile", p=0.68, fact=4.5,
        robust=TRUE, segN=FALSE, sn=0.75, index1=1, index2=2)
```

Arguments

x	- ".temp" formatted data structure.
offset	- numeric value 1 or greater dictating how many times to offset the knot points.
knots	- the number of knot points to use in spline fitting.
ntyp	- the type of noise calculation to use. c("percentile", "derivative", "combined"), defaults to "percentile".
p	- numeric value between 0 and 1, the quantile to use.
fact	- numeric value, the factor by which the noise estimation will be rised.
robust	- make robust (exclude points from spline) TRUE or FALSE.
segN	- use segmentation prior to noise estimation TRUE or FALSE (see segN).
sn	- the segmentation threshold.
index1	- index within data structure x where cy5 intensity values reside.
index2	- index within data structure x where cy3 intensity values reside.

Details

This method carries out natural cubic spline fitting and interpolation on aCGH dual color microarray data.

Value

Input data structure (x) is returned having had cy5 and cy3 intensity data adjusted.

Note

Jspline performs consistently over a large range of data qualities and array formats but adds most benefit to noisy, highly rearranged data.

The number of points included in the spline fit can be adjusted (this ensures that the dye bias is assessed on reliable data points).

This method is written in java and contained within the "Jspline" class.

Author(s)

Tomas William Fitzgerald

Examples

```
## Set up noisy data with a bias
v = seq(1,100000,0.5)
d = sin(2*pi/500 * v)
nd = d + rnorm(length(d),0,100) + 1000
dd = sin(2*pi/1000 * v)
ndd = dd + rnorm(length(dd),0,120) + 1000

## Create ".temp" data structure
mat = matrix(ncol=7,nrow=length(dd))
mat[,1] = nd
mat[,2] = ndd
mat[,3] = 0
mat[,4] = 0
mat[,5] = 0
mat[,6] = 0
mat[,7] = 0

## Add a few flags
mat[100:150,7] = 1

## Plot the data before and after Jspline
par(mfrow=c(2,1),mar=c(1,1,1,1))
MAPlot1(mat,ylim=c(-1,1),xlim=c(9.4,10.4))
aa = Jspline(mat)
MAPlot1(aa,ylim=c(-1,1),xlim=c(9.4,10.4))
```

MakePDF

Write a PDF containing some normalisation plots.

Description

This function creates a PDF containing various figures to show the quality of normalisation.

Usage

```
MakePDF(filename, x, raw, ntyp="percentile", p=0.68, fact=4.5, segN=FALSE, sn=0.75)
```

Arguments

<code>filename</code>	- character argument, the output file name.
<code>x</code>	- the ".temp" formatted data structure after normalisation.
<code>raw</code>	- the ".temp" formatted data structure before normalisation.
<code>ntyp</code>	- the type of noise calculation to use, c("percentile", "derivative", "combined").
<code>p</code>	- numeric value between 0 and 1, the quantile used.
<code>fact</code>	- numeric value, the factor by which the noise estimation was risen.
<code>segN</code>	- was segN used TRUE or FALSE.
<code>sn</code>	- the segmentation threshold.

Details

Produces a summary ".pdf" files containing various figures.

Value

PDF containing a "ProPlot", "GenomePlot" and two MAplots (MAplot1 and MAplot2).

Note

MA-plots a useful way of assessing the quality of the normalisation. Most points should be centered around zero and the outliers should have little effect on the overall fit (this is the key point of this normalisation method).

Author(s)

Tomas William Fitzgerald

Examples

```
# NA
```

`MAPlot1`*Produce a MAplot showing points retained vs. points excluded.*

Description

Produce a MA-plot showing points retained and points excluded.

Usage

```
MAPlot1(x, pch=46, Retcol="black", Excol="red", ylim=c(-5,5), xlim=c(0,20), xlab="1
```

Arguments

<code>x</code>	- ".temp" formatted data structure.
<code>pch</code>	- the point character to use defaults to 46.
<code>Retcol</code>	- the point color to use for the points retained after normalisation, defaults to "black".
<code>Excol</code>	- the point color to use for the points excluded after normalisation, defaults to "red".
<code>xlim</code>	- the x-axis limits defaults to c(0,20).
<code>ylim</code>	- the y-axis limits defaults to c(-5,5).
<code>xlab</code>	- the label for the x-axis.
<code>ylab</code>	- the label for the y-axis.
<code>main</code>	- the main title for the plot.

Value

Figure showing the $\log_2(\text{mean}(\text{red}, \text{green}))$ vs. the $\log_2(\text{red}/\text{green})$.

Author(s)

Tomas William Fitzgerald

Examples

