Package ‘simode’

December 1, 2019

Type Package

Title Statistical Inference for Systems of Ordinary Differential Equations using Separable Integral-Matching

Version 1.1.8

Description Implements statistical inference for systems of ordinary differential equations, that uses the integral-matching criterion and takes advantage of the separability of parameters, in order to obtain initial parameter estimates for nonlinear least squares optimization.


Depends R (>= 3.4.0)
Imports deSolve, pracma, quadprog
Suggests parallel, Rcgmin, Rvmmin, R.rsp, knitr, testthat
License GPL (>= 2)
Encoding UTF-8
LazyData true
RoxygenNote 6.1.1
VignetteBuilder R.rsp
NeedsCompilation no

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Repository CRAN

Date/Publication 2019-12-01 20:00:02 UTC

R topics documented:

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confint.profile.simode

Calculates confidence intervals for the model parameters

Description
Calculates confidence intervals for the model parameters, based on the given likelihood profiles

Usage
## S3 method for class 'profile.simode'
confint(object, parm = NULL, level = 0.95, ...)

Arguments
object A fitted model object: profile.simode object returned by a call to profile.
parm A specification of which parameters are to be given confidence intervals (named vector). If missing, all parameters are considered.
level The confidence level required.
... Additional argument(s) for methods.

Value
The confidence intervals.
plot.confint.simode  
Plot confidence intervals for the model parameters

Description
Plot confidence intervals for the model parameters of a simode object, calculated based on likelihood profiles

Usage
## S3 method for class 'confint.simode'
plot(x, which = NULL, pars_true = NULL,
     legend = F, cols = list(fit = "blue", true = "black"), ...)

Arguments
x  
confint.simode object returned by a call to confint
which
Which parameters to plot the confidence intervals for. If empty, the plot will include all of the parameters in x.
pars_true
The true parameter values (if are known).
legend
Whether or not to add a figure legend.
cols
List of colors for each element of the plot.
...  
Additional argument(s) for methods.

plot.list.simode  
Plot the fit/estimates of a list.simode object

Description
Plot the fit or parameter estimates obtained from a call to simode with obs_sets>1.

Usage
## S3 method for class 'list.simode'
plot(x, type = c("fit", "est"), show = c("nls", "im", "both"), which = NULL, pars_true = NULL, time = NULL,
     plot_mean_sd = F, plot_im_smooth = F, legend = F,
     mfrow = par("mfrow"), cols = list(nls_fit = "blue", im_fit = "green",
     true = "black", obs = "red", im_smooth = "magenta"), ...)


plot.profile.simode

Arguments

- **x**: list.simode object.
- **type**: Type of plot - 'fit' to plot the fitted equations and 'est' to plot the parameter estimates.
- **show**: Whether to plot the fit/estimates obtained using nonlinear least squares ('nls'), integral-matching ('im') or both ('both').
- **which**: Which variables to plot in case type='fit', or which parameters to plot in case type='est'. If empty, the plot will include all of the variables/parameters in x.
- **pars_true**: The true parameter values (if are known). Should be named using the parameter names. If given, the true values for the variables/parameters will be added to the plot.
- **time**: The time points to use for the fitted curves (relevant only for type='fit'). If not given then the time points of the observations in x will be used.
- **plot_mean_sd**: Plot the mean and standard deviation for the fit/estimates of the simode objects in x. To be used when x is the result of fitting monte-carlo simulations.
- **plot_im_smooth**: Whether or not to plot the smoothed curves created and used by the integral-matching procedure (relevant only for type='fit').
- **legend**: Whether or not to add a figure legend.
- **mfrow**: A vector of the form c(nr,nc) setting the layout of subplots in one plot (see also par).
- **cols**: List of colors for each element of the plot.
- **...**: Additional argument(s) for methods.

plot.profile.simode  
*Plot the likelihood profiles for the model parameters*

Description

Plot the likelihood profiles for the model parameters

Usage

```r
## S3 method for class 'profile.simode'
plot(x, which = NULL, mfrow = par("mfrow"),
     cols = list(fit = "blue", threshold = "red"), ...)
```

Arguments

- **x**: profile.simode object returned by a call to profile.
- **which**: Which parameters to plot the likelihood profiles for. If empty, the plot will include all of the parameters in x.
- **mfrow**: A vector of the form c(nr,nc) setting the layout of subplots in one plot (see also par).
- **cols**: List of colors for each element of the plot.
- **...**: Additional argument(s) for methods.
Description

Plot the fit or parameter estimates obtained from a call to simode.

