

# Package ‘ldlasso’

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**Type** Package

**Title** LD LASSO Regression for SNP Association Study

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**Description** ldlasso requires data be of class gwaa.data from the the package GenABEL

**License** GPL (>= 2)

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**LazyLoad** yes

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ldlasso-package	<i>LD LASSO for Case Control Genetic Association Study</i>
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## Description

Performs a modification of the fused LASSO for SNP subset selection in genetic association studies. The LD LASSO requires densely spaced SNP data and haplotype block structure.

## Details

The ldlasso package is a collection of functions designed to apply the LD LASSO methodology as described in Younkin and Rao 2010. Functions useful for displaying the results are also included.

```
Package: ldlasso
Version: 2.0
Date: February 1, 2011
```

## Note

See the vignette 'ldlasso\_vignette.pdf' in ldlasso package directory doc/.

For a package useful for creating haplotype block boundaries see MATILDE by Pattaro et al., available at <http://astor.som.jhmi.edu/~gp/software/matilde/>

The following function may be used to create block boundaries with MATILDE.

```
find.bounds <- function( block.obj, prob.threshold = 0.95, B = 1e4, frac = 2 ){
  Xa <- as.double.snp.data(block.obj@gtdata)
  X1 <- ifelse( Xa == 0, "A", "B" )
  X2 <- ifelse( Xa == 2, "B", "A" )
  X <- makeGenotypes(matrix(paste(X1,X2,sep=""), byrow = F, ncol = dim(Xa)[2] ))
  LD.obj <- LD(X)
  null.X <- null.density(X)
  nXr <- data.frame(null.X$x, null.X$yR)
  names(nXr) <- c("x", "y")
  matilde.obj <- matilde(LD.obj$r^2, nXr, B=B)
  n <- length(matilde.obj$L)
  b.vec <- apply(matilde.obj$b[(n/frac):n,], 2, mean)
  block.cood <- as.numeric((b.vec >= prob.threshold))
  return( list( matilde.obj = matilde.obj, prob.threshold = prob.threshold, block.cood = block.cood ) )
}
```

**Author(s)**

Samuel G. Younkin  
<samuel.younkin@gmail.com>

**References**

Samuel Younkin, Joseph Nadeau, Robert Elston and J. Sunil Rao, "The Linkage Disequilibrium LASSO for SNP Selection in a Genetic Association Study of Late Onset Alzheimer Disease," Technical Report, 2010

**See Also**

ld\_lasso\_method, ld\_lasso, plot\_ldlasso, plot\_beta, heatmap

**Examples**

```
# Load example data
data(ldlasso_example)
ls()

plot_ldlasso( ldlasso.obj )

heatmap(ldlasso.obj)
```

---

block.bounds

*Creates a vector of haplotype block boundary basepair positions.*

---

**Description**

This function takes a map vector and a block coordinate vector and creates a vector of block boundary positions for use when plotting block boundaries, as in plot\_ldlasso.

**Usage**

```
block.bounds(map, block.cood)
```

**Arguments**

map	a vector of SNP map positions in basepairs (or kilo-basepairs)
block.cood	A vector of length p+1, where p is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all p+1 SNP bounded intervals. Use find.bounds to create this vector.

**Value**

A vector of block boundary positions in basepairs

**Author(s)**

Samuel G. Younkin

**Examples**

```
data("ldlasso_example")
bpmmap <- (block.obj@gtdata@map-block.obj@gtdata@map[1])/1e3
block.bounds.vec <- block.bounds( map = bpmmap , block.cood = block.cood )
block.bounds.vec
```

---

block.cood	<i>Vector of Haplotype Block Boundaries</i>
------------	---

---

**Description**

This is an indicator vector for haplotpye block boundaries. If there are p SNPs in the data then this vector will be of length p+1. Each element in the vector indicates whether the inter-SNP interval is a block boundary. The first and last element must always be one.

