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Type Package

Title Extended Progression Models for Repeated Measures

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Description Extended progression models for repeated measures in progressive disease clinical trials. Provides nonlinear mixed-effects progression models (linear, plateau, Emax, exponential decay), delayed treatment onset estimation by profile likelihood, joint longitudinal-survival models for informative dropout, competing-risks extensions, biomarker-informed adaptive dosing rules, and simulation-based power and sample-size calculation. The progression-model view of treatment effects, in which effects are characterised on the underlying disease trajectory rather than as additive shifts on the outcome scale, follows Raket (2022) <[doi:10.1002/sim.9581](https://doi.org/10.1002/sim.9581)>. The nonlinear mixed-effects machinery is built on the 'nlme' implementation described by Pinheiro and Bates (2000, ISBN 978-0-387-98957-0), and the joint modelling of longitudinal and time-to-event data follows Rizopoulos (2012, ISBN 978-1-4398-7286-4).

License GPL (>= 3)

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adni_simulated	<i>Simulated ADNI-style Alzheimer's trial data</i>
----------------	--

Description

Longitudinal data from a simulated ADNI-style Alzheimer's disease trial with linear progression, a treatment effect with delayed onset, and subject-level dropout information.

Usage

```
adni_simulated
```

Format

A data frame with 2160 rows and 6 variables:

rid Subject identifier.

time Visit time in months.

trt Treatment indicator: 0 = control, 1 = active.

adas_cog ADAS-Cog score (higher values indicate worse cognition).

time_to_dropout Subject-level time to dropout.

dropout Dropout indicator: 1 = dropped out, 0 = censored.

Source

Simulated with `simulate_progression_trial()`; see `data-raw/create_data.R`.

Examples

```
head(adni_simulated)
table(adni_simulated$trt)
summary(adni_simulated$adas_cog)
```

biomarker_dosing_rule	<i>Biomarker-informed adaptive dosing rule</i>
-----------------------	--

Description

Adjusts the dose one step up/down when the measured biomarker falls outside the target range, otherwise maintains the current dose.

Usage

```
biomarker_dosing_rule(
  biomarker_value,
  target_range = c(80, 120),
  dose_levels = c(0, 50, 100, 150, 200),
  current_dose_idx = 3
)
```

Arguments

biomarker_value	Observed biomarker value.
target_range	Two numeric values giving the acceptable range.
dose_levels	Ordered vector of allowed doses.
current_dose_idx	Index of the subject's current dose.

Value

List with new_dose, new_dose_idx, and adjustment ("up", "down", or "maintain").

Examples

```
biomarker_dosing_rule(130) # above target range -> step the dose up
biomarker_dosing_rule(70)  # below target range -> step the dose down
biomarker_dosing_rule(100) # inside the range -> keep the current dose
```

check_convergence	<i>Convergence checks</i>
-------------------	---------------------------

Description

For Stan/NIMBLE draws, computes R-hat and effective sample size when the coda inputs are supplied as a list of chains. For nlme fits, reports optimization convergence code and random-effects variance.

Usage

```
check_convergence(object, ...)
```

```
## Default S3 method:
```

```
check_convergence(object, ...)
```

Arguments

object	A fitted model (nlme-based or an mcmc.list / list of chains).
...	Unused.

Value

List of diagnostic values.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmrm_nlme(y ~ time * trt, data = sim)
check_convergence(fit)$converged
# R-hat for a list of scalar chains
check_convergence(list(rnorm(200), rnorm(200), rnorm(200)))$rhat
```

default_priors	<i>Default priors for Bayesian progression models</i>
----------------	---

Description

Default priors for Bayesian progression models

Usage

```
default_priors(scale = 1)
```

Arguments

scale	Outcome scale factor (e.g., SD of the response) used to make weakly-informative priors scale-aware.
-------	---

Value

Named list of prior family and parameter values for fixed effects, random-effect SDs, residual SD, association parameters, and survival shape.

Examples

```
default_priors(scale = 5)
```

delayed_effect	<i>Delayed treatment effect function</i>
----------------	--

Description

Computes the fractional treatment effect at time `time` given treatment initiation time `trt_time` and a delay `delay`.

Usage

