

Package: nhm (via r-universe)

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Type Package

Title Non-Homogeneous Markov and Hidden Markov Multistate Models

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Description Fits non-homogeneous Markov multistate models and misclassification-type hidden Markov models in continuous time to intermittently observed data. Implements the methods in Titman (2011) <doi:10.1111/j.1541-0420.2010.01550.x>. Uses direct numerical solution of the Kolmogorov forward equations to calculate the transition probabilities.

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ematrix.nhm	<i>Compute the misclassification probability matrix from a fitted nhm model</i>
-------------	---

Description

Outputs the matrix of misclassification probabilities in a misclassification type hidden Markov multi-state model fitted using [nhm](#).

Usage

```
ematrix.nhm(object, covvalue=NULL)
```

Arguments

object	Fitted model object produced using nhm .
covvalue	Optional vector of covariate vectors (should be given in the order specified in the covariate option in nhm). If omitted the function will use the mean values of the covariates.

Details

The `emat_nhm` function used to fit the model is called to obtain the values of the misclassification probabilities at the supplied times for the supplied covariate value.

Value

Returns a list containing a matrix of misclassification probabilities and a matrix of corresponding standard errors computed using the delta method.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

See Also

[nhm](#), [plot.nhm](#), [predict.nhm](#), [qmatrix.nhm](#)

example_data1	<i>Example of data on a progressive 4 state process</i>
---------------	---

Description

The observed states and associated observation times for 1000 patients simulated from a 4 state process non-homogeneous Markov model

Usage

```
data("example_data1")
```

Format

A data frame with 3861 rows and 5 variables:

state Observed state at the time of observation

time Time at which the observation occurred

id Patient identification number

cov1 Binary covariate

cov2 Continuous covariate

example_data2	<i>Example of data on a progressive 4 state process with state misclassification</i>
---------------	--

Description

The observed states and associated observation times for 1000 patients simulated from a 4 state process non-homogeneous Markov model with misclassification to adjacent transient states.

Usage

```
data("example_data1")
```

Format

A data frame with 3864 rows and 5 variables:

state Observed state at the time of observation

time Time at which the observation occurred

id Patient identification number

cov1 Binary covariate

cov2 Continuous covariate

initialprob.nhm	<i>Compute the initial probability vector from a fitted nhm model</i>
-----------------	---

Description

Outputs the vector of initial state probabilities in a misclassification type hidden Markov multi-state model fitted using [nhm](#).

Usage

```
initialprob.nhm(object, covvalue=NULL)
```

Arguments

object	Fitted model object produced using nhm .
covvalue	Optional vector of covariate vectors (should be given in the order specified in the covariate option in nhm). If omitted the function will use the mean values of the covariates.

Details

The `initp_nhm` function used to fit the model is called to obtain the values of the initial state vector at the supplied times for the supplied covariate value.

Value

Returns a list containing a vector of initial state probabilities and a corresponding vector of standard errors computed using the delta method.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

See Also

[nhm](#), [ematrix.nhm](#)

model.nhm

*Model object set up for non-homogeneous Markov models***Description**

Sets up a model object in preparation for fitting a non-homogeneous Markov or misclassification type hidden Markov multi-state model.

Usage

```
model.nhm(formula, data, subject, covariates=NULL, type, trans,
nonh=NULL, covm=NULL, centre_time=NULL, emat=NULL, ecovm=NULL,
firstobs=NULL, initp=NULL, initp_value=NULL, initcovm=NULL,
splinelist=NULL, degrees=NULL, censor=NULL,
censor.states=NULL, death=FALSE, death.states=NULL, intens=NULL)
```

