# Package 'gfoRmulaICE'

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```
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Description Implements iterative conditional expectation (ICE) estimators of the plug-in g-
     formula (Wen, Young, Robins, and Hernán (2020) <doi:10.1111/biom.13321>).
     Both singly robust and doubly robust ICE estimators based on parametric models are available.
     The package can be used to estimate survival curves under sustained treatment strategies (inter-
     ventions) using longitudinal data with time-varying treatments, time-varying confounders, cen-
     soring, and competing events.
     The interventions can be static or dynamic, and deterministic or stochastic (including thresh-
     old interventions). Both prespecified and user-defined interventions are available.
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**Title** Parametric Iterative Conditional Expectation G-Formula

Type Package

2 compData

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# Description

A dataset with 26581 observations on 10000 individuals and 4 time points. The dataset is in long format with each row representing the record of one individual at one time point.

# Usage

compData

# **Format**

A data frame with 26581 rows and 9 variables:

- t0 Time index.
- id Unique identifier for each individual.
- L1 Binary covariate.
- L2 Continuous covariate.
- **A1** Categorical treatment variable with levels 1, 2, and 3.
- A2 Binary treatment variable.
- C Censoring event indicator.
- **D** Competing event indicator.
- Y Outcome indicator.

dynamic 3

#### **Description**

This function specifies a dynamic intervention on the treatment variable specified in data. This function follows the treatment strategy specified in strategy\_before until a user-defined condition that depends on covariate values is met. Upon the condition is met, the strategy specified in strategy\_after is followed.

# Usage

```
dynamic(
  condition,
  strategy_before,
  strategy_after,
  absorb = FALSE,
  id,
  time,
  data
)
```

# Arguments

condition	a string that specifies a logical expression, upon which is met, the strategy spec-
	'C . 1 ' t

ified in strategy\_after is followed.

strategy\_before

a function or vector of intervened values that specifies the strategy followed after condition is met. The vector of intervened values should be the same length as the number of rows in the data frame data.

the number of rows in the data frame data.

strategy\_after a function or vector of intervened values that specifies the strategy followed

before condition is met. The vector of intervened values should be the same

length as the number of rows in the data frame data.

absorb a logical value indicating whether the strategy specified in strategy\_after

becomes absorbing (always treat with the specified strategy) upon the first time

when condition is met.

id a string specifying the ID variable name in data.

time a string specifying the time variable name in data.

data a data frame containing the observed data.

#### Value

a vector containing the intervened value of the same size as the number of rows in data.

grace\_period

#### **Examples**

```
data <- gfoRmulaICE::compData</pre>
# Dynamic intervention example 1:
# treat when L1 = 0, and not treat otherwise.
dynamic1 <- dynamic(</pre>
condition = "L1 == 0",
strategy_before = static(0, data),
strategy_after = static(1, data),
absorb = FALSE,
id = "id",
time = "t0"
data = data
# Dynamic intervention example 2:
# never treat upon until L1 = 0, after which follows always treat.
dynamic2 <- dynamic(</pre>
condition = "L1 == 0",
strategy_before = static(0, data),
strategy_after = static(1, data),
absorb = TRUE,
id = "id",
time = "t0"
data = data
# Dynamic intervention example 3:
# never treat upon until L1 = 0, after which follows natural course.
dynamic3 <- dynamic(</pre>
condition = "L1 == 0",
strategy_before = static(0, data),
strategy_after = natural_course(data, "A1"),
absorb = FALSE,
id = "id",
time = "t0"
data = data
)
```

grace\_period

Strategy with Grace Period

# Description

This function specifies an intervention in which treatment is initiated within the grace period of nperiod time units. During the grace period, the treatment variable follows its natural value or initiate intervention with a uniform distribution at each time point.

### Usage

```
grace_period(type, nperiod, condition, data, id, time_name, outcome_name)
```

#### **Arguments**

a string specifying the type of grace period strategy. Possible values are "unitype form" and "natural". a number indicating the length of grace period. nperiod condition a string specifying the logical expression, upon which is met, the treatment is initiated within nperiod time units. a data frame containing the observed data. data id a string specifying the ID variable name in data. time\_name a string specifying the time variable name in data. a string specifying the outcome variable name in data. outcome\_name

#### Value

a vector containing the intervened value of the same size as the number of rows in data.

