

Package ‘simode’

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Type Package

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

Version 1.0.1

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.
Dattner & Yaari (2018) <arXiv:1807.04202>.
Dattner et al. (2017) <doi:10.1098/rsif.2016.0525>.
Dattner & Klaassen (2015) <doi:10.1214/15-EJS1053>.

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R topics documented:

confint.profile.simode	2
plot.confint.simode	2
plot.list.simode	3
plot.profile.simode	4
plot.simode	4
plot_trace	5
print.confint.simode	6
print.profile.simode	6
print.simode	6
print.summary.simode	7

profile.simode	7
simode	8
simode.control	11
sir_example	13
solve_ode	14
summary.list.simode	14
summary.simode	15

Index	16
--------------	-----------

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	<i>Plot the fit/estimates of a list.simode object</i>
------------------	---

Description

Plot the fit or parameter estimates obtained from a call to `simode` with `mc_sets>1`. Plots the mean and standard deviation obtained from the multiple fits.

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_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 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_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 <code>c(nr,nc)</code> 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

```
## 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.

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

Description

Plot the fit or parameter estimates obtained from a call to [simode](#).

Usage

```
## 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	<i>Plot optimization trace of a call to simode</i>
------------	--

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

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

Arguments

x	<code>simode</code> 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

```
## 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.
...	Additional argument(s) for methods.

```
print.simode  Print method for simode objects
```

Description

Print method for simode objects

Usage

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

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

```
## 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

```
## S3 method for class 'simode'
profile(fitted, which = NULL, optim_type = c("nls",
  "both"), step_size, max_steps, 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().
...	Additional argument(s) for methods.

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	<i>Statistical inference of ordinary differential equations using separable integral-matching</i>
--------	---

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

```
simode(equations, pars, time, obs, mc_sets = 1, nlin_pars = NULL,
       likelihood_pars = NULL, fixed = NULL, start = NULL, lower = NULL,
       upper = NULL, im_method = c("separable", "non-separable"),
       gen_obs = NULL, calc_nll = 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 <code>pars</code> , variables appearing in the equations names 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 <code>equations</code> (e.g., if an equation is named 'x' then 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	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 <code>obs</code> , of which each element is the length of the relevant element in <code>obs</code> .
obs	Named list. The observations. When <code>mc_sets=1</code> , <code>obs</code> should contain a list of vectors with length \leq <code>equations</code> (either partial or fully observed system). Each list member should be named according to the relevant equation name and should be the length of the relevant time vector. When <code>mc_sets>1</code> , <code>obs</code> should contain a list the length of <code>mc_sets</code> , where each list member is a list that fits the description in the case of <code>mc_sets=1</code> .

<code>mc_sets</code>	Number of monte-carlo experiments. When <code>mc_sets</code> >1, the function will fit each set of observations separately either sequentially or in parallel, according to the value of <code>parallel</code> in <code>simode_ctrl</code> .
<code>nlin_pars</code>	Names of parameters or initial conditions that will be estimated in stage 1 using nonlinear least squares optimization. The parameter names in <code>nlin_pars</code> must appear in <code>pars</code> .
<code>likelihood_pars</code>	Names of likelihood parameters not appearing in the ODE system, which are needed for the user-defined function <code>calc_nll</code> . The parameter names in <code>likelihood_pars</code> must appear in <code>pars</code> .
<code>fixed</code>	Named vector. Fixed values for one or more of the ODE system parameters or initial conditions. Parameters in this list will not be estimated.
<code>start</code>	Named vector. Starting values for optimization of parameters/initial conditions. Must contain starting values for all the parameters in <code>nlin_pars</code> and <code>likelihood_pars</code> . If <code>im_method</code> ="non-seperable", can optionally contain starting values for any other parameter/initial condition.
<code>lower</code>	Named vector. Lower bounds for any parameter/initial condition.
<code>upper</code>	Named vector. Upper bounds for any parameter/initial condition.
<code>im_method</code>	The method to use for integral-matching. Default "separable" means that linear parameters are estimated directly while "non-seperable" means that linear parameters are estimated using nonlinear least squares optimization. If none of the parameters are linear then the default can be used.
<code>gen_obs</code>	A user-defined function for completing missing observations (see Details).
<code>calc_nll</code>	A user-defined function for calculating negative log-likelihood for the model (see Details).
<code>simode_ctrl</code>	Various control parameters. See simode.control .
<code>...</code>	Additional arguments passed to <code>optim</code> , <code>gen_obs</code> and <code>calc_nll</code>

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 `gen_obs <- function(equations, pars, x0, time, obs, ...)`, where:

- `equations` the ODE equations
- `pars` the parameter values
- `x0` the initial conditions
- `time` the timing of the observations (vector or list)
- `obs` the observations
- `...` additional parameters passed from the call to [simode](#)

The function should return a list with two items:

- `time` the vector or list of time points of the observations
- `obs` the list of observations with the newly generated observations

`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 [profile](#), for the calculation of likelihood profiles. It must be defined as `calc_nll <- function(pars, time, obs, model_out, ...)`, where:

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

The function should return the negative log-likelihood.

