

Package ‘msprog’

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Type Package

Title Compute MS Progression from Longitudinal Data

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Description msprog provides tools for exhaustive and reproducible analysis of disability progression in multiple sclerosis (MS) from longitudinal data.

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compute_delta	<i>Definition of minimum valid shift for different tests.</i>
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Description

compute_delta() returns the minimum delta to be considered as a valid change from baseline of an outcome measure (EDSS, NHPT, T25FW, or SDMT).

Usage

```
compute_delta(baseline, outcome = "edss")
```

Arguments

baseline	Outcome value at baseline.
outcome	One of: <ul style="list-style-type: none"> 'edss' (Extended Disability Status Scale, default); 'nhpt' (Nine-Hole Peg Test); 't25fw' (Timed 25-Foot Walk); 'sdmt' (Symbol Digit Modalities Test).

Value

Minimum shift corresponding to a valid change from the provided baseline value. Specifically:

- EDSS: 1.5 if baseline==0, 1 if 0<baseline<=5, 0.5 if baseline>=5.5;
- NHPT and T25FW: 20% of baseline;
- SDMT: either 3 points or 10% of baseline.

Examples

```
compute_delta(4.5) # default outcome is 'edss'
compute_delta(55, outcome='sdmt')
```

is_event	<i>Compare value to reference.</i>
----------	------------------------------------

Description

is_event() checks if an outcome value determines a valid worsening, or improvement, or change, from a given reference value.

Usage

```
is_event(
    x,
    baseline,
    type,
    outcome = "edss",
    worsening = NULL,
    delta_fun = NULL,
    sub_threshold = FALSE
)
```

Arguments

x	Outcome value to test.
baseline	Outcome value at baseline.
type	One of: <ul style="list-style-type: none"> • 'wors' (worsening); • 'impr' (improvement); • 'change' (any valid change).
outcome	One of: <ul style="list-style-type: none"> • 'edss' (Extended Disability Status Scale, default); • 'nhpt' (Nine-Hole Peg Test); • 't25fw' (Timed 25-Foot Walk); • 'sdmt' (Symbol Digit Modalities Test); • NULL (only accepted when specifying the direction of worsening).
worsening	The direction of worsening ('increase' if higher values correspond to worse disease course, 'decrease' otherwise). This argument is only used when outcome is set to NULL. If outcome is specified, worsening is automatically set to 'increase' for EDSS, NHPT, T25FW, and to 'decrease' for SDMT.
delta_fun	Custom function specifying the minimum shift corresponding to a valid change from the provided baseline value. If none is specified (default), compute_delta() for the specified outcome is used.
sub_threshold	If TRUE, any confirmed worsening, or improvement, or change in the outcome measure is valid, regardless of delta_fun.

Value

A boolean value specifying if a valid event was found.

Examples

```
is_event(x=4.5, baseline=4, type='wors', outcome='edss')
is_event(x=50, baseline=57, type='wors', outcome='sdmt')
```

MSprog

Assess multiple sclerosis disability course from longitudinal data.

Description

MSprog() detects and characterises the confirmed disability worsening (CDW) or improvement events of an outcome measure (EDSS, NHPT, T25FW, or SDMT; or any custom outcome) for one or more subjects, based on repeated assessments through time (and on the dates of acute episodes, if any). Several qualitative and quantitative options are given as arguments that can be set by the user and reported as a complement to the results to ensure reproducibility.