Arguments

formula	A formula identifying the state and time variables within data, for instance <code>state ~ time</code> would imply the variables are state and time, respectively.
data	data frame containing the observed states, observation times, subject identifiers and covariates. Should include initial observation/recruitment times.
subject	Name of the subject identifier variable within the data data frame.
covariates	A character vector giving the variable names of the covariates to be used in the model
type	type of intensity model. 'bespoke': user supplied, 'weibull': Model with Weibull transition intensity functions with respect to time. 'gompertz': Gompertz/exponential growth intensity models. 'bspline': b-spline function of time model.
trans	Square matrix of viable transitions with dimension equal to the number of states. Impossible transitions should be 0. Others should be labelled consecutively from 1. Labelling transitions with the same value assumes the parameter is shared.
nonh	Square matrix to indicate non-homogeneous transitions with dimension equal to the number of states. Impossible transitions or homogeneous transitions should be 0. Otherwise label consecutively from 1. Labelling the same value implies the same non-homogeneity. Not required if <code>type='bespoke'</code> . If otherwise omitted a time homogeneous model is fitted.
covm	Either a named list of <code>nstate x nstates</code> indicating the covariate effects with respect to a particular covariate OR an <code>nstate x nstate x ncov</code> array to indicate covariate effects, where <code>ncov</code> is the length of the supplied <code>covariates</code> vector. 0 implies no covariate effect. Otherwise label consecutively from 1. Labelling the same value implies a common covariate effect. Not required if <code>type='bespoke'</code> .
centre_time	Value by which to centre time for Gompertz models. By default the model is of the form $h(t) = \exp(a+bt)$, centring by c reparametrizes this to $h(t) = \exp(a+b(t-c))$. Centring can improve the convergence of optimization routines.

emat	Square matrix of viable misclassification errors. Must be supplied if the model has misclassification. Impossible errors should be 0. Others should be labelled consecutively. Labelling the same implies a common parameter on the logit scale.
ecovm	Either a named list of nstate x nstates indicating the covariate effects with respect to a particular covariate OR an nstate x nstate x ncov array to indicate indicate covariate effects on misclassification, where ncov is the length of the supplied covariates vector. 0 implies no covariate effect. Otherwise label consecutively from 1. Labelling the same value implies a common covariate effect.
firstobs	For misclassification models: Form of the first observation for each subject in the data. 'exact': Initial state not subject to misclassification (default) 'absent': No initial state. First observation is ignored and state occupied is based on initial probabilities model. 'misc': Initial state is subject to misclassification.
initp	For misclassification models: Numerical vector of length nstate to define the model for the initial probabilities. The first entry should be zero. Should be numbered consecutively. If the same number is repeated implies a shared parameter. If absent then initial probabilities taken from initp_value.
initp_value	For misclassification models where firstobs="absent" or "misc": Fixed value of initial probabilities is missing. Should be a numerical vector of length nstate. Ignored if initp is present. Default if absent is $c(1, 0, \dots)$.
initcovm	For misclassification models; Either a named list of vectors of length nstate, or an nstate x ncovs matrix to specify the covariate effects on misclassification probabilities. 0 implies no covariate effect. Otherwise label consecutively from 1. Labelling the same value implies a common covariate effect.
splinelist	For bspline models only: list (of length equal to the number of nonhomogeneous transitions) of knot point locations including the boundary knots.
degrees	For bspline models only: optional vector (of length equal to number of nonhomogeneous transitions) of degrees of splines. Defaults to 3 if not specified.
cancel	Vector of censor state indicators in the data. Note that censored observations can only occur as the last observation for a subject.
cancel.states	List of vectors of states in which subject occupy if censored by corresponding censor state indicator. Can be a vector if only one censor state marker is present.
death	Setting TRUE assumes exact death times are present in the data set
death.states	Vector specifying which states have exact death times. Should only correspond to absorbing states.
intens	Optional supplied intensity function. See below for details.

Details

The function allows the model to be specified and creates the metadata needed to use nhm to fit it. The function automatically generates a function intens which defines the generator matrix of the model and its first derivatives as a function of time t , covariates z and the underlying parameters x , provided the model is of Weibull, Gompertz or B-spline type.

Alternatively, `type='bespoke'` can be chosen. In which case it is necessary for the user to supply a function `intens`. This must have arguments `t`, `z`, `x` and return a list consisting of a component `q` which is the `nstate x nstate` generator matrix, and `dq` which is the `nstate x nstate x nparQ` first derivatives of the generator matrix with respect to the parameters of the model, where `nparQ` is the number of parameters in the model for the intensities only (excludes parameters for the `emat` or `initp`). Since unrestricted maximization is used so the parameters must take values on `-Inf`, `Inf`. Note that using a hard-coded version via `type='bespoke'` can be substantially faster than the analogous automatically generated function, so for large models or datasets it may be advantageous to code directly.