```
delayed_effect(  
  time,  
  trt_time = 0,  
  delay = 0,  
  shape = c("exponential", "step", "linear"),  
  lambda = 0.1  
)
```

Arguments

<code>time</code>	Numeric vector of observation times.
<code>trt_time</code>	Treatment initiation time (default 0).
<code>delay</code>	Delay before onset begins (τ).
<code>shape</code>	One of "exponential", "step", "linear".
<code>lambda</code>	Onset rate for the exponential shape.

Value

Numeric vector in $[0, 1]$ giving the fraction of the full effect realized at each time.

Examples

```
t <- seq(0, 12, by = 2)  
delayed_effect(t, delay = 4, shape = "step")  
delayed_effect(t, delay = 0, shape = "exponential", lambda = 0.1)
```

emax_biomarker	<i>Emax biomarker model</i>
----------------	-----------------------------

Description

Emax biomarker model

Usage

```
emax_biomarker(conc, b_baseline = 100, emax = 30, ec50 = 5)
```

Arguments

conc	Drug concentration.
b_baseline	Baseline biomarker level.
emax	Maximum effect.
ec50	Concentration giving half-maximal effect.

Value

Numeric vector of the same length as conc giving the expected biomarker level, $b_baseline + emax * conc / (ec50 + conc)$. Values increase from b_baseline at zero concentration towards the asymptote b_baseline + emax at high concentrations.

Examples

```
conc <- seq(0, 20, by = 2)
emax_biomarker(conc, b_baseline = 100, emax = 30, ec50 = 5)
```

find_sample_size	<i>Find sample size by simulation</i>
------------------	---------------------------------------

Description

Find sample size by simulation

Usage

```
find_sample_size(target_power = 0.8, n_grid = seq(50, 300, by = 25), ...)
```

Arguments

target_power	Desired power.
n_grid	Grid of per-arm sample sizes to evaluate.
...	Arguments passed to power_pmm().

Value

List with `optimal_n` and a `power_curve` data frame.

Examples

```
ss <- find_sample_size(target_power = 0.8, n_grid = c(25, 50),
                      effect_size = -1.5, delay = 0, n_sims = 5,
                      measurement_times = seq(0, 24, by = 12), seed = 11)

ss$optimal_n
ss$power_curve
```

fit_pmm

Unified estimation wrapper

Description

Unified estimation wrapper

Usage

```
fit_pmm(model = c("nlme", "delayed", "joint"), ...)
```

Arguments

<code>model</code>	Model family: "nlme", "delayed", or "joint".
<code>...</code>	Arguments forwarded to the corresponding fitting function.

Value

The fitted model object.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- fit_pmm("nlme", y ~ time * trt, data = sim)
class(fit)
```

goodness_of_fit	<i>Goodness-of-fit summary</i>
-----------------	--------------------------------

Description

Goodness-of-fit summary

Usage

```
goodness_of_fit(fit, bins = 10)
```

Arguments

fit	A fitted pmm_nlme object.
bins	Number of bins for residual quantile grouping.

Value

List with population residuals, conditional (EB) residuals, RMSE, and information criteria.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmm_nlme(y ~ time * trt, data = sim)
g <- goodness_of_fit(fit)
g$rmse
g$AIC
```

initialize_subjects	<i>Initialize subjects for an adaptive trial simulation</i>
---------------------	---

Description

Initialize subjects for an adaptive trial simulation

Usage

```
initialize_subjects(
  n_subjects,
  n_visits = 12,
  dose_levels = c(0, 50, 100, 150, 200),
  start_dose_idx = 3,
  trt_prob = 0.5,
  seed = NULL
)
```

Arguments

n_subjects	Number of subjects.
n_visits	Number of planned visits.
dose_levels	Allowed dose levels.
start_dose_idx	Starting dose index.
trt_prob	Probability of assignment to active treatment.
seed	Random seed.

Value

Data frame of subject-level attributes.

Examples