```
## Set up noisy data with a bias
v = seq(1,100000,0.5)
d = sin(2*pi/500 * v)
nd = d + rnorm(length(d),0,100) + 1000
dd = sin(2*pi/1000 * v)
ndd = dd + rnorm(length(dd),0,120) + 1000

## Create ".temp" data structure
mat = matrix(ncol=7,nrow=length(dd))
mat[,1] = nd
```

```

mat[,2] = ndd
mat[,3] = 0
mat[,4] = 0
mat[,5] = 0
mat[,6] = 0
mat[,7] = 0

## Add a few flags
mat[100:150,7] = 1

## Plot the data
par(mfrow=c(2,1),mar=c(1,1,1,1))
MAPlot1(mat,ylim=c(-1,1),xlim=c(9.4,10.4))

```

MAPlot2

Produce a MAplot showing points fitted vs. points interpolated.

Description

Produce a MA-plot showing points fitted and point interpolated.

Usage

```
MAPlot2(x, raw, ntyp="percentile", p=0.68, fact=4.5, segN=FALSE, sn=0.75, pch=46, Fitcol="green", Intcol="red", xlim=c(0,20), ylim=c(-5,5), xlab, ylab, main)
```

Arguments

x	- the ".temp" formatted data structure after normalisation.
raw	- the ".temp" formatted data structure before normalisation.
ntyp	- the type of noise calculation to use, c("percentile", "derivative", "combined"), defaults to "percentile".
p	- numeric value between 0 and 1, the quantile to use.
fact	- numeric value, the factor by which the noise estimation will be risen.
segN	- use segmentation prior to noise estimation TRUE or FALSE (see segN).
sn	- the segmentation threshold.
pch	- the point character to use defaults to 46.
Fitcol	- the point color to use for the points used during spline fitting, defaults to "green".
Intcol	- the point color to use for the points excluded from spline fitting, defaults to "red".
xlim	- the x-axis limits defaults to c(0,20).
ylim	- the y-axis limits defaults to c(-5,5).
xlab	- the label for the x-axis.
ylab	- the label for the y-axis.
main	- the main title for the plot.

Value

MAplot showing relative number of points considered to be outside the normal distribution.

Note

Points outside the interpolation threshold are not used during the spline fitting. We believe that these points are highly unreliable for assessing the dye bias.

Author(s)

Tomas William Fitzgerald

Examples

```
# Create some noisy data with a bias
v = seq(1,100000,0.5)
d = sin(2*pi/500 * v)
nd = d + rnorm(length(d),0,100) + 1000
dd = sin(2*pi/1000 * v)
ndd = dd + rnorm(length(dd),0,120) + 1000

## Create ".temp" data stucture
mat = matrix(ncol=7,nrow=length(dd))
mat[,1] = nd
mat[,2] = ndd
mat[,3] = 0
mat[,4] = 0
mat[,5] = 0
mat[,6] = 0
mat[,7] = 0

# Add a few outliers
mat[100:150,1] = mat[100:150,1] * 1.5
mat[100:150,2] = mat[100:150,2] / 1.5

# Run Jspline and plot
aa = Jspline(mat)

MAPlot2(aa, mat, ylim=c(-1.5,1.5),xlim=c(9.4,10.4))
```

nim.read

Function to read a Nimblegen "SEG_MNT.txt" file.

Description

Function to read a Nimblgen "SEG_MNT.txt" file.

Usage

```
nim.read(file)
```

Arguments

`file` - Nimblegen "SEG_MNT.txt" file to read.

Details

This function reads the contents of a Nimblegen "SEG_MNT.txt" file into a ".temp" formatted dataframe and flags low intensity probes.

Value

The ".temp" dataframe contains seven columns:

- Cy5 intensity values.
- Cy3 intensity values.
- Chromosome number.
- Start position.
- Stop position.
- An index.
- A flag.

Note

This function reads spatially normalised intensity values from the Nimblegen input file. There is currently no option to output a "SEG_MNT.txt" format, however, signal-map gff format is supported.

Author(s)

Tomas William Fitzgerald

See Also

<http://www.nimblegen.com/>

Examples