Usage

```
MSprog(
  data,
  subj_col,
  value_col,
  date_col,
  outcome,
  relapse = NULL,
  rsubj_col = NULL,
  rdate_col = NULL,
  renddate_col = NULL,
  subjects = NULL,
  delta_fun = NULL,
  worsening = NULL,
  event = "firstCDW",
  baseline = "fixed",
  proceed_from = "firstconf",
  sub_threshold_rebl = "none",
  relapse_rebl = F,
  skip_local_extrema = F,
  validconf_col = NULL,
  conf_days = 12 * 7,
  conf_tol_days = c(7, 2 * 365.25),
  conf_unbounded_right = F,
  require_sust_days = 0,
  check_intermediate = T,
  relapse_to_bl = 30,
  relapse_to_event = 0,
  relapse_to_conf = 30,
  relapse_assoc = 90,
  relapse_indep = NULL,
  impute_last_visit = 0,
  date_format = NULL,
  include_dates = F,
  include_value = F,
  include_stable = T,
  verbose = 1
)
```

Arguments

<code>data</code>	<code>data.frame</code> containing longitudinal data, including: subject ID, outcome value, date of visit.
<code>subj_col</code>	Name of data column with subject ID.
<code>value_col</code>	Name of data column with outcome value.
<code>date_col</code>	Name of data column with date of visit.
<code>outcome</code>	Specifies the outcome type. Must be one of the following: <ul style="list-style-type: none"> • <code>'edss'</code> (Expanded Disability Status Scale); • <code>'nhpt'</code> (Nine-Hole Peg Test); • <code>'t25fw'</code> (Timed 25-Foot Walk); • <code>'sdmt'</code> (Symbol Digit Modalities Test); • <code>NULL</code> (only accepted when specifying a custom <code>delta_fun</code>)
<code>relapse</code>	<code>data.frame</code> containing longitudinal data, including: subject ID and relapse date.
<code>rsubj_col</code>	Name of subject ID column for relapse data, if different from outcome data.
<code>rdate_col</code>	Name of onset date column for relapse data, if different from outcome data.
<code>renddate_col</code>	Name of end date column for relapse data (if present).
<code>subjects</code>	Subset of subjects (list of IDs). If none is specified, all subjects listed in data are included.
<code>delta_fun</code>	Custom function specifying the minimum shift corresponding to a valid change from the provided reference value. It must take a numeric value (reference) as input, and return a numeric value corresponding to the minimum shift from baseline. If none is specified (default), function <code>compute_delta()</code> for the specified outcome is used.
<code>worsening</code>	The direction of worsening (<code>'increase'</code> if higher values correspond to worse disease course, <code>'decrease'</code> otherwise). This argument is only used when outcome is set to <code>NULL</code> . Otherwise, worsening is automatically set to <code>'increase'</code> if outcome is set to <code>'edss'</code> , <code>'nhpt'</code> , <code>'t25fw'</code> , and to <code>'decrease'</code> if outcome is set to <code>'sdmt'</code> .
<code>event</code>	Specifies which events to detect. Must be one of the following: <ul style="list-style-type: none"> • <code>'firstCDW'</code> (first confirmed disability worsening (CDW), default); • <code>'first'</code> (only the very first confirmed event - improvement or worsening); • <code>'firsteach'</code> (first confirmed disability improvement and first CDW - in chronological order); • <code>'firstCDWtype'</code> (first CDW of each kind - PIRA, RAW, and undefined, in chronological order); • <code>'firstPIRA'</code> (first PIRA); • <code>'firstRAW'</code> (first RAW); • <code>'multiple'</code> (all events in chronological order).
<code>baseline</code>	Specifies the baseline scheme. Must be one of the following: <ul style="list-style-type: none"> • <code>'fixed'</code> (first valid outcome value, default); • <code>'roving_impr'</code> (updated every time the value is lower than the previous measure and confirmed at the following visit; suitable for a first-CDW setting to discard fluctuations around baseline); • <code>'roving'``}`{</code> (updated after each event to last valid confirmed outcome value; suitable for a first-CDW setting to discard fluctuations around baseline); • <code>'roving'``}`{</code> (updated after each event to last valid confirmed outcome value; suitable for a first-CDW setting to discard fluctuations around baseline);