```
initialize_subjects(6, n_visits = 4, seed = 42)
```

parametric_bootstrap *Parametric bootstrap for confidence intervals*

Description

Refits the supplied model on n_boot datasets simulated from the fitted model's estimated parameters (resampling residuals conditional on the fixed-effects mean structure).

Usage

```
parametric_bootstrap(
  fit,
  statistic = function(f) stats::coef(f)[1],
  n_boot = 200,
  seed = NULL,
  level = 0.95
)
```

Arguments

fit	A pmrm_nlme object.
statistic	Function of the refit returning the scalar of interest.
n_boot	Number of bootstrap replicates.
seed	Random seed.
level	Confidence level.

Value

List with estimate, ci, and the bootstrap draws.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmm_nlme(y ~ time * trt, data = sim)
boot <- parametric_bootstrap(fit, n_boot = 5, seed = 1)
boot$estimate
boot$ci
```

parkinsons_simulated	<i>Simulated Parkinson's trial data with informative dropout</i>
----------------------	--

Description

Longitudinal UPDRS data from a simulated Parkinson's disease trial in which progression drives an informative dropout process, so that faster progressors leave the trial earlier. Intended for use with `pmm_joint()` and `pmm_competing()`.

Usage

```
parkinsons_simulated
```

Format

A data frame with 1800 rows and 6 variables:

id Subject identifier.

time Visit time in months.

trt Treatment indicator: 0 = control, 1 = active.

updrs UPDRS score (higher values indicate worse symptoms).

time_to_dropout Subject-level time to dropout.

dropout Dropout indicator: 1 = dropped out, 0 = censored.

Source

Simulated with `simulate_joint_trial()`; see `data-raw/create_data.R`.

Examples

```
head(parkinsons_simulated)
with(parkinsons_simulated, table(trt, dropout))
summary(parkinsons_simulated$updrs)
```

pkpd_concentration	<i>PK/PD helpers for biomarker dosing</i>
--------------------	---

Description

One-compartment oral PK concentration and an Emax biomarker response.

Usage

```
pkpd_concentration(time, dose, ka = 0.5, ke = 0.1, V = 10)
```

Arguments

time	Time(s) since dose.
dose	Administered dose.
ka	Absorption rate constant.
ke	Elimination rate constant.
V	Volume of distribution.

Value

Concentration at time.

Examples

```
t <- seq(0, 24, by = 4)
pkpd_concentration(t, dose = 100)
```

plot.pmm_delayed	<i>Plot a delayed-effect fit</i>
------------------	----------------------------------

Description

Plot a delayed-effect fit

Usage

```
## S3 method for class 'pmm_delayed'
plot(x, type = c("trajectory", "profile_likelihood"), ...)
```

Arguments

x	A pmm_delayed object.
type	"trajectory" plots fitted population means by arm with the delay marked; "profile_likelihood" plots the log-likelihood vs delay with the chi-squared threshold line.
...	Unused.

Value

A ggplot object (invisibly).

Examples

```
sim <- simulate_progression_trial(n_control = 40, n_treatment = 40,
                                effect_size = -0.8, delay = 6,
                                times = seq(0, 24, by = 6), seed = 7)
fit <- pmmr_delayed(y ~ time * trt, data = sim,
                   delay_estimation = "profile",
                   delay_grid = c(0, 6), lambda = 0.2)
plot(fit, type = "profile_likelihood")
```

pmmr_adaptive_trial	<i>Run a biomarker-informed adaptive trial simulation</i>
---------------------	---

Description

Simulates visits sequentially: measure biomarkers with noise, apply the dosing rule, simulate progression and terminal events.

Usage

```
pmmr_adaptive_trial(
  n_subjects,
  progression_model = list(intercept = 20, slope = 1.5, trt_effect = -0.6, sigma = 2),
  pkpd_model = list(emax = 30, ec50 = 5, b_baseline = 100, noise_sd = 3),
  dosing_rule = biomarker_dosing_rule,
  n_visits = 12,
  visit_interval = 4,
  dropout_rate = 0.15,
  target_range = c(pkpd_model$b_baseline - 10, pkpd_model$b_baseline + 10),
  dose_levels = c(0, 50, 100, 150, 200),
  seed = NULL
)
```

Arguments

n_subjects	Number of subjects.
progression_model	List describing progression: intercept, slope, treatment effect on slope, residual sd.
pkpd_model	List with elements emax, ec50, b_baseline, noise_sd.
dosing_rule	Function like biomarker_dosing_rule().
n_visits	Number of visits.
visit_interval	Weeks between visits.

dropout_rate	Annual dropout hazard.
target_range	Target biomarker range for dosing.
dose_levels	Allowed dose levels.
seed	Random seed.