```
# data <- nim.read("Nimblegen_SEG_MNT.txt")
```

ProPlot

Produce a simple overview plot of the data.

Description

Produce a figure showing the log2 ratio sorted by genomic location.

Usage

```
ProPlot(x, pch=46, col="black", ylim=c(-3,3), xlim=c(0,length(x[,1])), xlab="Index")
```

Arguments

<code>x</code>	- ".temp" formatted data structure.
<code>pch</code>	- the point character to use defaults to 46.
<code>col</code>	- the point color to use, defaults to "black".
<code>xlim</code>	- the x-axis limits.
<code>ylim</code>	- the y-axis limits defaults to c(-3,3).
<code>xlab</code>	- the label for the x-axis.
<code>ylab</code>	- the label for the y-axis.
<code>main</code>	- the main title for the plot.

Details

Provides an overall picture of array data.

Value

Figure showing log2 ratio sorted by genomic location.

Author(s)

Tomas William Fitzgerald

Examples

```
chr = rnorm(1000,1,0)

for (x in 2:24) {
  chr = c(chr, rnorm(1000,x,0))
}

mat = matrix(ncol=7, nrow=length(chr))
mat[,1] = rnorm(length(chr),1000,150)
mat[,2] = rnorm(length(chr),800,180)
```

```

mat[,3] = chr
mat[,4] = seq(1,length(chr), 1)
mat[,5] = seq(1,length(chr), 1)
mat[,6] = 0
mat[,7] = 0

ProPlot(mat)

```

run.spline *Function to process a single file.*

Description

Function to process a single file.

Usage

```

run.spline(file, format = "FE", robust = TRUE, offset=5, knots=1000, ntyp = "percentile",
           p = 0.68, fact = 4.5, segN = FALSE, sn = 0.75, writeFE = FALSE, QC = FALSE,

```

Arguments

file	- the file to process.
format	- the type of file format - c("FE", "NIM").
robust	- make the method robust to outliers (TRUE or FALSE).
offset	- parameters to set the number of time the knot point will be offset.
knots	- the number of knot points to use for spline fitting.
ntyp	- type of noise calculation to perform - c("percentile", "derivative", "combined").
p	- value between 0 and 1 (the percentile value).
fact	- numeric value (the factor by which the noise value will be rised).
segN	- option for robust noise calculation (recommended when data contains many outliers e.g. cancer sample) TRUE or FALSE.
sn	- value between 0 and 1 - threshold for segmentation (segN).
writeFE	- Output a Feature Extraction formatted file (only to be used when processing Agilent FE files).
QC	- produce a QC report TRUE or FALSE.
GFF	- produce a GFF formatted file TRUE or FALSE.
PDF	- produce a PDF containing normalisation figures TRUE or FALSE.

Details

In most cases running this function using default parameters (i.e. just providing the file input argument) will perform consistently across a wide range of data qualities. If method optimisation is required the number of knot point and offsets can be adjusted along with the various noise parameters.

Value

Output file containing seven columns (".temp" format):

- Cy5 intensity values.
- Cy3 intensity values.
- Chromosome number.
- Start position.
- Stop position.
- An index.
- A flag.

Author(s)

Tomas William Fitzgerald

Examples

```
# norm <- run.spline("InputFile")  
# This would run the method using default settings.
```

segN

Segmentation method for noise calculation.

Description

Segmentation method for noise calculation.

Usage

```
segN(r, t)
```

Arguments

- | | |
|---|---|
| r | - vector of ratio values. |
| t | - value between 0 and 1 (a percentile). |

Details

This method assesses the difference between consecutive points and median normalises segments above the threshold (t).

Value

A ratio which represents the noise of the original ratio(r) as if it were more normal.

Note

This method is useful when looking at highly aneuploid data (e.g. cancer samples). It can be used in an iterative manner if required.

It is important to make sure the data is sorted by genomic position before running this.

Author(s)

Tomas William Fitzgerald

Examples