	– i.e., when event is set to 'firstPIRA' or 'firstRAW').
proceed_from	After detecting a confirmed disability event, continue searching after the first qualifying confirmation visit if proceed_from='firstconf', after the event date if proceed_from='event'. When rebaselining after a confirmed disability event (if baseline='roving' or baseline='roving_impr'), the baseline is moved to the first qualifying confirmation visit if proceed_from='firstconf', to the event date if proceed_from='event'.
sub_threshold_rebl	This argument is only used if baseline='roving' or baseline='roving_impr'. Must be one of the following: <ul style="list-style-type: none"> • 'event': move roving baseline at any, possibly sub-threshold, confirmed event (i.e. any confirmed change in outcome measure, regardless of delta_fun); • 'improvement': move roving baseline at any, possibly sub-threshold, confirmed improvement (i.e. any confirmed improvement in outcome measure, regardless of delta_fun); • 'worsening': move roving baseline at any, possibly sub-threshold, confirmed only use valid confirmed events (as per delta_fun) for rebaseline.
relapse_rebl	If TRUE, re-baseline after every relapse to search for PIRA events.
skip_local_extrema	This argument is only used if baseline='roving' or baseline='roving_impr'. If TRUE, local minima or maxima of the outcome are skipped when moving the baseline. A visit i is a local minimum point for outcome if $\text{outcome}(i+1) - \text{outcome}(i) \geq \text{delta_fun}$ and $\text{outcome}(i-1) - \text{outcome}(i) \geq \text{delta_fun}(\text{outcome}(i))$. Local maxima are defined similarly.
validconf_col	Name of data column specifying which visits can (T) or cannot (F) be used as confirmation visits. The input data does not necessarily have to include such a column. If validconf_col=NULL, all visits are potentially used as confirmation visits.
conf_days	Period before confirmation (days). Can be a single value or list-like of any length if multiple windows are to be considered.
conf_tol_days	Tolerance window for confirmation visit (days); can be an integer (same tolerance on left and right) or list-like of length 2 (different tolerance on left and right). In all cases, the right end of the interval is ignored if conf_unbounded_right is set to TRUE.
conf_unbounded_right	If TRUE, confirmation window is unbounded on the right (regardless of the right end indicated by conf_tol_days).
require_sust_days	Minimum number of days over which a confirmed change must be sustained (i.e., confirmed at <i>all</i> visits occurring in the specified period) to be retained as an event. Events sustained for the remainder of the follow-up period are retained regardless of follow-up duration. Setting require_sust_days=Inf, events are retained only when sustained for the remainder of the follow-up period. (Warning: if check_intermediate is set to FALSE, <i>only the end</i> of the specified period will be checked for confirmation.)
check_intermediate	If TRUE (default), events are confirmed <i>over all intermediate visits</i> up to the confirmation visit. If set to FALSE (not recommended in most cases, as it may discard meaningful fluctuations), events will be confirmed <i>only at</i> the specified confirmation visit (and <i>only at the end</i> of the period defined by require_sust_days, if any).

relapse_to_bl Minimum distance from a relapse (days) for a visit to be used as baseline. Can be an integer (minimum distance from *last* relapse) or list-like of length 2 (minimum distance from *last* relapse, minimum distance from *next* relapse). Note that setting the distance to zero means keeping the baseline regardless of surrounding relapses. If relapse end dates are available (`renddate_col`), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0). If the designated baseline does not respect this constraint, the baseline is moved to the next available visit.

relapse_to_event Minimum distance from a relapse (days) for an event to be considered as such. Can be an integer (minimum distance from *last* relapse) or list-like of length 2 (minimum distance from *last* relapse, minimum distance from *next* relapse). Note that setting the distance to zero means keeping the event regardless of surrounding relapses. If relapse end dates are available (`renddate_col`), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0).

relapse_to_conf Minimum distance from a relapse (days) for a visit to be a valid confirmation visit. Can be an integer (minimum distance from *last* relapse) or list-like of length 2 (minimum distance from *last* relapse, minimum distance from *next* relapse). Note that setting the distance to zero means keeping a confirmation visit regardless of surrounding relapses. If relapse end dates are available (`renddate_col`), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0).