Value

A list with long-format outcomes `$long_data` and final subject states `$subjects`.

Examples

```
out <- pmrm_adaptive_trial(n_subjects = 12, n_visits = 4, seed = 1)
head(out$long_data)
# subjects whose dose was adapted at least once
table(out$subjects$dose_idx)
```

pmrm_competing	<i>Fit a competing-risks progression model</i>
----------------	--

Description

Fits cause-specific Cox proportional-hazards models for each terminal event type on top of the shared longitudinal mixed-effects submodel. Association with the longitudinal process enters through empirical-Bayes current value and slope at each subject's event/censoring time.

Usage

```
pmrm_competing(
  long_formula,
  surv_formulas = y ~ 1,
  data,
  time_var = "time",
  subject_var = "id",
  event_time_var = "time_to_dropout",
  event_var = "event",
  causes = c("dropout", "death"),
  association = c("current_value", "slope", "both"),
  ...
)
```

Arguments

long_formula	Longitudinal formula.
surv_formulas	Either a single survival formula or a named list of formulas, one per cause (right-hand side only; Surv response is added).
data	Long-format data frame.

time_var	Name of longitudinal time column.
subject_var	Name of subject id column.
event_time_var	Column holding time-to-event (defaults to the column name used by the shipped data sets).
event_var	Column holding the event code: 0 = censored, 1..K = cause.
causes	Character vector of cause labels in code order.
association	"current_value", "slope", or "both".
...	Additional arguments to pmmr_nlme().

Value

Object of class "pmmr_competing".

Examples

```
fit <- pmmr_competing(updrs ~ time * trt,
                     surv_formulas = ~ trt,
                     data = parkinsons_simulated,
                     event_var = "dropout",
                     causes = "dropout")
names(fit$cause_fits)
summary(fit)$hazard_ratios
```

pmmr_delayed

Fit a progression model with delayed treatment onset

Description

The treatment effect enters the model exclusively through a delayed term, $\delta * \text{Trt}_i * t_{ij} * d(t_{ij})$, where $d()$ is a fractional onset function: treatment terms already present in formula (such as the trt and $\text{time}:\text{trt}$ terms of $y \sim \text{time} * \text{trt}$) are replaced by this term. Keeping them alongside the delayed term would let an unrestricted treatment effect absorb the delay and make it unidentifiable, in which case the profile likelihood always peaks at zero delay. Because the delayed term is proportional to time, δ is the treatment effect on the progression slope at full onset.

Usage

```
pmmr_delayed(
  formula,
  data,
  delay_estimation = c("fixed", "profile", "bayesian"),
  delay_grid = seq(0, 24, by = 3),
  shape = c("exponential", "step", "linear"),
  lambda = 0.3,
  progression = "linear",
  conf_level = 0.95,
  ...
)
```

Arguments

<code>formula</code>	LME-style formula, e.g. <code>y ~ time * trt</code> . Terms involving the treatment indicator are replaced by the delayed treatment term; the remaining terms specify the common progression model.
<code>data</code>	Long-format data frame.
<code>delay_estimation</code>	One of "fixed", "profile", or "bayesian" ("bayesian" currently falls back to profile with a warning).
<code>delay_grid</code>	Grid of candidate delays (in the units of time).
<code>shape</code>	Onset shape passed to <code>delayed_effect()</code> .
<code>lambda</code>	Onset rate for exponential onset.
<code>progression</code>	Progression shape passed to <code>pmmr_nlme()</code> .
<code>conf_level</code>	Confidence level for the delay confidence interval.
<code>...</code>	Additional arguments to <code>pmmr_nlme()</code> .