#### **Examples**

ice

Iterative Conditional Expectation Estimator

# **Description**

This function implements iterative conditional expectation (ICE) estimators under user-defined treatment strategies. Available ICE estimators are classical and hazard-based pooling over treatment history ICE, classical and hazard-based stratifying on treatment history ICE, and doubly robust ICE estimators. See Wen et al. (2021) for more details regarding the parametric g-formula iterative conditional expectation estimator.

#### Usage

```
ice(
  data,
  time_points,
  id,
  time_name,
  outcome_name = NULL,
  compevent_name = NULL,
  comp_effect = 0,
  outcome_model,
  censor_model = NULL,
```

```
competing_model = NULL,
hazard_model = NULL,
global_hazard = FALSE,
ref_idx = 0,
estimator,
int_descript,
ci_method = "percentile",
nsamples = 0,
seed = 1,
coverage = 95,
parallel = FALSE,
ncores = 2,
verbose = TRUE,
...
)
```

#### Arguments

data a data frame containing the observed data in long format.

time\_points a number indicating the total number of time points.

id a string indicating the ID variable name in data.

time\_name a string specifying the time variable name in data.

outcome\_name a string specifying the outcome variable name in data.

censor\_name a string specifying the censor variable name in data. Default is NULL.

compevent\_name a string specifying the competing variable name in data. Default is NULL.

comp\_effect a number indicating how the competing event is handled for all the specified

interventions. Default is 0. 0 for controlled direct effect. 1 for total effect.

outcome\_model a formula specifying the model statement for the outcome.

censor\_model a formula specifying the model statement for the censoring event. Default is

NULL

competing\_model

a formula specifying the model statement for the competing event. Default is

NULL.

hazard\_model a formula specifying the model statement for the hazard, if hazard-based esti-

mator is used. Default is NULL. If specified, the model in hazard\_model will be

used. If NULL, the model in outcome\_model will be used.

global\_hazard a logical value indicating whether to use global pooled-over-time hazard model

or time-specific hazard models, for hazard-based pooled ICE only. If TRUE, use pooled-over-time hazard model. If FALSE, use time-specific hazard models.

Default is FALSE.

ref\_idx a number indicating which intervention to be used as the reference to calculate

the risk ratio and risk difference. Default is 0. 0 refers to the natural course as the reference intervention. Any other numbers refer to the corresponding

intervention that users specify in the keyword arguments.

estimator a function specifying which ICE estimator to use for the estimation. Please see Details for all available specifications.

int\_descript a vector of strings containing descriptions for each specified intervention.

ci\_method a string specifying the method for calculating the confidence interval, if nsamples is larger than 0. Possible values are "percentile" and "normal." Default is "percentile."

a number larger than 0 indicating the number of bootstrap samples. Default is 0.

seed a number indicating the starting seed for bootstrapping. Default is 1.

coverage a number greater than 0 and less than 100 indicating the coverage of the confidence interval. Default is 95.

parallel a logical value indicating whether to parallelize the bootstrap process. Default is FALSE.

a number indicating the number of CPU cores to use in parallel computing. Default is 2.

a logical specifying whether progress of the algorithm is printed. Default is TRUE.

keyword arguments to specify intervention inputs. If stratified ICE is used, keyword arguments also allow intervention-specific outcome models and competing models

To specify interventions, please follow the input convention below:

- Each intervention is specified using the keyword argument name with *intervention* prefix.
- Use *i* after *intervention* prefix in keyword argument name to represent the ith strategy.
- Use . followed with *treatment variable name* after *interventioni* in keyword argument name to represent the treatment name within the ith strategy.