Usage

```r
## S3 method for class 'simode'
plot(x, type = c("fit", "est"), show = c("nls", "im", "both"), which = NULL, pars_true = NULL, time = NULL, plot_im_smooth = F, legend = F, mfrow = par("mfrow"), cols = list(nls_fit = "blue", im_fit = "green", true = "black", obs = "red", im_smooth = "magenta"), ...)```

Arguments

- `x` simode object returned by a call to `simode`.
- `type` Type of plot - 'fit' to plot the fitted variables and 'est' to plot the parameter estimates.
- `show` Whether to plot the fit/estimates obtained using nonlinear least squares ('nls'), integral-matching ('im') or both ('both').
- `which` Which variables to plot in case `type='fit'`, or which parameters to plot in case `type='est'`. If empty, the plot will include all of the variables/parameters in x.
- `pars_true` The true parameter values (if are known). Should be named using the parameter names. If given, the true values for the variables/parameters will be added to the plot.
- `time` The time points to use for the fitted curves (relevant only for `type='fit'`). If not given then the time points of the observations in x will be used.
- `plot_im_smooth` Whether or not to plot the smoothed curves created and used by the integral-matching procedure (relevant only for `type='fit'`).
- `legend` Whether or not to add a figure legend.
- `mfrow` A vector of the form c(nr,nc) setting the layout of subplots in one plot (see also `par`).
- `cols` List of colors for each element of the plot.
- `...` Additional argument(s) for methods.
**plot_trace**  
*Plot optimization trace of a call to simode*

**Description**
Plot a trace of the loss values and parameter estimates during the integral-matching/nonlinear least squares optimization within a call to simode. For the traces to exist, the arguments `save_im_trace` and/or `save_nls_trace` in `simode.control` should be set to true, when calling `simode`.

**Usage**
```r
plot_trace(x, show = c("nls", "im", "both"), which = NULL,
           mfrow = par("mfrow"), cols = list(nls_fit = "blue", im_fit = "green"), ...)
```

**Arguments**
- `x`: simode object returned by a call to `simode`.
- `show`: Whether to plot the estimates obtained using nonlinear least squares (`"nls"`), integral-matching (`"im"`) or both (`"both"`).
- `which`: Which parameters’ traces to plot. If NULL, the trace for all the parameters in `x` will be plotted.
- `mfrow`: A vector of the form `c(nr,nc)` setting the layout of subplots in one plot (see also `par`).
- `cols`: List of colors for each element of the plot.
- `...`: Additional argument(s) for methods.

**print.confint.simode**  
*Print method for confint.simode objects*

**Description**
Print method for `confint.simode` objects.

**Usage**
```r
## S3 method for class 'confint.simode'
print(x, ...)
```

**Arguments**
- `x`: The `confint.simode` object.
- `...`: Additional argument(s) for methods.
print.profile.simode  

Print method for profile.simode objects

Description

Print method for profile.simode objects

Usage

## S3 method for class 'profile.simode'
print(x, ...)

Arguments

x The profile.simode object.
...

Arguments

x The simode object.
...

Arguments

x The simode object.
...

Additional argument(s) for methods.
print.summary.simode  

**Print method for summary.simode objects**

**Description**

Print method for summary.simode objects

**Usage**

```r
## S3 method for class 'summary.simode'
print(x, ...)
```

**Arguments**

- `x`  The summary.simode object.
- `...` Additional argument(s) for methods.

(profile.simode  

**Calculate likelihood profiles for the model parameters**

**Description**

Calculate likelihood profiles for the model parameters

**Usage**