Details

The data must contain a treatment indicator column named `trt` (any case), which is what identifies the treatment terms to replace. Pass other `pmmr_nlme()` options – most importantly `subject_var` and `time_var` – through `...`

When `delay_estimation = "profile"`, the delay is estimated by grid search over `delay_grid`, selecting the value maximizing log-likelihood; an approximate confidence set is derived from the chi-squared threshold (log-lik drop of $qchisq(0.95, 1)/2$). All candidates use the same fixed-effects structure, so the REML log-likelihoods are comparable across the grid.

Value

Object of class "pmmr_delayed" containing the best fit, the estimated delay, the profile likelihood, and the delay CI.

References

Raket LL (2022). Progression models for repeated measures: Estimating novel treatment effects in progressive diseases. *Statistics in Medicine*. doi:10.1002/sim.9581.

Examples

```
sim <- simulate_progression_trial(n_control = 40, n_treatment = 40,
                                effect_size = -0.8, delay = 6,
                                times = seq(0, 24, by = 6),
                                residual_sd = 1.5, random_sd = 0.2, seed = 7)
fit <- pmmr_delayed(y ~ time * trt, data = sim,
                   delay_estimation = "profile",
                   delay_grid = c(0, 6, 12), lambda = 0.2)
fit$delay_estimate
summary(fit)$delay_ci
```

pmmr_joint

*Fit a joint longitudinal-survival model***Description**

Fit a joint longitudinal-survival model

Usage

```
pmmr_joint(
  long_formula,
  surv_formula,
  data,
  event_data = NULL,
  time_var = "time",
  subject_var = "id",
  event_time_var = "time_to_dropout",
  event_var = "dropout",
  association = c("current_value", "slope", "both"),
  surv_model = c("weibull", "exponential", "stan_jm"),
  ...
)
```

Arguments

long_formula	Longitudinal mixed-model formula, e.g. <code>y ~ time * trt</code> .
surv_formula	Survival formula, e.g. <code>Surv(time_to_dropout, dropout) ~ trt</code> .
data	Long-format data frame with one row per observation; the event data are extracted from <code>event_data</code> if supplied, otherwise from per-subject columns in <code>data</code> .
event_data	Optional data frame with one row per subject containing the subject id and the variables on the right-hand side of <code>surv_formula</code> .
time_var	Name of the longitudinal time column.
subject_var	Name of the subject identifier column.
event_time_var	Name of the column holding time-to-event (defaults to the column name used by the shipped data sets).
event_var	Name of the event indicator column (1 = event).
association	One of "current_value", "slope", "both".
surv_model	Baseline hazard family: "weibull" or "exponential". The legacy value "stan_jm" is accepted for backward compatibility but currently warns and falls back to "weibull".
...	Additional arguments passed to the fitting engine.

Value

Object of class "pmmr_joint" with elements long_fit, surv_fit, association, and helper summaries.

References

Rizopoulos D (2012). Joint Models for Longitudinal and Time-to-Event Data: With Applications in R. Chapman and Hall/CRC Biostatistics Series. ISBN 978-1-4398-7286-4.

Examples

```
fit <- pmmr_joint(updrs ~ time * trt,
                 Surv(time_to_dropout, dropout) ~ trt,
                 data = parkinsons_simulated,
                 association = "current_value")

class(fit)
fit$assoc_terms
```

pmmr_nlme

Fit a nonlinear progression mixed-effects model

Description

Fits repeated-measures progression data using one of four common shapes (linear, plateau, emax, exponential). Linear models use nlme::lme; nonlinear shapes use nlme::nlme.

Usage

```
pmmr_nlme(
  formula,
  data,
  progression = c("linear", "plateau", "emax", "exponential"),
  random = NULL,
  treatment_var = "trt",
  time_var = "time",
  subject_var = "id",
  heteroscedastic = FALSE,
  start = NULL,
  ...
)
```

Arguments

formula	Formula such as $y \sim \text{time} + \text{trt}$ (linear shape).
data	Data frame in long format.
progression	Progression shape: one of "linear", "plateau", "emax", "exponential".
random	Random effects specification; the grouping variable is taken from subject_var.

treatment_var	Name of the treatment indicator column.
time_var	Name of the time column.
subject_var	Name of the subject identifier column.
heteroscedastic	If TRUE allow residual variance to increase with time via a power variance function.
start	Optional named starting values for nonlinear shapes.
...	Additional arguments passed on to the fitting engine.