relapse_assoc Maximum distance from a relapse (days) for a CDW event to be considered as RAW. Can be an integer (maximum distance from *last* relapse) or list-like of length 2 (maximum distance from *last* relapse, maximum distance from *next* relapse). If relapse end dates are available (`renddate_col`), the maximum distance from last relapse is overwritten by the relapse duration.

relapse_indep Specifies relapse-free intervals for PIRA definition. Must be given in the form produced by function `relapse_indep_from_bounds()` by calling `relapse_indep_from_bounds(b0, b1, e0, e1, c0, c1)` to specify the intervals around baseline (`b0` and `b1`), event (`e0` and `e1`), and confirmation (`c0` and `c1`). For instance:

- No relapses within event-90dd->event+30dd and within confirmation-90dd->confirmation+30dd [1]:
`relapse_indep <- relapse_indep_from_bounds(0, 0, 90, 30, 90, 30)` (default);
- No relapses between baseline and confirmation (high-specificity definition from [1]):
`relapse_indep <- relapse_indep_from_bounds(0, NULL, NULL, NULL, NULL, 0);`
- No relapses within baseline->event+30dd and within confirmation+-30dd [2]:
`relapse_indep <- relapse_indep_from_bounds(0, NULL, NULL, 30, 30, 30)`

If relapse end dates are available (`renddate_col`), it is possible to define PIRA based on those by setting `use_end_dates=T` in `relapse_indep_from_bounds()`.

impute_last_visit

Imputation probability for worsening events occurring at last visit (i.e. with no confirmation). Unconfirmed worsening events occurring at the last visit are never imputed if `impute_last_visit=0`; they are always imputed if `impute_last_visit=1`; they are imputed with probability `p`, $0 < p < 1$, if `impute_last_visit=p`. If a

	value $N > 1$ is passed, unconfirmed worsening events are imputed only if occurring within N days of follow-up (e.g., in case of early discontinuation).
<code>date_format</code>	Format of dates in the input data. If not specified, it will be inferred by function <code>as.Date()</code> .
<code>include_dates</code>	If TRUE, report dates of events.
<code>include_value</code>	If TRUE, report value of outcome at event.
<code>include_stable</code>	If TRUE, subjects with no confirmed events are included in extended output data.frame, with <code>time2event</code> = total follow up.
<code>verbose</code>	One of: <ul style="list-style-type: none"> • 0 (print no info); • 1 (print concise info, default); • 2 (print extended info).

Details

The events are detected sequentially by scanning the outcome values in chronological order. Valid time windows for confirmation visits are determined by arguments `conf_days`, `conf_tol_days`, `conf_unbounded_right`, `relapse_to_conf`. CDW events are classified as relapse-associated or relapse-independent based on their relative timing with respect to the relapses. Specifically, relapse-associated worsening (RAW) events are defined as CDW events occurring within a specified interval (`relapse_assoc` argument) from a relapse; the definition of progression independent of relapse activity (PIRA) is established by specifying relapse-free intervals around the baseline, CDW event, and confirmation visits (`relapse_indep` argument).

Value

An object of class 'MSprogOutput' with the following attributes:

- `event_count`: a data.frame containing the event sequence detected for each subject, and the counts for each event type
- `results`: a data.frame with extended info on each event for all subjects
- `settings`: a list containing all the arguments used to compute the output.

References

- [1] Müller J, Cagol A, Lorscheider J, Tsagkas C, Benkert P, Yaldizli Ö, et al. Harmonizing definitions for progression independent of relapse activity in multiple sclerosis: A systematic review. *JAMA Neurol.* 2023;80:1232–45.
- [2] Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol.* 2020;77:1132–40.

