Package ‘microbiomeDASim’

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Description A toolkit for simulating differential microbiome data designed for longitudinal analyses. Several functional forms may be specified for the mean trend. Observations are drawn from a multivariate normal model. The objective of this package is to be able to simulate data in order to accurately compare different longitudinal methods for differential abundance.
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Description

Generating the final combined bug output

Usage

final_output_gen(
  no_diff_feat,
  diff_abun_features,
  diff_Y,
  null_Y,
  diff_bugs,
  nodiff_bugs,
  final_output = NULL
)

Arguments

  no_diff_feat number of non differentially abundant features
  diff_abun_features number of differentially abundant features
  diff_Y simulated outcome for differentially abundant features
null_Y  simulated outcome for non differentially abundant features
diff_bugs  sample information for differentially abundant features
nodiff_bugs  sample information for non differentially abundant features
final_output  final object that will store the simulated data

Value

final output list with the OTU table and corresponding bug feature data.frame

form_beta_check  Beta Specification Check

Description

Function for checking that the appropriate beta parameters are specified for each of the mean trend specifications

Usage

form_beta_check(form, beta, IP, timepoints)

Arguments

form  character value specifying the type of time trend. Options include 'linear', 'quadratic', 'cubic', 'M', 'W', 'L_up', and 'L_down'.
beta  vector specifying the appropriate parameters for functional trend. See details of mean_trend for explanation for each form
IP  vector specifying the inflection points. See details of mean_trend for explanation for each form
timepoints  numeric vector specifying the points to fit the functional trend.
@keywords internal

Value

Nothing returned unless an error is returned.
**gen_norm_microbiome_norm_feature_check**

*Checking that features are specified appropriately*

**Description**
Checking that features are specified appropriately

**Usage**
```
gen_microbiome_norm_feature_check(features, diff_abun_features)
```

**Arguments**
- **features** Numeric value specifying the total number of features to simulate in the microbiome. Must be greater than zero
- **diff_abun_features** Number of features to simulate with differentially abundant pattern. Must be between zero and number of features specified

**Value**
Potential warning message if no differentially abundant features or all differentially abundant features are specified

---

**gen_norm_microbiome**

*Generate Longitudinal Differential Abundance from Multivariate Normal*

**Description**
Generate Longitudinal Differential Abundance from Multivariate Normal

**Usage**
```
gen_norm_microbiome(
    features = 10,
    diff_abun_features = 5,
    n_control,
    n_treat,
    control_mean,
    sigma,
    num_timepoints,
    t_interval,
    rho,
```
gen_norm_microbiome

corr_str = c("ar1", "compound", "ind"),
func_form = c("linear", "quadratic", "cubic", "M", "W", "L_up", "L_down"),
beta,
IP = NULL,
missing_pct,
missing_per_subject,
miss_val = NA,
dis_plot = FALSE,
plot_trend = FALSE,
zero_trunc = TRUE,
asynch_time = FALSE
)

Arguments

features numeric value specifying the number of features/microbes to simulate. Default is 10.
diff_abun_features numeric value specifying the number of differentially abundant features. Default is 5.
n_control integer value specifying the number of control individuals
n_treat integer value specifying the number of treated individuals
control_mean numeric value specifying the mean value for control subjects. all control sub-
djects are assummed to have the same population mean value.
sigma numeric value specifying the global population standard deviation for both con-
trol and treated individuals.
num_timepoints integer value specifying the number of timepoints per subject.
t_interval numeric vector of length two specifying the interval of time from which to draw observatoins \([t_1, t_q]\). Assumed to be equally spaced over the interval unless asynch_time is set to TRUE.
rho value for the correlation parameter. must be between \([0, 1]\). see mvrnorm_corr_gen for details.
corr_str correlation structure selected. see mvrnorm_corr_gen for details.
func_form character value specifying the functional form for the longitudinal mean trend. see mean_trend for details.
beta vector value specifying the parameters for the differential abundance function. see mean_trend for details.
IP vector specifying any inflection points. depends on the type of functional form specified. see mean_trend for details. by default this is set to NULL.
missing_pct numeric value that must be between \([0, 1]\) that specifies what percentage of the individuals will have missing values.
missing_per_subject integer value specifying how many observations per subject should be dropped. note that we assume that all individuals must have baseline value, meaning that the maximum number of missing_per_subject is equal to num_timepoints - 1.
miss_val value used to induce missingness from the simulated data. By default missing values are assumed to be NA but other common choices include 0.