Each input of intervention keyword arguments is a list consisting of a vector of intervened values and an optional vector of time points on which the intervention is applied. If the intervention time points are not specified, the intervention is applied to all time points. For example, an input considers a simultaneous intervention with always treat on A1 and never treat on A2 at all time points looks like:

```
intervention1.A1 = list(static(1))
intervention1.A2 = list(static(0))
```

The above intervention applies to all time points. The following is an example of custom intervention time points, with always treat on A1 at time point 1 and 2 and never treat on A2 at time point 3 to 5.

```
intervention1.A1 = list(static(1), 1:2)
intervention1.A2 = list(static(0), 3:5)
```

If there is no intervention keyword argument specified, the function returns the natural course risk only. Please see the "Examples" section for more examples.

verbose

ncores

nsamples

. . .

To specify different outcome model and/or competing model for different intervention, please follow the input convention below:

- Each outcome model is specified using keyword argument name starting with *outcomeModel* or *compModel* prefix for outcome model or competing model correspondingly.
- Use .n after *outcomeModel* or *compModel* prefix in keyword argument name to specify which intervention being applied to, where n represents the nth intervention.

The input to each outcome or competing model keyword argument is a model statement formula. If no outcome model and competing model keyword argument is specified, the models specified in outcome\_model and comp\_model are used. Please refer to the "Examples" section for more examples.

#### **Details**

Users could specify which version ICE estimator to use through estimator.

- pool (hazard = FALSE) specifies the classical pooling over treatment history ICE estimator.
- pool(hazard = TRUE) specifies the hazard-based pooling over treatment history ICE estimator.
- strat(hazard = FALSE) specifies the classical stratifying on treatment history ICE estimator.
- strat(hazard = TRUE) specifies the hazard-based stratifying on treatment history ICE estimator.
- weight(treat\_model) specifies the doubly robust weighted ICE estimator where treat\_model specifies the treatment model.

To provide flexible choices on model inputs for stratified ICE and doubly robust ICE, we allow users to specify intervention-specific model statements through keyword arguments. In the case where intervention-specific model statements are specified, treatment variables that are not intervened under some strategies will be considered as a covariate and automatically added into the model specification at each time point. Please see more details on how to specify intervention-specific model specifications in the "Arguments" section.

For example, the following input specifies  $Y \sim L1$  as outcome model for intervention 1,  $D \sim L1$  as competing model for intervention 2,  $D \sim L1 + L2$  as outcome model for intervention 1,  $Y \sim L1 + L2$  as outcome model for intervention 2.

 $compModel.2 = D \sim L1$ 

Because the keyword argument for outcome model is not specified for intervention 2, the outcome model for intervention 2 is Y ~ L1 + L2 as specified in outcome\_model. Similarly, because the keyword argument for competing model is not specified for intervention 1, the competing model for intervention 1 is D ~ L1 + L2 as specified in competing\_model. In the case of controlled direct effect, the keyword arguments for competing models are ignored. Please see more examples in the "Examples" section.

Both built-in interventions and user-defined interventions are available.

The following are the built-in intervention functions in the package:

- Static Intervention: static(value) specifies a constant intervention with value.
- Dynamic Intervention: dynamic(condition, strategy\_before, strategy\_after, absorb) specifies a dynamic intervention where the strategy in strategy\_before is followed until condition is met. Upon condition is met, the strategy in strategy\_after is followed. If absorb is TRUE, the intervention becomes absorbing (always treat with the specified strategy) once condition is met.
- Threshold Intervention: threshold(lower\_bound, upper\_bound) specifies a threshold intervention. If the treatment value is between lower\_bound and upper\_bound inclusively, follow the natural value of the treatment. Otherwise, set to lower\_bound or upper\_bound, if the treatment value is below lower\_bound or above upper\_bound, correspondingly.
- Grace Period: grace\_period(type, nperiod, condition) specifies a dynamic intervention with grace period. Once condition is met, the intervention is initiated within nperiod time units. During the grace period, the treatment variable follows its natural value or initiate intervention with a uniform distribution at each time point.

The following is the user-defined intervention:

• User-defined Interventions: The output of the user-defined intervention should contain the intervened value for each individual at each time point, and should be of the same size as the number of rows in data.

Please see examples in the "Examples" section.