```r
## S3 method for class 'simode'
profile(fitted, which = NULL, optim_type = c("nls", "both"),
        step_size, max_steps = 100, alpha = 0.05, skip_err = T,
        trace = 0, save_to_log = F, ...)
```

**Arguments**

- `fitted`  simode object returned by a call to simode.
- `which`  Which parameters to estimate the profile for.
- `optim_type`  Whether to calculate the profiles based on maximum-likelihood optimization only ("nls") or based on integral-matching followed by maximum-likelihood optimization ("both").
- `step_size`  Step size for profiling (one value for all parameters or a value for each parameter in which).
- `max_steps`  Maximum number of steps to take in each direction.
- `alpha`  Maximum (two-sided) likelihood ratio test confidence level to find.
- `skip_err`  Whether on not to stop the calculation if encountering a problem with one point in the profile.
trace Report level (0-4), with higher values producing more tracing information.
save_to_log Whether to redirect output to log file. The log file will be saved to tempdir().
...

Details

If the call to `simode`, which returned the fitted object given to this method, included a user-defined likelihood function (with the `calc_nll` argument), then the likelihood profiles will be calculated using this function. Otherwise, the profiles will be calculated using a likelihood based on a Gaussian distribution with fixed sigma, where sigma will be estimated in the background together with the rest of the model parameters.

Value

The likelihood profiles.

---

**simode**  
Statistical inference of ordinary differential equations using separable integral-matching

Description

Estimating the parameters of an ODE system in two stages: 1) Estimate the parameters using separable integral-matching, 2) Estimate the parameters using nonlinear least squares starting from the values obtained in stage 1.

Usage

```r
simode(equations, pars, time, obs, obs_sets = 1, nlin_pars = NULL, likelihood_pars = NULL, fixed = NULL, start = NULL, lower = NULL, upper = NULL, im_method = c("separable", "non-separable"), decouple_equations = F, gen_obs = NULL, calc_nll = NULL, scale_pars = NULL, simode_ctrl = simode.control(), ...)
```

Arguments

- **equations** Named vector. The equations describing the ODE system. Each element of the vector should contain a character representation of the right-hand side of an equation, and should be named according to the left-hand side of the equation (i.e., the variable name). An equation can contain parameters appearing in `pars`, variables appearing in the equations names, observed non-modeled variables appearing in `obs`, and/or any function of `t`, which is a reserved symbol for the time domain.
- **pars** The names of the parameters and initial conditions to be estimated. An initial condition name for a certain variable is the name given to the relevant equation in `equations` (e.g., if an equation is named 'x' than its initial condition should be named 'x' as well). Note: The symbol 't' is reserved for the time domain and cannot be used as a parameter name.
Time points of the observations. Either a vector, if the same time points were used for observing all variables, or a list of vectors the length of obs, of which each element is the length of the relevant element in obs.

Named list. The observations. When obs_sets=1, obs should contain a list of vectors with observations of either a variable described by one of the equations (named according to the relevant equation name) or a non-modeled variable appearing in one of the equations. Each observations vector should be the length of the relevant time vector. When obs_sets>1, obs should contain a list, where each list member is a list that fits the description in the case of obs_sets=1.

Number of observations sets. When obs_sets>1, the function will fit the set of observations according to the value of obs_sets_fit in simode_ctrl.

Names of parameters or initial conditions that will be estimated in stage 1 using nonlinear least squares optimization. The parameter names in nlin_pars must appear in pars.

Names of likelihood parameters not appearing in the ODE system, which are needed for the the user-defined function calc_nll. The parameter names in likelihood_pars must appear in pars.

Named vector. Fixed values for one or more of the ODE system parameters or initial conditions. Parameters in this list will not be estimated.

Named vector. Starting values for optimization of parameters/initial conditions. Must contain starting values for all the parameters in nlin_pars and likelihood_pars. If im_method="non-seperable", can optionally contain starting values for any other parameter/initial condition.

Named vector. Lower bounds for any parameter/initial condition.

Named vector. Upper bounds for any parameter/initial condition.

The method to use for integral-matching. Default "separable" means that linear parameters are estimated directly while "non-separable" means that linear parameters are estimated using nonlinear least squares optimization. If none of the parameters are linear then the default can be used.

Whether to fit each equation separately in the integral-matching stage.

An optional user-defined function for completing missing observations (see Details).

An optional user-defined function for calculating negative log-likelihood for the model (see Details).

An optional user-defined function for scaling transformations of parameters estimated using non-linear optimization (see Details).

Various control parameters. See simode.control.

Additional arguments passed to optim, gen_obs and calc_nll

Details

gen_obs can be used in cases of a partially observed system, for which observations of the missing variables can be generated given values for the system parameters. The function will be called
during the optimization using integral-matching. It must be defined as
\[
\text{gen Obs} \leftarrow \text{function(equations, pars, x0, time, obs,...)}, \text{where:}
\]
- \text{equations} the ODE equations
- \text{pars} the parameter values
- \text{x0} the initial conditions
- \text{time} the timing of the observations (vector or list)
- \text{obs} the observations
- \ldots additional parameters passed from the call to \text{simode}

The function should return a list with two items:
- \text{time} the vector or list of time points of the observations
- \text{obs} the list of observations with the newly generated observations

\text{calc_nll} allows the user to pass his own likelihood function to be used in the optimization in the second stage (if not defined, the default nonlinear least squares optimization will be used). The likelihood function will also be used in a following call to \text{profile}, for the calculation of likelihood profiles. It must be defined as \text{calc_nll} \leftarrow \text{function(pars, time, obs, model_out,...), where:}

- \text{pars} the parameter values
- \text{time} the timing of the observations (vector or list)
- \text{obs} the observations
- \text{model_out} the model output returned from a call to \text{solve_ode}. If \text{time} is a list with possibly different times for each variable \text{model_out} will contain a union of all these times.
- \ldots additional parameters passed from the call to \text{simode}

The function should return the negative log-likelihood.

\text{scale_pars} allows the user to pass a function for rescaling transformations of some/all of the parameters estimated using non-linear optimization. The function will be called at each step of the optimization with the current values of the parameters, as the optimization algorithm sees them, and will return rescaled parameters values to be used in estimation of the direct parameters (stage 1) and in solving the ODE equations (stage 2). It must be defined as \text{scale_pars} \leftarrow \text{function(pars,...), where:}

- \text{pars} the parameter values
- \ldots additional parameters passed from the call to \text{simode}

The function should return the rescaled parameter values.

**Value**

If \text{obs_sets}=1, the function returns a \text{simode} object containing the parameter estimates and solutions after integral-matching (stage 1) and after nonlinear least squares optimization (stage 2). If \text{obs_sets}>1 and \text{obs_sets_fit}="together" in \text{simode_ctrl}, the function returns a list.\text{simode} object which is a list of \text{simode} objects the length of \text{obs_sets}. 
References


Examples