dis_plot logical argument on whether to plot the simulated data or not. By default plotting is turned off.

plot_trend specifies whether to plot the true mean trend. See `mean_trend` for details.

zero_trunc logical indicator designating whether simulated outcomes should be zero truncated. Default is set to TRUE.

asynch_time logical indicator designed to randomly sample timepoints over a specified interval if set to TRUE. Default is FALSE.

Value

This function returns a list with the following objects:

Y The full simulated feature sample matrix where each row represent a feature and each column a sample. Note that the differential and non-differential bugs are marked by row.names.

Examples

```r
gen_norm_microbiome(features = 5, diff_abun_features = 2, 
                      n_control = 10, n_treat = 10, control_mean = 8, sigma = 1, 
                      num_timepoints = 5, t_interval=c(0, 4), rho = 0.8, 
                      corr_str = "compound", func_form = "linear", beta = c(0, 1), 
                      missing_pct = 0.3, missing_per_subject = 2)
```

---

**gen_norm_microbiome_obs**

*Generate Longitudinal Differential Abundance from Multivariate Normal with Observed Data*

**Description**

Generate Longitudinal Differential Abundance from Multivariate Normal with Observed Data

**Usage**

```r
gen_norm_microbiome_obs( 
  features = 10, 
  diff_abun_features = 5, 
  id, 
  time, 
  group, 
  ref, 
  control_mean, 
  sigma, 
  rho, 
  
  
  
```
Arguments

features numeric value specifying the number of features/microbes to simulate. Default is 10.

diff_abun_features numeric value specifying the number of differentially abundant features. Default is 5.

id vector of length N that identifies repeated measurements for each unit

time vector of length N that determines when values will be sampled for each unit

group factor vector with two levels indicating the group assignment for each respective id

ref character value identifying which group value to treat as control and which value to treat as treatment

control_mean numeric value specifying the mean value for control subjects. All control subjects are assumed to have the same population mean value.

sigma numeric value specifying the global population standard deviation for both control and treated individuals.

rho value for the correlation parameter. Must be between [0, 1]. See mvrnorm_cor_gen for details.

corr_str correlation structure selected. See mvrnorm_cor_gen for details.

func_form character value specifying the functional form for the longitudinal mean trend. See mean_trend for details.

beta vector value specifying the parameters for the differential abundance function. See mean_trend for details.

IP vector specifying any inflection points. Depends on the type of functional form specified. See mean_trend for details. By default this is set to NULL.

dis_plot logical argument on whether to plot the simulated data or not. By default plotting is turned off.

plot_trend specifies whether to plot the true mean trend. See mean_trend for details.

zero_trunc logical indicator designating whether simulated outcomes should be zero truncated. By default is set to TRUE

Value

This function returns a list with the following objects

Y The full simulated feature sample matrix where each row represent a feature and each column a sample. Note that the differential and non-differential bugs are marked by row.names
Examples

```r
set.seed(011520)
id_list <- lapply(seq_len(60), function(i){
  obs <- sample(5:10, size=1)
  id_rep <- rep(i, obs)
})

time_interval <- c(0, 10)
time_list <- lapply(id_list, function(x){
  time_len <- length(x)
  times <- runif(time_len, min=time_interval[1], max=time_interval[2])
  times <- times[order(times)]
})

group_list <- lapply(id_list, function(x){
  group_len <- length(x)
  tx_ind <- sample(seq_len(2), 1)
  tx_group <- ifelse(tx_ind==1, "Control", "Treatment")
  groups <- rep(tx_group, group_len)
})
id <- unlist(id_list)
group <- factor(unlist(group_list), levels = c("Control", "Treatment"))
time <- unlist(time_list)

# control times
ct <- unlist(lapply(unique(id[group=="Control"]), function(x){
  length(id[id==x])
}))

# treatment times

tt <- unlist(lapply(unique(id[group=="Treatment"]), function(x){
  length(id[id==x])
}))

mean(ct)
mean(tt)

gen_norm_microbiome_obs(features=4, diff_abun_features=2, id=id, time=time, group=group, ref="Control", control_mean=2, sigma=1, rho=0.7, corr_str="compound", func_form="L_up", beta=1, IP=5, zero_trunc=TRUE)
```