Value

An object of class "pmm_nlme".

References

Pinheiro JC, Bates DM (2000). Mixed-Effects Models in S and S-PLUS. Springer Statistics and Computing. ISBN 978-0-387-98957-0.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmm_nlme(y ~ time * trt, data = sim)
summary(fit)$tTable
```

population_trajectory *Population-level trajectory over a time grid*

Description

Population-level trajectory over a time grid

Usage

```
population_trajectory(object, times, trt = 0)
```

Arguments

object	A pmm_nlme or pmm_delayed object.
times	Numeric vector of times.
trt	Treatment arm value (default 0).

Value

Data frame with columns time, trt, predicted.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmm_nlme(y ~ time * trt, data = sim)
population_trajectory(fit, times = seq(0, 24, by = 6), trt = c(0, 1))
```

power_pmm

*Simulation-based power for progression trials***Description**

Simulation-based power for progression trials

Usage

```
power_pmm(
  n_per_arm,
  effect_size = -0.5,
  delay = 0,
  dropout_rate = 0.15,
  measurement_times = seq(0, 24, by = 6),
  n_sims = 200,
  alpha = 0.05,
  seed = NULL,
  ...
)
```

Arguments

n_per_arm	Subjects per arm.
effect_size	Treatment effect on slope (per year).
delay	Delayed onset in months.
dropout_rate	Annual dropout rate.
measurement_times	Visit schedule in months.
n_sims	Number of simulations.
alpha	One-sided... actually two-sided type-I error level.
seed	Random seed.
...	Passed to <code>simulate_progression_trial()</code> .

Value

List with power, mean estimate/SE, bias, MSE, and the non-convergence rate.

Examples

```
p <- power_prm(n_per_arm = 30, effect_size = -1.5, delay = 0,
               n_sims = 5, measurement_times = seq(0, 24, by = 12),
               seed = 11)

p$power
p$mean_estimate
```

predict.prm_nlme	<i>Predict from a fitted progression model</i>
------------------	--

Description

Predict from a fitted progression model

Usage

```
## S3 method for class 'prmlme'
predict(object, newdata, level = c("population", "individual"), ...)
```

Arguments

object	A prmlme object.
newdata	New data frame containing the predictor columns.
level	Either "population" (fixed effects only) or "individual" (includes empirical-Bayes random effects).
...	Unused.

Value

Numeric vector of predictions.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- prmlme(y ~ time * trt, data = sim)
nd <- data.frame(time = c(0, 6, 12, 24), trt = c(0, 0, 1, 1))
predict(fit, newdata = nd)           # population level
head(predict(fit, level = "individual")) # subject-specific
```

```
print.prmr_delayed      Print method for delayed-effect fits
```

Description

Print method for delayed-effect fits

Usage

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

Arguments

`x` A `pmrm_delayed` object.
`...` Passed to `print`.

Value

The input object `x`, invisibly (of class `c("pmrm_delayed", "lme")`). Called for its side effect of printing a concise summary (progression shape, estimated delay and, when available, delay confidence interval) to the console.

Examples

```
sim <- simulate_progression_trial(n_control = 40, n_treatment = 40,
                                effect_size = -0.8, delay = 6,
                                times = seq(0, 24, by = 6), seed = 7)
fit <- pmrm_delayed(y ~ time * trt, data = sim,
                   delay_estimation = "profile",
                   delay_grid = c(0, 6), lambda = 0.2)
print(fit)
```

```
scenario_base      Scenario builders for trial simulation studies
```

Description

Named scenario lists consumed by `power_pmr()` via `do.call`.

Usage