For misclassification type models, the function also automatically creates functions `emat_nhm` and `initp_nhm`, to allow the misclassification probability matrix and the initial probability vectors and their derivatives to be calculated at given parameter and covariate values. In each case, a multinomial logistic regression is used for the covariate model. User specification of the misclassification probability function or initial probability vector is not currently possible.

Value

Returns an object of class `nhm_model` containing the necessary metadata needed to use `nhm` to fit the model.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

See Also

[nhm](#)

nhm

Fit a non-homogeneous Markov model using maximum likelihood

Description

Fit a continuous-time Markov or hidden Markov multi-state model by maximum likelihood. Observations of the process can be made at arbitrary times, or the exact times of transition between states can be known. Covariates can be fitted to the Markov chain transition intensities or to the hidden Markov observation process.

Usage

```
nhm(model_object, initial=NULL, gen_inits=FALSE,  
control, score_test=FALSE, fixedpar=NULL)
```

Arguments

<code>model_object</code>	Model object created using <code>model.nhm</code>
<code>initial</code>	Vector of initial parameter values
<code>gen_inits</code>	If TRUE, then initial values for the transition intensities are generated automatically using the method in <code>crudeinits.msm</code> from the msm package. This is not available for models with misclassified states. If FALSE a BHHH algorithm implemented using maxLik is used.
<code>control</code>	Object of class <code>nhm.control</code> specifying various settings for the solution of the KFEs and the optimization. See <code>nhm.control</code> for default settings.
<code>score_test</code>	If TRUE just the gradient and Fisher information at the supplied values will be computed to allow score tests to be performed.
<code>fixedpar</code>	Numerical vector indicating which parameters are taken as fixed at the value specified by <code>initial</code> .

Details

For more details about the methodology behind the **nhm** package, see Titman (2011) and the package vignette.

Value

By default returns an object of class `nhm` containing model output data such as the estimated parameters, maximized likelihood value, information matrix etc. The object can be used with `print`, `predict`, `plot` and `anova`.

If `score.test=TRUE` then returns an object of class `nhm_score`. See `print.nhm_score` for more details.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

Titman AC. Flexible Nonhomogeneous Markov Models for Panel Observed Data. *Biometrics*, 2011. 67, 780-787.

See Also

`model.nhm`, `nhm.control`, `plot.nhm`, `predict.nhm`, `print.nhm_score`

Examples

```
### Example dataset
### For further examples, see the vignette
trans <- rbind(c(0,1,0,0),c(0,0,2,0),c(0,0,0,3),rep(0,4))
nonh <- rbind(c(0,1,0,0),c(0,0,2,0),c(0,0,0,3),rep(0,4))
gomp_model <- model.nhm(state~time, data=example_data1, subject = id,
                       type="gompertz", trans=trans, nonh=nonh)
```



```

initial_val <- c(-0.65,-0.45,-0.55,0,0,0)
gomp_fit <- nhm(gomp_model,initial=initial_val,control=nhm.control(obsinfo=FALSE))
gomp_fit
plot(gomp_fit)
plot(gomp_fit,what="intensities")

```

nhm.control

Ancillary arguments for controlling nhm fits

Description

This is used to set various logical or numeric parameters controlling a non-homogeneous Markov model fit. Usually to be used within a call to nhm.

Usage

```

nhm.control(tmax=NULL, coarsen=FALSE, coarsen.vars=NULL, coarsen.lv=NULL,
checks=FALSE,rtol=1e-6, atol=1e-6, fishscore=NULL, linesearch=FALSE, damped=FALSE,
damppar=0,obsinfo=TRUE,splits=NULL,ncores=1,print.level=2, maxLikcontrol=NULL)