Value

If `mc_sets=1`, returns a `simode` object containing the parameter estimates after integral-matching (stage 1) and after nonlinear least squares optimization (stage 2). If `mc_sets>1` returns a `list.simode` object which is a list of `simode` objects the length of `mc_sets`.

References

Dattner & Klaassen (2015). Optimal Rate of Direct Estimators in Systems of Ordinary Differential Equations Linear in Functions of the Parameters, *Electronic Journal of Statistics*, Vol. 9, No. 2, 1939-1973.

Dattner, Miller, Petrenko, Kadouriz, Jurkevitch & Huppert (2017). Modelling and Parameter Inference of Predator-prey Dynamics in Heterogeneous Environments Using The Direct Integral Approach, *Journal of The Royal Society Interface* 14.126: 20160525.

Examples

```
## =====
## 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=theta)

## 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)
ci_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, save_to_log = F, parallel = 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).
------------	---

<code>im_optim_method</code>	Method for optimization during the integral-matching stage. Accepted values are any method supported by the <code>method</code> argument in <code>optim</code> , as well as “Rvmin” and “Rcgmin”, if the relevant packages are installed.
<code>nls_optim_method</code>	Method for optimization during the nonlinear least squares stage. Accepted values are the same as in <code>im_optim_method</code> .
<code>im_optim_control</code>	A list with control parameters for optimization during the integral-matching stage. Can include anything that would appear in the <code>control</code> argument in <code>optim/Rvmin/Rcgmin</code> (depending on the choice of <code>im_optim_method</code>). See <code>optim</code> , <code>Rvmin</code> , <code>Rcgmin</code> .
<code>nls_optim_control</code>	Control parameters for optimization during the nonlinear least squares stage (as in <code>im_optim_control</code>)
<code>ode_control</code>	A list with control parameters for the ODE solver. Can include the argument <code>method</code> appearing in the arguments to <code>ode</code> , as well as any other control parameters accepted as additional parameters in the call to <code>ode</code> .
<code>im_smoothing</code>	Choice of type of smoothing during the integral-matching stage (see Details).
<code>im_grid_size</code>	Number of points used in integral-matching grid (not relevant when <code>im_smoothing='kernel'</code>). Value ≤ 0 means the grid size will be set according to maximum number of observations for any of the equations in the call to <code>simode</code> .
<code>bw_factor</code>	Controls the bandwidth when <code>im_smoothing='kernel'</code> . The bandwidth for each equation will be <code>bw_factor</code> *the maximum time interval between two observations (should be ≥ 1).
<code>use_pars2vars_mapping</code>	Whether to use <code>pars2vars</code> mapping (see Details).
<code>trace</code>	Report level (0-4), with higher values producing more tracing information (see Details).
<code>save_im_trace</code>	Whether to save trace information of integral-matching optimization, which can then be plotted using <code>plot_trace</code> .
<code>save_nls_trace</code>	Whether to save trace information of nonlinear least squares optimization, which can then be plotted using <code>plot_trace</code> .
<code>save_to_log</code>	Controls whether to redirect output to a log file. If true, output will be saved to the file ‘simode.log’ in <code>tempdir</code> .
<code>parallel</code>	Controls whether to fit multiple <code>mc_sets</code> in the call to <code>simode</code> sequentially or in parallel. Fitting in parallel requires that the <code>parallel</code> package will be installed. When running in parallel, output will not be displayed regardless of the trace level. Instead, one can set <code>save_to_log</code> to true to save the output to a log file.

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” or 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.

sir_example

Example dataset for a multi-group SIR model

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	<i>Ordinary differential equations solver</i>
-----------	---

Description

A wrapper for the [ode](#) function that solves a system of ordinary differential equations described using symbolic equations.

Usage

```
solve_ode(equations, pars, x0, time, ...)
```

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.
...	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.

summary.list.simode	<i>Summary method for list.simode objects</i>
---------------------	---

Description

Summary method for `list.simode` objects

Usage

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

Arguments

object	<code>list.simode</code> object returned by a call to simode with <code>mc_sets>1</code>
pars_true	The true parameter values (if known).
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.simode	<i>Summary method for simode objects</i>
----------------	--

Description

Summary method for simode objects

Usage

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

Arguments

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

Index

*Topic **datasets**

`sir_example`, [13](#)

`confint`, [3](#)

`confint.profile.simode`, [2](#)

`ode`, [12](#), [14](#)

`optim`, [12](#)

`par`, [3–5](#)

`plot.confint.simode`, [2](#)

`plot.list.simode`, [3](#)

`plot.profile.simode`, [4](#)

`plot.simode`, [4](#)

`plot_trace`, [5](#), [12](#)

`print.confint.simode`, [6](#)

`print.profile.simode`, [6](#)

`print.simode`, [6](#)

`print.summary.simode`, [7](#)

`profile`, [2](#), [4](#), [10](#)

`profile.simode`, [7](#)

`Rcgmin`, [12](#)

`Rvmmmin`, [12](#)

`simode`, [3–5](#), [7](#), [8](#), [8](#), [9](#), [10](#), [14](#)

`simode.control`, [5](#), [9](#), [11](#)

`sir_example`, [13](#)

`smooth.spline`, [12](#)

`solve_ode`, [10](#), [14](#)

`summary.list.simode`, [14](#)

`summary.simode`, [15](#)