```
scenario_base()

scenario_optimistic()

scenario_pessimistic()
```

Value

A list of simulation arguments.

Examples

```
scenario_optimistic()
scenario_base()
scenario_pessimistic()
```

simulate_biomarker	<i>Simulate biomarker measurements under the PK/PD model</i>
--------------------	--

Description

Simulate biomarker measurements under the PK/PD model

Usage

```
simulate_biomarker(
  subjects,
  visit,
  visit_interval = 4,
  dose_levels = c(0, 50, 100, 150, 200),
  noise_sd = 3,
  emax = 30,
  ec50 = 5,
  b_baseline = 100
)
```

Arguments

subjects	Subject data frame from initialize_subjects().
visit	Current visit index.
visit_interval	Interval between visits.
dose_levels	Dose levels vector.
noise_sd	Residual measurement SD.
emax, ec50, b_baseline	Emax-model parameters.

Value

Named numeric vector of observed biomarkers.

Examples

```
subj <- initialize_subjects(6, n_visits = 4, seed = 42)
simulate_biomarker(subj, visit = 2)
```

`simulate_joint_trial` *Simulate a trial with informative dropout via a joint model mechanism*

Description

Progression drives a Weibull hazard for dropout through the current latent value, so faster progressors leave earlier.

Usage

```
simulate_joint_trial(
  n_control = 50,
  n_treatment = 50,
  effect_size = -0.5,
  delay = 0,
  times = seq(0, 24, by = 3),
  intercept = 20,
  slope = 1,
  random_sd = 0.5,
  residual_sd = 2,
  alpha = 0.05,
  weibull_scale = 100,
  weibull_shape = 1.4,
  seed = NULL
)
```

Arguments

<code>n_control, n_treatment</code>	Subjects per arm.
<code>effect_size</code>	Treatment effect on the slope per unit of time (negative = slower progression).
<code>delay</code>	Delayed onset (same units as <code>times</code>).
<code>times</code>	Vector of measurement times.
<code>intercept</code>	Population intercept at time 0.
<code>slope</code>	Control-arm slope per unit time.
<code>random_sd</code>	SD of subject random slope.
<code>residual_sd</code>	Residual SD.
<code>alpha</code>	Association of current value with the log-hazard.
<code>weibull_scale, weibull_shape</code>	Weibull parameters for baseline hazard.
<code>seed</code>	Random seed.

Value

A long-format data frame (one row per subject per visit time) with columns `id` (subject identifier), `time` (visit time), `trt` (treatment indicator, 0 = control, 1 = active), `y` (longitudinal outcome, NA after dropout), `time_to_dropout` (subject-level simulated event/censoring time) and `dropout` (subject-level event indicator, 1 = dropout observed, 0 = censored). Larger latent progression values produce larger hazards through alpha, so faster progressors tend to drop out earlier.

Examples

```
sim <- simulate_joint_trial(n_control = 20, n_treatment = 20,
                           times = seq(0, 24, by = 6), seed = 1)

head(sim)
# share of subjects with an observed dropout event
mean(tapply(sim$dropout, sim$id, function(z) z[1]))
```

`simulate_progression_trial`

Simulate a progression trial

Description

Simulate a progression trial

Usage

```
simulate_progression_trial(
  n_control = 50,
  n_treatment = 50,
  effect_size = -0.5,
  delay = 0,
  dropout_rate = 0.15,
  times = seq(0, 24, by = 6),
  intercept = 20,
  slope = 1,
  random_sd = 0.3,
  residual_sd = 2,
  seed = NULL
)
```

Arguments

<code>n_control</code> , <code>n_treatment</code>	Subjects per arm.
<code>effect_size</code>	Treatment effect on the slope per unit of time (negative = slower progression).
<code>delay</code>	Delayed onset (same units as times).
<code>dropout_rate</code>	Annual dropout probability.

times	Vector of measurement times.
intercept	Population intercept at time 0.
slope	Control-arm slope per unit time.
random_sd	SD of subject random slope.
residual_sd	Residual SD.
seed	Random seed.

Value

Long-format data frame with columns id, time, trt, y.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20,
                                effect_size = -0.5, delay = 6,
                                times = seq(0, 24, by = 6), seed = 1)

head(sim)
aggregate(y ~ trt, data = sim, FUN = mean, na.rm = TRUE)
```

subject_summaries	<i>Extract subject-level summary (EB intercept and slope)</i>
-------------------	---

Description

Extract subject-level summary (EB intercept and slope)

Usage

```
subject_summaries(fit)
```

Arguments

fit A pmm_nlme object.