Examples

```
# EDSS course
output_edss <- MSprog(toydata_visits, 'id', 'EDSS', 'date', 'edss',
  relapse=toydata_relapses, conf_days=12*7, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=1)
print(output_edss$results) # extended info on each event for all subjects
```



```

print(output_edss$event_count) # summary of event sequence for each subject
# SDMT course
output_sdmtdmtdt <- MSprog(toydata_visits, 'id', 'SDMT', 'date', 'sdmt',
  relapse=toydata_relapses, conf_days=12*7, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=1)
print(output_sdmtdmtdt$results) # extended info on each event for all subjects
print(output_sdmtdmtdt$event_count) # summary of event sequence for each subject

```

print.MSprogOutput	<i>Textual description of criteria used to assess disability course.</i>
--------------------	--

Description

print method for class 'MSprogOutput'.

Usage

```

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

```

Arguments

x	An object of class 'MSprogOutput' (result of a call to MSprog()).
...	Optional arguments for print methods. They are ignored in this function.

Details

The method prints out a short paragraph describing the set of criteria used to obtain the output.

Examples

```

output <- MSprog(toydata_visits, 'id', 'EDSS', 'date', 'edss',
  relapse=toydata_relapses, conf_days=7*12, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=2)
print(output) # textual description of parameters used to obtain output

```

relapse_indep_from_bounds	<i>Define relapse-free intervals for PIRA definition.</i>
---------------------------	---

Description

relapse_indep_from_bounds() organises the given interval bounds around baseline, event, and confirmation into a named list to be given as argument relapse_indep to function [MSprog\(\)](#).

Usage

```
relapse_indep_from_bounds(
  b0 = 0,
  b1 = 0,
  e0 = 90,
  e1 = 30,
  c0 = 90,
  c1 = 30,
  use_end_dates = F
)
```

Arguments

b0	Days before baseline (≥ 0).
b1	Days after baseline (≥ 0), or NULL.
e0	Days before event (≥ 0), or NULL.
e1	Days after event (≥ 0), or NULL.
c0	Days before confirmation (≥ 0), or NULL.
c1	Days after confirmation (≥ 0).
use_end_dates	If TRUE, only the right bounds (e1, c1) are used, as the right bounds will be defined by the onset-to-end interval of each relapse. This option is only relevant when relapse end dates are available.

Details

If the right end is NULL, the interval is assumed to extend up to the left end of the next interval. If the left end is NULL, the interval is assumed to extend up to the right end of the previous interval.

Value

A named list to be given as argument relapse_indep to function [MSprog\(\)](#)

References

- [1] Müller J, Cagol A, Lorscheider J, Tsagkas C, Benkert P, Yaldizli Ö, et al. Harmonizing definitions for progression independent of relapse activity in multiple sclerosis: A systematic review. *JAMA Neurol.* 2023;80:1232–45.
- [2] Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol.* 2020;77:1132–40.

Examples

```
# No relapses between baseline and confirmation (high-specificity definition from [1]):
relapse_indep <- relapse_indep_from_bounds(0,NULL,NULL,NULL,NULL,0)
# No relapses within event-90dd->event+30dd
# and within confirmation-90dd->confirmation+30dd [1]:
relapse_indep <- relapse_indep_from_bounds(0,0,90,30,90,30)
# No relapses within baseline->event+30dd and within confirmation+-30dd [2]:
relapse_indep <- relapse_indep_from_bounds(0,NULL,NULL,30,30,30)
```

toydata_relapses	<i>Synthetic Relapse Data</i>
------------------	-------------------------------

Description

Artificially generated relapse dates for some example patients in [toydata_visits](#) to illustrate the use of the package.

Usage

```
data(toydata_relapses)
```

Format

An object of class `data.frame`

id Subject ID

date The relapse date

References

This data set was artificially created for the `msprog` package.

Examples

```
data(toydata_relapses)
head(toydata_relapses)
```

toydata_visits	<i>Synthetic Longitudinal EDSS and SDMT Data</i>
----------------	--

Description

Small, artificially generated toy data set providing Extended Disability Status Scale (EDSS) and Symbol Digit Modalities Test (SDMT) information on 4 example patients to illustrate the use of the package.

Usage

```
data(toydata_visits)
```

Format

An object of class `data.frame`

id Subject ID

date The visit date

EDSS A value between 0 and 10

SDMT A value between 0 and 110

References

This data set was artificially created for the msprog package.