**Usage**

```
block.cood
```

**Format**

A vector containing 86 entries

**References**

Samuel Younkin, Joseph Nadeau, Robert Elston and J. Sunil Rao, "The Linkage Disequilibrium LASSO for SNP Selection in a Genetic Association Study of Late Onset Alzheimer Disease," Technical Report, 2010

---

block.map.matrix	<i>Creates an indicator matrix for haplotype block boundaries, for use in ld_lasso.</i>
------------------	---

---

**Description**

Simple function that maps the block boundary vector to an indicator matrix for use in the definition of constraint matrix. This matrix ensures that only within block SNP pairs are considered.

**Usage**

```
block.map.matrix(block.cood)
```

**Arguments**

block.cood      A vector of length  $p+1$ , where  $p$  is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all  $p+1$  SNP bounded intervals. Use find.bounds to create this vector.

**Value**

A matrix of logical variables. If the  $(i,j)$  entry is TRUE than SNP  $i$  and SNP  $j$  are in the same haplotype block.

**Author(s)**

Samuel G. Younkin

**See Also**

ld\_lasso

---

block.obj

*GenABEL Object with Genotype and Phenotype Data*

---

**Description**

This object is of class 'gwaa.data' from the package GenABEL. It contains both genotype and phenotype data in slots 'gtdata' and 'phdata' respectively. It is a small portion of a case-control genome-wide association study of Late-Onset Alzheimer's Disease performed at Mayo Clinic Florida.

**Usage**

block.obj

**Format**

An object of class 'gwaa.data' from the package GenABEL

**References**

Samuel Younkin, Joseph Nadeau, Robert Elston and J. Sunil Rao, "The Linkage Disequilibrium LASSO for SNP Selection in a Genetic Association Study of Late Onset Alzheimer Disease," Technical Report, 2010  
Y.S. Aulchenko, S. Ripke, A. Isaacs, and C.M. van Duijn, "GenABEL: An R Library for Genome-wide Association Analysis," *Bioinformatics*, vol. 23(10), pp. 1294-1296, 2007

---

chi2	<i>Creates a vector of chi-squared values from the allelic test of association</i>
------	--

---

**Description**

One degree of freedom Chi-squared test of allelic counts

**Usage**

```
chi2(Xa, Y)
```

**Arguments**

Xa	A matrix of genotype values coded as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively. Rows are subjects and columns are SNPs. May be created with method <code>as.double.snp.data</code> from the GenABEL package.
Y	A vector of disease phenotypes, diseased = 1, non-diseased = 0

**Value**

This function returns a vector of chi-squared, one degree of freedom, statistics for the allelic test of association. The length of this vector is the number of SNPs.

**Author(s)**

Samuel G. Younkin

---

get.cp	<i>Uses bootstrap sampling over a vector of LD LASSO constraint parameters, s2, to compute a vector of cp estimates.</i>
--------	--

---

**Description**

The vector of cp estimates is used to identify the cp-optimal solution.

**Usage**

```
get.cp(s2low, s2high, s2.vec.length, block.obj, Xa = NA, Y = NA, s1, r2.cut, block.cood, B = 20)
```

**Arguments**

s2low	The lower limit for the s2 vector.
s2high	The upper limit for the s2 vector.
s2.vec.length	The number of exponentially spaced values in the s2 vector.
block.obj	An object of class gwaa.data from GenABEL.
Xa	If block.obj is NA then a genotype matrix must be provided. Xa is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.
Y	If block.obj is NA then a phenotype vector Y must be provided. Y is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
s1	The LASSO parameter
r2.cut	Only SNP pairs with correlation greater than r2.cut are bounded by the LD LASSO constraint.
block.cood	A vector of length p+1, where p is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all p+1 SNP bounded intervals. Use find.bounds to create this vector.
B	Number of bootstrap samples

**Value**

s2.vec	A vector of s2 values
cp.vec	A vector of cp estimates
beta0.mat	A matrix of LD LASSO estimates
s1	The LASSO parameter

**Author(s)**

Samuel G. Younkin

**See Also**

ld\_lasso\_method

---

get.s1	<i>Finds an estimate for s1 based on an estimate of the expected false positive rate. This function is a wrapper for p0tos1.</i>
--------	--

---

**Description**

This function calls the function p0tos1, which finds an estimate for s1, given p0, where p0 is the number of nonzero estimates found with a permuted phenotype vector.