```
v = seq(1,100000,0.5)
d = sin(2*pi/500 * v)
red = d + rnorm(length(d),0,100) + 1000
dd = sin(2*pi/1000 * v)
green = dd + rnorm(length(dd),0,120) + 1000
rat = log2(red / green) - median(log2(red / green), na.rm=TRUE)
rat[20000:30000] = abs(rat[20000:30000] * 2)
rat[60000:70000] = -abs(rat[60000:70000] * 2)
seg = segN(rat,0.50)
par(mfrow=c(2,1))
plot(rat, pch=46, ylim=c(-2,2), main="Before_segN")
plot(seg, pch=46, ylim=c(-2,2), main="After_segN")
```

SetJ

Function to set the java class path and heap size.

Description

Sets the java class path and adjusts the heap size.

Usage

```
SetJ()
```

Note

R seems to be limited at -Xmx1600, this allows FE files containing 1 million rows to be read (much more may start to cause problems).

Author(s)

Tomas William Fitzgerald

Examples

```
SetJ()
```

`WriteGFF`*Function to write a GFF formatted file.*

Description

Output a GFF formatted file for use in the Signal-Map software (Nimblegen software).

Usage

```
WriteGFF(filename, x)
```

Arguments

```
filename    - the name for the output file.  
x           - a ".temp" formatted data stucture.
```

Details

This will output a GFF formatted file containing the log2 ratio for all probes which were not flagged.

Value

GFF file for input into the Signal-Map software.

Author(s)

Tomas William Fitzgerald

See Also

<http://www.nimblegen.com/products/lit/signalmap1.9usersguide.pdf>

Examples

```
chr = rnorm(1000,1,0)  
  
for (x in 2:24) {  
    chr = c(chr, rnorm(1000,x,0))  
}  
  
mat = matrix(ncol=7, nrow=length(chr))  
mat[,1] = rnorm(length(chr),1000,150)  
mat[,2] = rnorm(length(chr),800,180)  
mat[,3] = chr  
mat[,4] = seq(1,length(chr), 1)  
mat[,5] = seq(1,length(chr), 1)  
mat[,6] = 0  
mat[,7] = 0
```

```
WriteGFF("test.gff", mat)
```

WriteQC

Function to produce a QC report.

Description

Write a QC report containing some summery statistics

Usage

```
WriteQC(filename, batch, x)
```

Arguments

filename - the name for the output file.
batch - TRUE or FALSE (is it being run in batch mode).
x - a ".temp" formatted data stucture.

Value

Produces a table containing the filename, 68th percentile, dLRs and chromosme X median.

Author(s)

Tomas William Fitzgerald

Examples

```
chr = rnorm(1000,1,0)

for (x in 2:24) {
  chr = c(chr, rnorm(1000,x,0))
}

mat = matrix(ncol=7, nrow=length(chr))
mat[,1] = rnorm(length(chr),1000,150)
mat[,2] = rnorm(length(chr),800,180)
mat[,3] = chr
mat[,4] = seq(1,length(chr), 1)
mat[,5] = seq(1,length(chr), 1)
mat[,6] = 0
mat[,7] = 0

WriteQC("test", batch=FALSE, mat)
```

Index

*Topic **IO**

- batch.spline, 2
- fe.extract, 5
- fe.read, 6
- fe.write, 7
- MakePDF, 11
- nim.read, 15
- run.spline, 18
- WriteGFF, 21
- WriteQC, 22

*Topic **aplot**

- GenomePlot, 9
- MAPlot1, 13
- MAPlot2, 14
- ProPlot, 17

*Topic **environment**

- SetJ, 20

*Topic **interface**

- batch.spline, 2
- fe.read, 6
- fe.write, 7
- Jspline, 10
- run.spline, 18

*Topic **manip**

- batch.spline, 2
- Jspline, 10
- run.spline, 18
- segN, 19

*Topic **math**

- dLRs, 3

*Topic **optimize**

- f.Noise, 5

*Topic **package**

- aCGH.Spline-package, 1

aCGH.Spline

(*aCGH.Spline-package*), 1

aCGH.Spline-package, 1

batch.spline, 2

dLRs, 3

f.Noise, 5

fe.extract, 5

fe.read, 6

fe.write, 7

GenomePlot, 9

Jspline, 10

MakePDF, 11

MAPlot1, 13

MAPlot2, 14

nim.read, 15

ProPlot, 17

run.spline, 18

segN, 19

SetJ, 20

WriteGFF, 21

WriteQC, 22