---

### Description

This function allows the user to create spaghetti plots for individuals with time varying covariates. You can also break this down into subgroups to analyze different trends.
Usage

```r
ggplot_spaghetti(
  y,
  id,
  time,
  alpha = 0.2,
  method = "loess",
  jit = 0,
  group = NULL
)
```

Arguments

- **y**: This is the y-axis parameter to specify. Generally it is a continuous variable.
- **id**: This is the id parameter that identifies the unique individuals or units.
- **time**: This is the time vector and must be numeric.
- **alpha**: Scalar value between [0,1] that specifies the transparency of the lineplots.
- **method**: Character value that specifies which type of method to use for fitting. Optional methods come from `geom_smooth` function.
- **jit**: Scalar value that specifies how much you want to jitter each individual observation. Useful if many of the values share the same y values at a time point.
- **group**: Specifies a grouping variable to be used, and will plot it by color on one single plot.

Details

Note that the data must be in long format.

Value

Plots a time series data by each individual/unit with group trends overlayed.

Examples

```r
library(ggplot2)
num_subjects_per_group <- 15
sim_obj <- mvrnorm_sim(n_control=num_subjects_per_group,
                        n_treat=num_subjects_per_group,
                        control_mean=5, sigma=1, num_timepoints=5,
                        t_interval = c(0, 4),
                        rho=0.95, corr_str='ar1', func_form='linear',
                        beta=c(0, 0.25),
                        missing_pct=0.6, missing_per_subject=2)

with(sim_obj$df, suppressWarnings(ggplot_spaghetti(y=Y_obs, id=ID, time=time,
                                                    jit=0.1, group=group)))+
  labs(title="Simulated Microbiome Data from Multivariate Normal",
       y="Normalized Reads", x="Time")
```
mean_trend

scale_linetype_manual(values=c("solid","dashed"), name="Group") +
scale_color_manual(values=c("#F8766D", "#00BFC4"), name="Group")

IP_form_check  
Inflection point check for mean_trend

Description
Inflection point check for mean_trend

Usage
IP_form_check(form, beta, IP, timepoints)

Arguments

form  character value specifying the type of trend. Options include 'linear', 'quadratic', 'cubic', 'M', 'W', 'L_up', and 'L_down'.
beta  vector specifying the appropriate parameters for functional trend. See details of mean_trend for explanation for each form
IP  vector specifying the inflection points. See details of mean_trend for explanation for each form
timepoints  numeric vector specifying the points to fit the functional trend.

Value
Updated inflection point vector

mean_trend  Function for Generating Various Longitudinal Mean Trends

Description
In order to investigate different functional forms of longitudinal differential abundance we allow the mean time trend to take a variety of forms. These functional forms include linear, quadratic, cubic, M, W, L_up, or L_down. For each form the direction/concavity/fold change can be specified using the beta parameter.

Usage
mean_trend(
  timepoints,
  form = c("linear", "quadratic", "cubic", "M", "W", "L_up", "L_down"),
  beta,
  IP = NULL,
  plot_trend = FALSE
)
mean_trend

Arguments

timepoints numeric vector specifying the points to fit the functional trend.
form character value specifying the type of time trend. Options include 'linear', 'quadratic', 'cubic', 'M', 'W', 'L_up', and 'L_down'.
beta vector specifying the appropriate parameters for the equation. In the case of 'linear', beta should be a two-dimensional vector specifying the intercept and slope. See details for the further explanation of the beta value for each form.
IP vector specifying the inflection points where changes occur for functional forms M, W, and L trends.
plot_trend logical value indicating whether a plot should be produced for the time trend. By default this is set to TRUE.