**Usage**

```
get.s1(i, block.obj, Xa = NA, Y = NA, r2.cut, s1high, s1low, max.iter, tol)
```

**Arguments**

<code>i</code>	Number of nonzero estimates in permuted model. If the expected false positive rate is desired to be 0.10, then set $i = 0.10 * p$ , where $p$ is the number of SNPs.
<code>block.obj</code>	An object of class <code>gwaa.data</code> from GenABEL.
<code>Xa</code>	If <code>block.obj</code> is NA then a genotype matrix must be provided. <code>Xa</code> is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.
<code>Y</code>	If <code>block.obj</code> is NA then a phenotype vector <code>Y</code> must be provided. <code>Y</code> is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
<code>r2.cut</code>	Value for the cutoff value of r-squared. Can be found with <code>r2.cut.fn</code> .
<code>s1high</code>	The initial upper limit in the bisection algorithm
<code>s1low</code>	The lower upper limit in the bisection algorithm
<code>max.iter</code>	The maximum number of iterations allowed in the bisection algorithm before NA is returned
<code>tol</code>	If $p$ never equals $i$ the bisection algorithm stops when $ s1.old - s1.new  < tol$ . Otherwise algorithm stops when $p = i$ .

**Details**

This function increases the value for  $p_0$  if NA is returned from `p0tos1`. The bisection algorithm is contained in the function `p0tos1`

**Value**

Given the number of nonzero SNPs allowed with permuted phenotype vector,  $p_0$ , this function returns an estimate for  $s_1$ .

**Author(s)**

Samuel G. Younkin

**See Also**

`p0tos1`



---

`heatmap`*Plots the heat map for the LD LASSO solution space*

---

### Description

This function uses the matrix `beta0.mat`, computed by the function `ld_lasso_method`, to plot a heat map of LD LASSO solutions. Increasing darkness corresponds to increasing values for the SNP LD LASSO estimate.

### Usage

```
heatmap( ldlasso.obj, s2.indx )
```

### Arguments

<code>ldlasso.obj</code>	An ld lasso object
<code>s2.indx</code>	<code>s2</code>

### Details

See vignette.

### Value

A heat map is a visual representation of the matrix of LD LASSO estimates. Rows correspond to `s2` values and columns correspond to SNP indices. The magnitude of the SNP estimate is represented by the degree to which the element is shaded. Increasing darkness corresponds to increasing magnitude.

### Author(s)

Samuel G. Younkin

### See Also

`plot_ldlasso`, `plot_beta`, `image`

---

ldlasso.obj                      *LD LASSO Object created by the function ld\_lasso\_method*

---

### Description

This is a data frame created by the function `ld_lasso_method`. It contains information about the parameters used to generate the three LD LASSO solutions, as well as the solutions themselves. It also contains the results from the grid search performed to estimate the cp-optimal solution. (see `cp.obj`) Some basic map information is also stored here for use when plotting.

### Usage

`ldlasso.obj`

### Format

data.frame

<code>beta1</code>	numeric	cp-optimal solution
<code>beta2</code>	numeric	fused solution
<code>beta3</code>	numeric	un-fused solution
<code>s2star</code>	numeric	s2 parameter used for cp-optimal solution
<code>cp.obj</code>	data.frame	s2 and cp vectors along with solution matrix used to find s2star
<code>log10p</code>	numeric	log base 10 of p-values from allelic test of association for each SNP
<code>bpmap</code>	numeric	vector of physical SNP positions in kb from left boundary
<code>block.bounds.vec</code>	numeric	position of block boundaries in kb from left boundary (does not include endpoints)
<code>s1</code>	numeric	LASSO parameter
<code>B</code>	numeric	number of bootstrap samples used by <code>ld_lasso_method</code> to find s2star
<code>s2.vec.length</code>	numeric	length of vector of s2 values used in <code>ld_lasso_method</code>