In order to obtain an inverse probability (IP) weighted natural course risk based on the observed data, users must specify a censoring variable through censor\_name and a corresponding censoring model through censor\_model. Please see Chiu et al. (2023) for more details regarding the IP weighted estimate of the natural course risk.

If competing event exists in the data, users need to specify the name of the competing variable through competing\_name and the model specification through competing\_model for hazard-based ICE estimator. Users need to specify whether to treat the competing event as censoring or total effect through total\_effect.

We provide flexible term options in model specification for the outcome, censoring, competing, and hazard model. Users could specify polynomial terms using functions I and poly and spline terms using ns from splines package and rcspline.eval from Hmisc package. In addition, users could specify lagged terms using the format lagn\_var to indicate lagging the variable *var* with *n* periods. If the lagged variable is a treatment variable, this variable is automatically intervened based on user-defined intervention. The polynomial and spline terms could be used on lagged variables.

ice ice

#### Value

A list containing the following components. Each component that contains the fitted models includes the model fits, the summary of the fitted model, standard errors of the coefficients, variance-covariance matrices of the parameters, and the root mean square error (RMSE) values.

estimator.type A string describing the type of the estimator.

summary A summary table containing the estimated risk, risk ratio, and risk difference for

user-defined interventions including estimated natural course risk and the observed risk. If nsamples is greater than 0, the summary table includes standard

error and confidence interval for the point estimates.

risk.over.time A data frame containing the estimated risk at each time point for each interven-

tion.

initial.outcome

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the outcome model

in the first step of algorithm.

initial.comp A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the competing model

in the first step of algorithm (if applicable).

np.risk.model A list containing the fitted models for the censoring and/or competing model in

estimating observed risk (if applicable).

outcome.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the outcome model

in each iteration of algorithm.

comp.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the competing model

in each iteration of algorithm (if applicable).

hazard.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the hazard model (if applicable), either time-specific models at all time points or one pooled-over-

time global model.

boot.data A list of bootstrap samples. If nsamples is set to 0, a NULL value is returned.

boot.initial.outcome

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the outcome model in the first step of algorithm on the bootstrap samples. If nsamples is set to 0, a

NULL value is returned.

boot.initial.comp

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the competing model in the first step of algorithm on the bootstrap samples (if applicable). If nsamples is set to 0, a NULL value is returned.

boot.np.risk.model

A list containing the fitted models for the censoring and/or competing model in estimating observed risk on the bootstrap samples (if applicable). If nsamples is set to 0, a NULL value is returned.

boot.outcome.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the outcome model in each iteration of algorithm on the bootstrap samples (if applicable). If nsamples is set to 0, a NULL value is returned.

boot.comp.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the competing model in each iteration of algorithm on the bootstrap samples (if applicable). If nsamples is set to 0, a NULL value is returned.

boot.hazard.models.by.step

A list, where the name of each sublist corresponds to each specified intervention description, and each sublist contains the fitted models for the hazard model (if applicable), either time-specific models at all time points or one pooled-overtime global model, on the bootstrap samples. If nsamples is set to 0, a NULL value is returned.

#### References

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McGrath S, Lin V, Zhang Z, Petito LC, Logan RW, Hernán MA, and JG Young. gfoRmula: An R package for estimating the effects of sustained treatment strategies via the parametric g-formula. Patterns. 2020;1:100008.

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Haneuse S, Rotnitzky A. Estimation of the effect of interventions that modify the received treatment. Statistics in medicine. 2013;32(30):5260-5277.

McGrath S, Young JG, Hernán MA. Revisiting the g-null Paradox. Epidemiology. 2022;33(1):114-120.

ice ice

Chiu YH, Wen L, McGrath S, Logan R, Dahabreh IJ, Hernán MA. Evaluating model specification when using the parametric g-formula in the presence of censoring. American Journal of Epidemiology. 2023;192:1887–1895.