```

Arguments

tmax	Optional parameter to set the maximum time to which the Kolmogorov Forward equations should be integrated. Defaults to 1+max(time) if left unspecified.
coarsen	If TRUE the covariate values will be subjected to coarsening using K-means clustering, so there are fewer unique values. This is useful for large datasets with continuous covariates.
coarsen.vars	Vector of the index of covariates which require coarsening. Must be supplied if coarsen=TRUE.
coarsen.lv	Number of unique covariate values to which the covariates should be coarsened.
checks	If TRUE some basic checks will be performed to ensure the accuracy of the supplied intens function. Mainly useful if a user defined type="bespoke" intensity function is used for which the default is TRUE, otherwise default is FALSE
rtol	Relative error tolerance to be passed to lsoda, default is 1e-6
atol	Absolute error tolerance to be passed to lsoda, default is 1e-6
fishscore	If TRUE then the Fisher scoring algorithm will be used provided the model has no censoring, exact death times or misclassification. This is generally faster, but less robust than the BHHH algorithm.
linesearch	If TRUE and fishscore=TRUE then a line search will be performed to find the best step length in the Fisher scoring algorithm.
damped	If TRUE the Fisher scoring algorithm will be damped (e.g. Levenberg type algorithm). Useful if some parameters are close to being unidentifiable.
damppar	Numerical damping parameter to be applied if damped=TRUE

obsinfo	If TRUE the observed Fisher information will be computed in addition to the expected information when the Fisher scoring algorithm is used. For optimization with <code>maxLik</code> the observed Fisher information will be used as the Hessian rather than the squared gradient vectors.
splits	Optional vector of intermediate split times for solving the ODEs. Only needed if $P(0,t)$ becomes singular for some t causing the optimization to stop. Should be a set of consecutive values less than <code>tmax</code> .
ncores	Number of cores to use. 1= no parallelization, 2 or more: Uses <code>mclapply</code> when solving ODEs with different covariates patterns.
print.level	For <code>maxLik</code> optimization; level of detail to print. Integer from 0 to 3. Defaults to 2.
maxLikcontrol	For <code>maxLik</code> optimization; optional list of control parameters to be passed to <code>maxLik</code> .

Details

`tmax`, `rtol` and `atol` refer directly to parameters with the `lsoda` function in `deSolve` and relate to how the Kolmogorov Forward Equations are numerically solved.

`coarsen`, `coarsen.vars` and `coarsen.lv` are useful in situations where it is computationally infeasible (or unattractive) to compute the exact solution for all covariate patterns. Implements an approximate solution in which the covariates are coarsened using K-means clustering (as proposed in Titman (2011)).

`linesearch`, `damped`, `damppar` are specific to the Fisher scoring algorithm.

Setting `obsinfo=TRUE` will tend to give more accurate standard error estimates and gives more opportunity to check for non-convergence of the maximum likelihood procedure.

The option `splits` modifies the way in which the transition probabilities are computed. By default, `nhm` solves a single system of differential equations starting from 0 to obtain $P(0, t)$ and then uses inversion of the Chapman-Kolmogorov equation $P(0, t) = P(0, t_0)P(t_0, t)$ to find $P(t_0, t)$ for a given $t_0 > 0$. In some cases $P(0, t_0)$ will be singular or effectively singular. If a split is specified at s then `nhm` will find $P(t_0, t)$ for $t_0 > t^*$ by solving the system of equations $P(t^*, t)$ where t^* is the smallest interval start time greater than or equal to s within the data. If `nhm` fails due to the lack of split times, the error message will advise on the interval in which the split should be introduced. Note that the need for splits can also arise if the initial parameters specified are inappropriate. It may often be better to find more appropriate initial parameter estimates, for instance by fitting the analogous homogeneous model in `msm`, rather than adding multiple split times.

`ncores` allows parallel processing to be used, through the **parallel** package, to simultaneously solve the systems of differential equations for each covariate pattern. If `ncores > 1` then `ncores` defines the `mc.cores` value in `mclapply`. Note that the data needs to include multiple covariate patterns for this to successfully increase computation speed.

Value

A list containing the values of each of the above constants

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

Titman AC. Flexible Nonhomogeneous Markov Models for Panel Observed Data. *Biometrics*, 2011. 67, 780-787.

See Also

[nhm](#)

plot.nhm

Plot transition probabilities or intensities from a fitted nhm model.

Description

Produces plots of the transition probabilities or intensities from a non-homogeneous Markov or misclassification type hidden Markov multi-state model fitted using [nhm](#).