### References

Samuel Younkin, Joseph Nadeau, Robert Elston and J. Sunil Rao, "The Linkage Disequilibrium LASSO for SNP Selection in a Genetic Association Study of Late Onset Alzheimer Disease," Technical Report, 2010

---

ld\_lasso                      *The main function of the LD LASSO method*

---

### Description

The LD LASSO uses the correlation of SNP genotypes in a penalized least squares regression framework. The estimator is the solution to a convex optimization problem, and here we use the solution from the package `quadprog`.

**Usage**

```
ld_lasso(block.obj, block.cood = NA, Xa = NA, Y = NA, s1, s2, r2.cut = 0.5, delta =
1e-10, form = 3, ytype = 1, solve = TRUE )
```

**Arguments**

block.obj	An object of class gwaa.data from GenABEL.
block.cood	A vector of length p+1, where p is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all p+1 SNP bounded intervals. Use find.bounds to create this vector.
Xa	If block.obj is NA then a genotype matrix must be provided. Xa is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.
Y	If block.obj is NA then a phenotype vector Y must be provided. Y is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
s1	The LASSO constraint parameter – the sum of the magnitude of the estimates is bounded by s1.
s2	The LD LASSO constraint parameter – the absolute difference of SNP pair estimates is bounded by s2 times the log of r-squared
r2.cut	Only SNP pairs with correlation greater than r2.cut are bounded by the LD LASSO constraint.
delta	Included so that optimization is numerically feasible in cases when r-squared = 1
form	Form of constraint matrix. form is either 1, 2 or 3: 1 for $\text{cpcc.vec} <- 1e6 * \text{rep}(1, \text{length}(r2))$ – LASSO solution 2 for $\text{cpcc.vec} <- -s2 * \log(r2) + \text{delta}$ , $s1 <- 1e6$ – LD fused solution 3 for $\text{cpcc.vec} <- -s2 * \log(r2) + \text{delta}$ – LD LASSO
ytype	If ytype is 1 then Y is a vector of binary disease phenotypes, 0 for non-disease, 1 for diseased. If ytype is 2 then Y is the normalized log OR.
solve	logical variable indicating whether or not to solve regression problem. Useful when ld_lasso is used to construct constraint matrix, and the solution is not necessary, as in the selection of the r2 cutoff.

**Details**

This function performs the ld lasso regression with parameters s1, s2 and r2.cut on block.obj with haplotype block boundaries defined by block.cood.

**Value**

qp	List from the function solve.QP in the package quadprog. This object contains the solutions for c( beta, beta+, beta- ) and so the LD LASSO estimates are the first p elements, or qp\$solution[1:p]
y	A vector of normalized log OR
A	The constraint matrix

r2	The vector of r-squared values used to define constraint matrix. Elements in this vector are the correlation estimates for all inter-block SNP pairs.
b0	The vector of ld lasso constraints with length 3p
OR	A vector of odds ratios

**Author(s)**

Samuel G. Younkin

**References**

D. Goldfarb and A. Idnani, "A numerically stable dual method for solving strictly convex quadratic programs," *Mathematical Programming*, vol. 27, pp. 1-33, 1983.

**See Also**

ld\_lasso\_method, quadprog, solve.QP

**Examples**

```
data("ldlasso_example")
ldlasso.test <- ld_lasso( block.obj, block.cood, s1 = 1, s2 = 0.5 )
```

---

ld\_lasso\_method      *The LD LASSO function*

---

**Description**

This function implements a method for the automatic selection of parameters for the LD LASSO. It returns three solutions, the fused, cp-optimal, and unfused solutions. It also creates a matrix of solutions needed for creating the trace plot.