```r
## ==============
## Predator-Prey Lotka-Volterra model
## ==============

# generate model equations and parameters (X=Prey, Y=Predator)
pars <- c("alpha", "beta", "gamma", "delta")
vars <- c("X", "Y")
eq_X <- 'alpha*X-beta*X*Y'
eq_Y <- 'delta*X*Y-gamma*Y'
equations <- c(eq_X, eq_Y)
names(equations) <- vars
x0 <- c(0.9, 0.9)
names(x0) <- vars
theta <- c(2/3, 4/3, 1, 1)
names(theta) <- pars

# generate observations
n <- 50
time <- seq(0, 25, length.out = n)
model_out <- solve_ode(equations, theta, x0, time)
x_det <- model_out[, vars]
set.seed(1000)
sigma <- 0.05
obs <- list()
for (i in 1:length(vars)) {
  obs[[i]] <- pmax(0, rnorm(n, x_det[, i], sigma))
}
names(obs) <- vars

# estimate model parameters with known initial conditions
simode_fit1 <- simode(equations = equations, pars = pars, fixed = x0, time = time, obs = obs)
plot(simode_fit1, type = 'fit', time = seq(0, 25, length.out = 100), pars_true = theta, mfrow = c(2, 1))
plot(simode_fit1, type = 'est', pars_true = c(theta, x0), mfrow = c(2, 1))