Examples

```
head(toydata_visits)
```

value_milestone	<i>Time to disability milestone.</i>
-----------------	--------------------------------------

Description

value_milestone() scans the visits in chronological order to detect the first outcome value exceeding a specified disability milestone (e.g., EDSS \geq 6), *with confirmation*. Note: "exceeding" means either value \geq milestone or value \leq milestone, depending on the outcome measure (see arguments outcome and worsening).

Usage

```
value_milestone(
  data,
  milestone,
  value_col,
  date_col,
  subj_col,
  outcome,
  worsening = NULL,
  relapse = NULL,
  rsubj_col = NULL,
  rdate_col = NULL,
  conf_days = 24 * 7,
  conf_tol_days = c(7, 365),
  conf_unbounded_right = F,
  require_sust_days = 0,
  relapse_to_event = 0,
  relapse_to_conf = 30,
  impute_last_visit = F,
  verbose = 0
)
```

Arguments

data	a data.frame containing longitudinal data, including: subject ID, outcome value, date of visit.
milestone	Disability milestone (outcome value to check data against).
value_col	Name of data column with outcome value.
date_col	Name of data column with date of visit.
subj_col	Name of data column with subject ID.

outcome	Specifies the outcome type. Must be one of the following: <ul style="list-style-type: none"> • 'edss' (Expanded Disability Status Scale); • 'nhpt' (Nine-Hole Peg Test); • 't25fw' (Timed 25-Foot Walk); • 'sdmt' (Symbol Digit Modalities Test); • NULL (only accepted when specifying argument worsening)
worsening	The direction of worsening ('increase' if higher values correspond to worse disease course, 'decrease' otherwise). This argument is only used when outcome is set to NULL. Otherwise, worsening is automatically set to 'increase' if outcome is set to 'edss', 'nhpt', 't25fw', and to 'decrease' if outcome is set to 'sdmt'.
relapse	data.frame containing longitudinal data, including: subject ID and relapse date.
rsubj_col	Name of subject column for relapse data, if different from outcome data.
rdate_col	Name of date column for relapse data, if different from outcome data.
conf_days	Period before confirmation (days).
conf_tol_days	Tolerance window for confirmation visit (days); can be an integer (same tolerance on left and right) or list-like of length 2 (different tolerance on left and right). In all cases, the right end of the interval is ignored if conf_unbounded_right is set to TRUE.
conf_unbounded_right	If TRUE, confirmation window is unbounded on the right (regardless of the right end indicated by conf_tol_days).
require_sust_days	Minimum number of days over which the milestone must be sustained (i.e., confirmed at <i>all</i> visits occurring in the specified period). If the milestone is sustained for the remainder of the follow-up period, it is considered reached regardless of follow-up duration. Setting require_sust_days=Inf, values are retained only when sustained for the remainder of the follow-up period.
relapse_to_event	Minimum distance from a relapse (days) for the milestone to be considered reached.
relapse_to_conf	Minimum distance from a relapse (days) for a valid confirmation visit.
impute_last_visit	If TRUE, impute milestone occurring at last visit (i.e. with no confirmation). If FALSE, censor it.
verbose	One of: <ul style="list-style-type: none"> • 0 (print no info); • 1 (print concise info, default); • 2 (print extended info).

Details

An event is only retained if **confirmed**, i.e., if all values *up to* the confirmation visit exceed the milestone. Valid time windows for confirmation visits are determined by arguments conf_days, conf_tol_days, conf_unbounded_right, relapse_to_conf.

Value

A `data.frame` containing the following columns:

- `date_col`: the date of first reaching a value \geq milestone (or last date of follow-up if milestone is not reached);
- `value_col`: the first value \geq milestone, if present, otherwise no value;
- `'time2event'`: the time to reach a value \geq milestone (or total follow-up length if milestone is not reached);
- `'observed'`: whether the milestone was reached (1) or not (0).

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