**Usage**

```
ld_lasso_method(block.obj, block.cood = NA, Xa = NA, Y = NA, bmap = NA,
maxcol = 5e3, p.frac = 0.10, B = 5, s2low = 5e-3, s2high = 5e1, s2.vec.length = 4, null = FALSE)
```

**Arguments**

block.obj	An object of class gwaa.data from GenABEL.
block.cood	A vector of length p+1, where p is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all p+1 SNP bounded intervals. Use find.bounds to create this vector.
Xa	If block.obj is NA then a genotype matrix must be provided. Xa is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.

Y	If block.obj is NA then a phenotype vector Y must be provided. Y is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
bpmmap	A vector of map positions in terms of kB from the left boundary
maxcol	The upper limit on the number of columns in the constraint matrix. This is to prevent computational overload. Increasing maxcol may increase computation time and memory needed.
p.frac	The fraction of SNPs allowed in LASSO model under null hypothesis. This parameter is used in the function get.s1.
B	The number of bootstrap iterations for cp estimate.
s2low	The lower limit of the s2 vector
s2high	The upper limit of the s2 vector
s2.vec.length	The number of exponentially spaced values of s2.
null	A logical variable that indicates if analysis should be performed on permuted phenotype vector.

### Details

Use function find.bounds to create block.cood vector with MATILDE MCMC methods. See ldlasso help page for details on the package MATILDE.

### Value

beta1	The ld lasso solution with s2 that minimizes cp (cp-optimal solution)
beta2	The ld lasso solution for lower limit of s2 interval (fused solution)
beta3	The ld lasso solution for upper limit of s2 interval (unfused solution)
s2star	The s2 value that minimizes cp
cp.obj	A list that contains information used for cp estimation
log10p	A vector of log10 p values for test of allelic association
bpmmap	A vector of map positions in base pairs
block.bounds.vec	A vector of block boundaries in kB from left boundary
s1	the LASSO constraint
B	Number of bootstrap samples
s2.vec.length	The length of the s2 vector

### Author(s)

Samuel G. Younkin

### References

Samuel Younkin, Joseph Nadeau, Robert Elston and J. Sunil Rao, "The Linkage Disequilibrium LASSO for SNP Selection in a Genetic Association Study of Late Onset Alzheimer Disease," Technical Report, 2010

**See Also**

ld\_lasso

**Examples**

```
# Load example data
# data(ldlasso_example)

# Run the method with low B and s2.vec.length first to test.
# ldlasso.obj <- ld_lasso_method( block.obj, block.cood, B = 3, s2.vec.length = 2 )
```

---

p0tos1	<i>Finds the LASSO parameter s1 that corresponds to desired false positive rate</i>
--------	---

---

**Description**

Estimates the LASSO parameter that corresponds to desired false positive rate. More specifically, it is a bisection algorithm designed to find an s1 that corresponds to p0 nonzero estimates from the ld\_lasso with a permuted phenotype vector.

**Usage**

```
p0tos1(p0, block.obj, Xa = NA, Y = NA, r2.cut = 0.01, s1high, s1low, max.iter = 100, tol = 0.1)
```

**Arguments**

p0	The number of nonzero estimates in permuted model. If the expected false positive rate is set at 0.10, then $i = 0.10 * p$ , where p is the number of SNPs.
block.obj	An object of class gwaa.data from GenABEL.
Xa	If block.obj is NA then a genotype matrix must be provided. Xa is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.
Y	If block.obj is NA then a phenotype vector Y must be provided. Y is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
r2.cut	The value for the cutoff value of r-squared. Can be found with r2.cut.fn.
s1high	The initial upper limit in the bisection algorithm
s1low	The initial lower upper limit in the bisection algorithm
max.iter	The maximum number of iterations allowed in the bisection algorithm before NA is returned
tol	If p never equals i the bisection algorithm stops when $ s1.old - s1.new  < tol$ . Otherwise algorithm stops when $p = i$ .