Usage

```
## S3 method for class 'nhm'
plot(x, what="probabilities",time0=0, state0=1, times=NULL,
     covvalue=NULL, ci=TRUE, sim=FALSE, coverage=0.95, B=1000, rtol=1e-6,
     atol=1e-6, main_arg=NULL, xlab="Time", ...)
```

Arguments

x	Fitted model object produced using nhm .
what	Character string to indicate what should be plotted. Options are probabilities (the default which produces transition probabilities) or intensities (to produce a plot of the intensities)
time0	Starting time from which to compute the transition probabilities or intensities. Defaults to 0.
state0	Starting state from which to compute the transition probabilities. Defaults to 1. Not required for transition intensities
times	Optional vector of times at which to compute the transition probabilities or intensities. If omitted, the probabilities/intensities will be computed at a sequence of times of length 100 from time0 to the maximum observed time in the data.
covvalue	Optional vector of covariate vectors (should be given in the order specified in the covariate option in nhm). If omitted the function will use the mean values of the covariates.
ci	If TRUE pointwise confidence intervals will be shown in addition to the point estimates.
sim	If TRUE a simulation Delta method (Mandel, 2013) will be used to calculate the confidence intervals. Otherwise the standard Delta method will be applied.
coverage	Coverage level (should be a value between 0 and 1) for the confidence intervals. Defaults to 0.95.

B	Number of simulations to be performed to compute the simulation Delta method.
rtol	Relative tolerance parameter to be used by lsoda when solving the differential equations for the transition probabilities.
atol	Absolute tolerance parameter to be used by lsoda when solving the differential equations for the transition probabilities.
main_arg	Character string specifying beginning of title to be given to each of the plot panes generated.
xlab	Character string specifying x-axis label to be given to each plot.
...	Other items to be passed to the function. Currently not used.

Details

Computation is performed by calling `predict.nhm`, for the transition probabilities, or `qmatrix.nhm` for the intensities (see for more details).

Value

Generates a multi-pane plot for each state. If values are required they can be obtained using `predict.nhm`.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

Mandel M. Simulation-based confidence intervals for functions with complicated derivatives. 2013. *The American Statistician*, 67. 76-81.

See Also

`nhm`, `predict.nhm`, `qmatrix.nhm`

predict.nhm	<i>Compute state occupation or transition probabilities from a fitted nhm model</i>
-------------	---

Description

Outputs the transition probabilities from a non-homogeneous Markov or misclassification type hidden Markov multi-state model fitted using `nhm`.

Usage

```
## S3 method for class 'nhm'
predict(object, time0=0, state0=1, times=NULL, covvalue=NULL,
ci=TRUE, sim=FALSE, coverage=0.95, B=1000, rtol=1e-6,
atol=1e-6, ...)
```

Arguments

object	Fitted model object produced using nhm .
time0	Starting time from which to compute the transition probabilities. Defaults to 0.
state0	Starting state from which to compute the transition probabilities. Defaults to 1.
times	Optional vector of times at which to compute the transition probabilities. If omitted, the probabilities will be computed at a sequence of times from time0 to the maximum observed time in the data.
covvalue	Optional vector of covariate vectors (should be given in the order specified in the covariate option in nhm). If omitted the function will use the mean values of the covariates.
ci	If TRUE pointwise confidence intervals will be shown in addition to the point estimates.
sim	If TRUE a simulation Delta method (Mandel, 2013) will be used to calculate the confidence intervals. Otherwise the standard Delta method will be applied.
coverage	Coverage level (should be a value between 0 and 1) for the confidence intervals. Defaults to 0.95.
B	Number of simulations to be performed to compute the simulation Delta method.
rtol	Relative tolerance parameter to be used by <code>lsoda</code> when solving the differential equations
atol	Absolute tolerance parameter to be used by <code>lsoda</code> when solving the differential equations
...	Other items to be passed to the function. Currently not used.

Details

The same approach as in the main [nhm](#) function of numerically solving the system of differential equations is used to compute transition probabilities based on the maximum likelihood estimates found in [nhm](#) and assuming a specific vector of covariates.