# estimate model parameters and initial conditions
simode_fit2 <- simode(equations = equations, pars = c(pars, vars), time = time, obs = obs)
plot(simode_fit2, type = 'fit', time = seq(0, 25, length.out = 100), pars_true = c(theta, x0), mfrow = c(2, 1))
plot(simode_fit2, type = 'est', pars_true = c(theta, x0))
```
profiles_fit2 <- profile(simode_fit2, step_size=0.01, max_steps=50)
plot(profiles_fit2, mfrow=c(2,3))

ci_fit2 <- confint(profiles_fit2)
plot(ci_fit2, pars_true=c(theta, x0), legend=T)

---

simode.control

Class containing control parameters for a call to simode

Description

Class containing control parameters for a call to simode

Usage

simode.control(optim_type = c("both", "im", "nls"),
im_optim_method = c("BFGS", "Nelder-Mead", "CG", "L-BFGS-B", "SANN",
"Brent", "Rcgmin", "Rvmmin"), nls_optim_method = c("BFGS",
"Nelder-Mead", "CG", "L-BFGS-B", "SANN", "Brent", "Rcgmin", "Rvmmin"),
im_optim_control = list(), nls_optim_control = list(),
ode_control = list(method = "lsoda"), im_smoothing = c("splines",
"kernel", "none"), im_grid_size = 0, bw_factor = 1.5,
use_pars2vars_mapping = F, trace = 0, save_im_trace = F,
save_nls_trace = F, obs_sets_fit = c("separate", "separate_x0",
"together"), parallel = F, save_to_log = F)

Arguments

optim_type Controls what optimization will be performed: either only integral-matching
('im'), only nonlinear least squares ('nls') or both (the default, i.e., first integral-
matching then nonlinear least squares starting from the integral-matching estimates).
im_optim_method Method for optimization during the integral-matching stage. Accepted values
are any method supported by the method argument in optim, as well as \Rvmmin\ and \Rcgmin\, if the relevant packages are installed.
nls_optim_method Method for optimization during the nonlinear least squares stage. Accepted
values are the same as in im_optim_method.
im_optim_control A list with control parameters for optimization during the integral-matching
stage. Can include anything that would appear in the control argument in optim/Rvmmin/Rcgmin (depending on the choice of im_optim_method). See optim,Rvmmin,Rcgmin.
nls_optim_control
Control parameters for optimization during the nonlinear least squares stage (as in `im_optim_control`)

ode_control
A list with control parameters for the ODE solver. Can include the argument `method` appearing in the arguments to `ode`, as well as any other control parameters accepted as additional parameters in the call to `ode`.

im_smoothing
Choice of type of smoothing during the integral-matching stage (see Details).

im_grid_size
Number of points used in integral-matching grid (not relevant when `im_smoothing='kernel'`). Value <=0 means the grid size will be set according to maximum number of observations for any of the equations in the call to `simode`.

bw_factor
Controls the bandwidth when `im_smoothing='kernel'`. The bandwidth for each equation will be `bw_factor*the maximum time interval between two observations` (should be >= 1).

use_pars2vars_mapping
Whether to use pars2vars mapping (see Details).

trace
Report level (0-4), with higher values producing more tracing information (see Details).

save_im_trace
Whether to save trace information of integral-matching optimization, which can then be plotted using `plot_trace`.

save_nls_trace
Whether to save trace information of nonlinear least squares optimization, which can then be plotted using `plot_trace`.

obs_sets_fit
Controls the way multiple observation sets are fitted: either "separate" (each set can be fitted with its own parameter values and initial conditions), "separate_x0" (same parameter values fitted for all sets while initial conditions may be different for each set) or "together" (fitting the mean of all observations sets).

parallel
Controls whether to fit sequentially or in parallel multiple observation sets (obs_sets>1 in the call to `simode`) that are fitted separately (obs_sets_fit="separate"). Fitting in parallel requires that the parallel package will be installed. When running in parallel, output will not be displayed regardless of the trace level. Instead, one can set `save_to_log` to true to save the output to a log file.

save_to_log
Controls whether to redirect output to a log file. If true, output will be saved to the file `simode.log` in tempdir.

Details
Possible values for `im_smoothing` are \'splines\' (the default), in which case smoothing will be performed using `smooth.spline` with generalized cross-validation, \'kernel\', using own kernel smoother function, or \'none\' (using the observations as is, with interpolation if necessary). `use_pars2vars_mapping` controls whether to use a mapping of which equations are affected by each of the parameters. When set to true, previous matrices computed as part of the integral-matching estimation are stored during the integral-matching optimization, and are updated only for the equations that were affected by the change in the parameter estimates from the previous iteration. When the number of equations is large and some of the parameters affect only a few equations, setting this option to true can significantly reduce the optimization time during the integral-matching stage (while increasing the storage usage). This is especially true with derivative based optimization methods (such as \'BFGS\' of `optim`) which updates only one of the optimized parameters in each iteration. `trace` has 5 possible
levels:
With trace=0, there would be no output displayed if there are no errors.
With trace=1, a message will be displayed at the beginning and end of each optimization stage.
With trace=2, non-critical errors occurring during the optimization iterations will be displayed.
With trace=3, non-critical warnings occurring during the optimization iterations will be displayed.
With trace=4, the calculated loss value for each iteration of the integral-matching and nonlinear least squares optimizations will be displayed.

Description
A model for the spread of a seasonal influenza epidemics in two groups over five seasons.

Usage
sir_example

Format
A list containing the following variables:

- **equations** The ODE equations describing the system, including ten equations for the susceptible dynamics (2 groups * 5 seasons) and ten equations for the infected dynamics.
- **beta** The 2x2 transmission matrix parameters (in time unit of weeks).
- **gamma** The recovery rate parameter (in time unit of weeks).
- **kappa** The relative infectiousness of seasons 2-5 compared to season 1.
- **S0** The initial conditions for the susceptible variables.
- **I0** The initial conditions for the infected variables.
- **time** Times in which the observations were made (in weeks).
- **obs** A list of observations of the infected variables, generated using Gaussian measurement error with sigma=1e-3.
### solve_ode

**Ordinary differential equations solver**

**Description**

A wrapper for the `ode` function that solves a system of ordinary differential equations described using symbolic equations.

**Usage**