**Value**

An estimate for s1

**Author(s)**

Samuel G. Younkin

**See Also**

get.s1

---

plot\_beta                      *Plot the LD LASSO solution by physical position.*

---

**Description**

Creates a plot of LD LASSO estimates using the physical map, bmap

**Usage**

```
plot_beta( beta, bmap=NA, block.bounds.vec=NA )
```

**Arguments**

beta                      A vector of ldlasso estimates.  
bmap                      A vector of map positions in terms of kb from the left boundary  
block.bounds.vec                      A vector of block boundaries positions in kilobases from the left boundary.  
Boundaries are plotted at the midpoint of SNP intervals.

**Details**

Includes haplotpye block boundaries as vertical broken lines.

**Value**

A plot object.

**Author(s)**

Samuel G. Younkin

**See Also**

plot\_ldlasso

---

plot\_ldlasso                      *Diagnostic plot for an ldlasso object*

---

**Description**

Creates four plots; Top-left: Allelic test of association; Top- right: cp-optimal, fused, and unfused solutions (black, red, green); Bottom-left: Trace plot with fixed s1 ; Bottom-right: cp estimates vs. s2

**Usage**

```
plot_ldlasso( ldlasso.obj )
```

**Arguments**

ldlasso.obj      An ld lasso object

**Details**

Note that often two solutions overlap, and one is therefore concealed. The vertical line in the cp plot is drawn at the value of s2 used in the cp-optimal solution.

**Value**

A plot object

**Author(s)**

Samuel G. Younkin

**See Also**

ld\_lasso\_method, ld\_lasso

---

r2.cut.fn                      *Find the r-squared cutoff*

---

**Description**

Returns the minimum value of r2 in r2.vec that keeps the number of constraint matrix columns less than maxcol.

**Usage**

```
r2.cut.fn(block.obj, block.cood, Xa, Y, maxcol, r2.cut.min, r2.cut.max, r2.vec.length)
```



**Arguments**

block.obj	An object of class gwaa.data from GenABEL.
block.cood	A vector of length p+1, where p is the number of SNPs. block.cood is an indicator vector that indicates block boundaries at all p+1 SNP bounded intervals. Use find.bounds to create this vector.
Xa	If block.obj is NA then a genotype matrix must be provided. Xa is a matrix of genotype values codes as 0, 1 or 2 for homozygous major, heterozygous, or homozygous minor, respectively.
Y	If block.obj is NA then a phenotype vector Y must be provided. Y is a vector of diagnoses, where 0 is non-diseased and 1 is diseased.
maxcol	The maximum number of columns allowed in the constraint matrix. Default is 5,000.
r2.cut.min	The lower bound of the r2.cut interval
r2.cut.max	The upper bound of the r2.cut interval
r2.vec.length	The number of r2.cut values uniformly spaced in r2.cut interval

**Value**

The function r2.cut.fn returns the minimum value of r2.cut that satisfies,  $\text{ncol}(A) < \text{maxcol}$ , where A is the constraint matrix

**Author(s)**

Samuel G. Younkin

**See Also**

ld\_lasso

---

trace.plot

*Creates a trace plot for the LD LASSO*

---

**Description**

This function creates a trace plot as a function of s2, the LD LASSO constraint

**Usage**

```
trace.plot(beta0.mat, s2.vec, type = "l", indx = NA, s2star = NA, abs = TRUE)
```

**Arguments**

<code>beta0.mat</code>	A matrix where rows are ld lasso estimates. This matrix has number of rows equal to <code>length(s2.vec)</code> and number of columns equal to the number of SNPs
<code>s2.vec</code>	The vector of <code>s2</code> values used to generate the rows of <code>beta0.mat</code>
<code>type</code>	Type of plot, "l" for lines, "p" for points
<code>indx</code>	If index is NA then <code>indx</code> , is a vector of SNP indices to be plotted in red.
<code>s2star</code>	Value of <code>s2star</code> from <code>cp</code> object. If <code>s2star</code> is not NA, a vertical line is plotted at this value.
<code>abs</code>	A logical variable indicating whether to plot absolute value of beta instead of beta

**Details**

In this trace plot each line represents a SNP estimate and we see the behavior of the solution as the LD LASSO constraint is varied.

**Value**

Creates a trace plot.

**Author(s)**

Samuel G. Younkin

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