If the simulation delta method approach is specified then the function will generate B parameter vectors from the asymptotic distribution of the MLE and solve the system of equations for each of them, before finding pointwise percentile bootstrap confidence intervals from them.

Value

Returns a list containing the vector of times at which the probabilities are computed, a matrix of probabilities for each state at each of the times. If confidence intervals are requested then the lower and upper limits are also provided.

If transition intensity (as opposed to probability) estimates are required then [qmatrix.nhm](#) should be used.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

Mandel M. Simulation-based confidence intervals for functions with complicated derivatives. 2013. *The American Statistician*, 67. 76-81.

See Also

[nhm](#), [plot.nhm](#), [qmatrix.nhm](#)

print.nhm_score	<i>Print output from a score test of a nhm object</i>
-----------------	---

Description

Print output from a score test based on parameters supplied to [nhm](#) with `score_test=TRUE` specified.

Usage

```
## S3 method for class 'nhm_score'
print(x, which_comp = NULL, ...)
```

Arguments

<code>x</code>	An object of class <code>nhm_code</code> generated using nhm .
<code>which_comp</code>	Optional vector to specify which of the parameters are to be tested. If omitted, the function will assume all parameters governing non-homogeneity are to be tested. Must be supplied if <code>type='bespoke'</code> was specified when creating the object.
<code>...</code>	Other parameters to be supplied. Currently ignored.

Details

The function provides usable output from specifying `score_test=TRUE` when using [nhm](#). It is most useful to provide a quick(er) test of whether there may be non-homogeneity in a specific model. Note that the model assumes the initial parameters correspond to the constrained maximum likelihood estimate (for instance a model with all the parameters relating to time homogeneity).

The method can be used to compute the local score tests of homogeneity proposed by de Stavola (1988) if `type="gompertz"` is specified in [nhm](#).

If `fisherscore=TRUE` in [nhm](#) then the expected Fisher information is used. Otherwise, the empirical mean of the squared gradient terms (as used in the BHHH algorithm) is used to estimate the information.

Value

Prints the results of a score test.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

de Stavola BL. Testing Departures from Time Homogeneity in Multistate Markov Processes. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 1988. 37. 242-250.

See Also

[nhm](#)

qmatrix.nhm

Compute transition intensities from a fitted nhm model

Description

Outputs the transition intensities from a non-homogeneous Markov or misclassification type hidden Markov multi-state model fitted using [nhm](#).

Usage

```
qmatrix.nhm(object, time0=0, times=NULL, covvalue=NULL, ci=TRUE, sim=FALSE,
coverage=0.95, B=1000)
```

Arguments

object	Fitted model object produced using nhm .
time0	Starting time from which to compute the transition intensities. Defaults to 0.
times	Optional vector of times at which to compute the transition intensities. If omitted, the intensities will be computed at a sequence of times from time0 to the maximum observed time in the data.
covvalue	Optional vector of covariate vectors (should be given in the order specified in the covariate option in nhm). If omitted the function will use the mean values of the covariates.
ci	If TRUE pointwise confidence intervals will be shown in addition to the point estimates.
sim	If TRUE a simulation Delta method (Mandel, 2013) will be used to calculate the confidence intervals. Otherwise the standard Delta method will be applied.
coverage	Coverage level (should be a value between 0 and 1) for the confidence intervals. Defaults to 0.95.
B	Number of simulations to be performed to compute the simulation Delta method.

Details

The `intens` function used to fit the model is called to obtain the values of the transition intensities at the supplied times for the supplied covariate value.

If the simulation delta method approach is specified then the function will generate `B` parameter vectors from the asymptotic distribution of the MLE and compute the intensities for each of them, before finding pointwise percentile bootstrap confidence intervals from them.

Value

Returns a list containing the vector of times at which the intensities are computed, a matrix of probabilities for each state at each of the times. If confidence intervals are requested then the lower and upper limits are also provided.

If transition probability (as opposed to intensity) estimates are required then `predict.nhm` should be used.

Author(s)

Andrew Titman <a.titman@lancaster.ac.uk>

References

Mandel M. Simulation-based confidence intervals for functions with complicated derivatives. 2013. *The American Statistician*, 67. 76-81.

See Also

[nhm](#), [plot.nhm](#), [predict.nhm](#)

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