Value

Data frame with id, b0 and b1.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20, seed = 1)
fit <- pmm_nlme(y ~ time * trt, data = sim)
head(subject_summaries(fit))
```

`summary.prmr_competing`*Summarize a competing-risks fit*

Description

Summarize a competing-risks fit

Usage

```
## S3 method for class 'prmr_competing'  
summary(object, ...)
```

Arguments

<code>object</code>	A <code>prmr_competing</code> object.
<code>...</code>	Unused.

Value

A list with the longitudinal fixed effects, the cause labels, the cause-specific hazard ratios, and per-cause concordance.

Examples

```
fit <- prmr_competing(updrs ~ time * trt,  
                      surv_formulas = ~ trt,  
                      data = parkinsons_simulated,  
                      event_var = "dropout",  
                      causes = "dropout")  
summary(fit)$fixed_effects  
summary(fit)$concordance
```

`summary.prmr_delayed` *Summarize a delayed-effect fit*

Description

Summarize a delayed-effect fit

Usage

```
## S3 method for class 'prmr_delayed'  
summary(object, ...)
```

Arguments

object A prmr_delayed object.
 ... Unused.

Value

List with fixed effects, delay estimate/CI, and information criteria.

Examples

```
sim <- simulate_progression_trial(n_control = 40, n_treatment = 40,
                                effect_size = -0.8, delay = 6,
                                times = seq(0, 24, by = 6), seed = 7)
fit <- prmr_delayed(y ~ time * trt, data = sim,
                   delay_estimation = "profile",
                   delay_grid = c(0, 6), lambda = 0.2)
s <- summary(fit)
s$delay_estimate
s$delay_ci
```

summary.prmr_joint	<i>Summarize a joint model fit</i>
--------------------	------------------------------------

Description

Summarize a joint model fit

Usage

```
## S3 method for class 'pmrm_joint'
summary(object, ...)
```

Arguments

object A prmr_joint object.
 ... Unused.

Value

A list with the progression fixed/random effects, the survival coefficients, the association structure and its coefficients, and the longitudinal/survival AIC values.

Examples

```
fit <- pmrm_joint(updrs ~ time * trt,
                  Surv(time_to_dropout, dropout) ~ trt,
                  data = parkinsons_simulated,
                  association = "both")
s <- summary(fit)
s$survival
s$association_coefficients
```

to_event_data	<i>Reshape long trial data to per-subject event data</i>
---------------	--

Description

Reshape long trial data to per-subject event data

Usage

```
to_event_data(
  long_data,
  id_var = "id",
  time_to_event_var = "time_to_dropout",
  event_var = "dropout"
)
```

Arguments

long_data Long-format data frame.
 id_var, time_to_event_var, event_var
 Column names.

Value

One-row-per-subject data frame.

Examples

```
sim <- simulate_joint_trial(n_control = 20, n_treatment = 20, seed = 1)
ev <- to_event_data(sim, id_var = "id",
                    time_to_event_var = "time_to_dropout",
                    event_var = "dropout")
head(ev)
```

vpc	<i>Visual predictive check (VPC)</i>
-----	--------------------------------------

Description

Visual predictive check (VPC)

Usage

```
vpc(fit, n_sims = 50, probs = c(0.05, 0.5, 0.95), seed = NULL)
```

Arguments

fit	Fitted pmrm_nlme object.
n_sims	Number of simulated datasets for the VPC.
probs	Quantiles to report.
seed	Random seed.

Value

Data frame of observed vs simulated quantiles by time bin.

Examples

```
sim <- simulate_progression_trial(n_control = 20, n_treatment = 20,  
                                times = seq(0, 24, by = 6), seed = 2)  
fit <- pmrm_nlme(y ~ time * trt, data = sim)  
vpc(fit, n_sims = 5, seed = 1)
```

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