# **Examples**

```
data <- gfoRmulaICE::compData</pre>
# Example: Built-in and User-defined Interventions
# We consider the following interventions.
# We intervene at all time points.
# Intervention 1 on A1: always treat with value 3.
# Intervention 2 on L2: when the natural value of L2 at time t is lower than -3,
# set its value to -3. Otherwise, do not intervene.
# Intervention 3 on A2: dynamic intervention (treat when L1 = 0)
# with uniform grace period of 2 periods
# Intervention 4 on A2: at time t, if L1 = 0, then treat; otherwise, not treat.
# We use classical pooled ICE estimator,
# natural course as the reference intervention,
# and the following models:
# a. outcome model: Y \sim L1 + L2 + A1 + A2
\# b. censor model: C \sim L1 + L2 + A1 + A2.
ice_fit <- ice(</pre>
data = data,
time_points = 4,
id = "id".
time_name = "t0".
censor_name = "C"
outcome_name = "Y"
compevent_name = "D",
comp_effect = 0,
outcome_model = Y \sim L1 + L2 + A1 + A2,
censor_model = C \sim L1 + L2 + A1 + A2,
ref_idx = 0,
estimator = pool(hazard = FALSE),
int_descript = c("Static Intervention", "Threshold Intervention",
"Dynamic Intervention with Grace Period", "Dynamic Intervention"),
intervention1.A1 = list(static(3)),
intervention2.L2 = list(threshold(-3, Inf)),
intervention3.A2 = list(grace_period("uniform", 2, "L1 == 0")),
intervention4.A2 = list(dynamic("L1 == 0", static(0), static(1)))
summary(ice_fit)
plot(ice_fit)
```

natural\_course 13

|--|

#### **Description**

This function specifies the natural course intervention on the treatment variable in data.

#### Usage

```
natural_course(data, treat_var)
```

# **Arguments**

data a data frame containing the observed data.

treat\_var a string specifying the treatment variable in data.

#### Value

a vector containing the intervened values of the same size as the number of rows in data.

# **Examples**

```
data <- gfoRmulaICE::compData
natural_course <- natural_course(data = data, treat_var = "A1")</pre>
```

plot.ICE

Plot method for ICE estimator objects

#### **Description**

This function provides visualization of estimated risk for all specified interventions, estimated natural course risk, and observed risk at each time point.

#### **Usage**

```
## S3 method for class 'ICE'
plot(..., plot_obs = TRUE, label = 0)
```

# **Arguments**

... ICE estimator objects.

plot\_obs a logical value indicating whether to plot the observed risk over time. Default is

TRUE.

label a number specifying which time label is used in x-axis. 0 represents using

generic numerical time index, and 1 represents using the original time label

from the data. Default is 0.

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#### Value

a plot for risks of all the interventions specified in . . . .

# **Examples**

```
data <- gfoRmulaICE::compData</pre>
ice_fit1 <- ice(</pre>
data = data,
time_points = 4,
id = "id",
time_name = "t0",
censor_name = "C",
outcome_name = "Y";
compevent_name = "D",
comp_effect = 0,
outcome_model = Y \sim L1 + L2 + A1 + A2,
censor_model = C \sim L1 + L2 + A1 + A2,
ref_idx = 0,
estimator = pool(hazard = FALSE),
int_descript = "Static Intervention",
intervention1.A1 = list(static(3)),
intervention1.A2 = list(static(1))
ice_fit2 <- ice(</pre>
data = data,
time_points = 4,
id = "id",
time_name = "t0",
censor_name = "C"
outcome_name = "Y"
compevent_name = "D",
comp_effect = 0,
outcome_model = Y \sim L1 + L2 + A1 + A2,
censor_model = C \sim L1 + L2 + A1 + A2,
competing_model = D \sim L1 + L2 + A1 + A2,
ref_idx = 0,
estimator = pool(hazard = TRUE),
int_descript = "Static Intervention",
intervention1.A1 = list(static(3)),
intervention1.A2 = list(static(1))
plot(ice_fit1, ice_fit2)
```

static 15

## **Description**

This function identifies the pooling over treatment history ICE estimator. The classical pooling over treatment history ICE estimator is specified by pool(hazard = FALSE). The hazard based pooling over treatment history ICE estimator is specified by pool(hazard = TRUE).

# Usage

```
pool(hazard)
```

# **Arguments**

hazard

a logical value indicating whether to use hazard-based ICE estimator.