```r
solve_ode(equations, pars, x0, time, xvars = NULL, ...)
```

**Arguments**

- `equations`: The equations describing the ODE system. See `simode`.
- `pars`: The parameter values. Named according to their names in `equations`.
- `x0`: The initial conditions. Named according to the names of `equations`.
- `time`: The time points for which the ODE variables' values will be computed.
- `xvars`: External observations of time-dependant variables refered to in `equations`.
- `...`: Additional argument(s) for methods.

**Value**

A matrix whose first column contains the given time points and subsequent columns hold the computed ODE equations' values at these time points.

### solve_ode2

**Ordinary differential equations solver using a simode object**

**Description**

A wrapper for the `ode` function that solves a system of ordinary differential equations described using symbolic equations.

**Usage**

```r
solve_ode2(x, type = c("both", "im", "nls"))
```

**Arguments**

- `x`: A simode object returned from a call to `simode`.
- `type`: Which solution to generate (`both`, `im`, `nls`).

**Value**

A matrix whose first column contains the given time points and subsequent columns hold the computed ODE equations' values at these time points.
Summary method for `list.simode` objects

**Description**

Summary method for `list.simode` objects

**Usage**

```r
## S3 method for class 'list.simode'
summary(object, sum_mean_sd = F,
         pars_true = NULL, digits = max(3, getOption("digits") - 3), ...)
```

**Arguments**

- `object`: `list.simode` object returned by a call to `simode` with `obs_sets>1`
- `sum_mean_sd`: Whether to calculate mean and standard deviation for the parameter estimates in the fits included in the given object. To be used when `object` is the result of fitting monte-carlo simulations.
- `pars_true`: The true parameter values (relevant only for when `sum_mean_sd=T`). When given, the summary will also include the bias and RMSE for each parameter estimate.
- `digits`: The number of significant digits to use.
- `...`: Additional argument(s) for methods.

**Value**

The mean and standard deviation for the loss values and parameter estimates obtained from the integral-matching and nonlinear least squares optimizations. If `pars_true` is given, then will also calculate bias and RMSE for the parameter estimates.

---

Summary method for `simode` objects

**Description**

Summary method for `simode` objects

**Usage**

```r
## S3 method for class 'simode'
summary(object, digits = max(3, getOption("digits") - 3), ...)
```

**Value**

The mean and standard deviation for the loss values and parameter estimates obtained from the integral-matching and nonlinear least squares optimizations. If `pars_true` is given, then will also calculate bias and RMSE for the parameter estimates.
Arguments

- **object**: The simode object.
- **digits**: The number of significant digits to use.
- **...**: Additional argument(s) for methods.
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