#### Value

a logical value on whether to use hazard-based ICE estimator.

static

Static

# Description

This function specifies the static intervention, either treat with a constant value or never treat, on the treatment variable in data.

### Usage

```
static(value, data)
```

# **Arguments**

value a number specifying the intervention value. 0 for never treat.

data a data frame containing the observed data.

# Value

a vector containing the intervened values of the same size as the number of rows in data.

# **Examples**

```
data <- gfoRmulaICE::compData
always_treat <- static(value = 1, data = data)</pre>
```

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strat

Indicator for the stratifying on treatment history ICE estimator

# Description

This function identifies the stratifying on treatment history ICE estimator. The classical stratifying on treatment history ICE estimator is specified by strat(hazard = FALSE). The hazard based stratifying on treatment history ICE estimator is specified by strat(hazard = TRUE).

# Usage

```
strat(hazard)
```

# **Arguments**

hazard

a logical value indicating whether to use hazard-based ICE estimator.

#### Value

a logical value on whether to use hazard-based ICE estimator.

summary.ICE

Summary method for ICE Estimator Objects

# Description

This function returns a summary table for ICE estimator objects.

# Usage

```
## S3 method for class 'ICE'
summary(...)
```

# Arguments

... the ICE estimator objects.

#### Value

a data frame containing the summary table for all specified ICE estimator objects.

threshold 17

#### **Examples**

```
data <- gfoRmulaICE::compData</pre>
fit_classical_pool <- ice(</pre>
data = data.
time_points = 4,
id = "id",
time_name = "t0",
censor_name = "C"
outcome_name = "Y"
compevent_name = "D",
comp_effect = 0,
outcome_model = Y \sim L1 + L2 + A1 + A2,
censor_model = C \sim L1 + L2 + A1 + A2,
ref_idx = 0,
estimator = pool(hazard = FALSE),
int_descript = c("Static Intervention"),
intervention1.A1 = list(static(3)),
intervention1.A2 = list(static(1))
)
fit_hazard_pool <- ice(</pre>
data = data,
time_points = 4,
id = "id",
time_name = "t0",
censor_name = "C"
outcome_name = "Y"
compevent_name = "D",
comp_effect = 0,
outcome_model = Y \sim L1 + L2 + A1 + A2,
censor_model = C \sim L1 + L2 + A1 + A2,
competing_model = D \sim L1 + L2 + A1 + A2,
ref_idx = 0,
estimator = pool(hazard = TRUE),
int_descript = c("Static Intervention"),
intervention1.A1 = list(static(3)),
intervention1.A2 = list(static(1))
)
summary(fit_classical_pool, fit_hazard_pool)
```

threshold

Threshold

#### **Description**

This function specifies the threshold intervention on the treatment variable in data. If treatment value is between the lower bound and the upper bound, it follows the natural value of the treatment. If treatment value is either below the lower bound or above the upper bound, it is set to the lower bound or the upper bound, correspondingly. See Young et al. (2014) for more details.

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#### Usage

```
threshold(lower_bound, upper_bound, var, data)
```

#### **Arguments**

lower\_bound a number indicating the lower bound of the threshold.

upper\_bound a number indicating the upper bound of the threshold.

var a string specifying the treatment variable for the intervention.

data a data frame containing the observed data.

#### Value

a vector containing the intervened values of the same size as the number of rows in data.

#### References

Young JG, Herńan MA, Robins JM. Identification, estimation and approximation of risk under interventions that depend on the natural value of treatment using observational data. Epidemiologic Methods. 2014;3(1):1-19.

# **Examples**

```
data <- gfoRmulaICE::compData
threshold_treat <- threshold(lower_bound = 0, upper_bound = 2, var = "A1", data = data)</pre>
```

weight

Indicator for the doubly robust ICE estimator

# Description

This function identifies the doubly robust ICE estimator. The treatment models could be specified by treat\_model.

#### Usage

```
weight(treat_model = list())
```

# **Arguments**

treat\_model

a list of formulas specifying the treatment model for the corresponding treatment variable. The length of list must match the number of treatment variables.

### Value

treatment model specifications and treatment variable names.

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