Details

Linear Form Notes:

\[ f(x) = \beta_0 + \beta_1 x + \beta_2 x^2 \]

- Sign of \( \beta_1 \) determines whether the trend is increasing (+) or decreasing (-)

Quadratic Form Notes:

\[ f(x) = \beta_0 + \beta_1 x + \beta_2 x^2 \]

- Critical point for quadratic function occurs at the point \( -\frac{\beta_1}{2\beta_2} \)
- \( \beta_2 \) determines whether the quadratic is concave up (+) or concave down (-)

Cubic Form Notes:

\[ f(x) = \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 x^3 \]

- Point of Inflection for cubic function occurs \( -\frac{\beta_2}{3\beta_3} \)
- Critical points for cubic function occur at \( -\frac{\beta_2 \pm \sqrt{\beta_2^2 - 3\beta_1 \beta_3}}{3\beta_3} \)
- Can generate piecewise linear trends, i.e. 'V' form, by placing either one of the IP points outside of the timepoints specified

M/W Form Notes:

- Must specify beta as \((\beta_0, \beta_1)\) and IP as \((IP_1, IP_2, IP_3)\)
- This form should be specified with an initial intercept, \( \beta_0 \), and slope, \( \beta_1 \), that will connect to the first point of change (IP) specified.
- Subsequent slopes are constructed such that the mean value at the second IP value and final timepoint are 0
- The mean value at the third IP is set to be equal to the calculated mean value at the first IP based on the specified intercept and slope.
- \( \beta_0 \)=intercept, i.e. timepoint when \( y=0 \)
- \( \beta_1 \)=slope between \( \beta_0 \) and \( IP_1 \)
L_up Form Notes:
The structure of this form assumes that there is no trend from \( t_1 \) to \( IP_1 \). Then at the point of change specified, \( IP_1 \), there occurs a linearly increasing trend with slope equal to \( \beta_{\text{slope}} \) up to the last specified timepoint \( t_q \).

- Must specify beta as \( (\beta_{\text{slope}}) \), and must be positive
- Specify a single point of change (IP) variable where positive trend will start
- IP must be between \([t_1, t_q]\)

L_down Form Notes:
Similarly, the L_down form assumes that there are two regions within the range of timepoints. The first region is a decreasing trend and the second region has no trend. The decreasing trend must start with a Y intercept greater than zero, and the slope must be specified as negative. There is one point of change (IP), but this is calculated automatically based on the values of the Y intercept and slope provided, \( IP = -\beta_{\text{yintercept}}/\beta_{\text{slope}} \).

- Must specify beta as \( (\beta_{\text{yintercept}}, \beta_{\text{slope}}) \) where \( \beta_{\text{yintercept}}>0 \) and \( \beta_{\text{slope}}<0 \)
- IP variable should be specified as NULL, if value is provided it will be ignored.

Value
This function returns a list of the following
form - character value repeating the form selected
trend - data.frame with the variables \( \mu \) representing the estimated mean value at timepoints used for fitting the trend
beta - returning the numeric vector used to fit the functional form

Examples

# Quadratic Form
mean_trend(timepoints=seq(0, 6, length.out=20),
          form='quadratic', beta=1/4 * c(-1, 3, -0.5), plot_trend=TRUE)

# M Form
mean_trend(timepoints=seq(0, 10, length.out=100), form='M',
          beta=c(0, 5), IP=10 * c(1/4, 2/4, 3/4), plot_trend=TRUE)

## in this case the IP points are selected so that peaks are evenly distributed but this does not have to be true in general

# L_up Form
mean_trend(timepoints=seq(0, 10, length.out=100), form='L_up',
          beta=1, IP=5, plot_trend=TRUE)

# L_down Form
mean_trend(timepoints=seq(0, 10, length.out=100), form='L_down',
          beta=c(4, -0.5), IP=NULL, plot_trend=TRUE)
mean_trend_beta_vec  
*Create beta vector for mean_trend for all functional forms*

**Description**
Create beta vector for mean_trend for all functional forms

**Usage**
```r
mean_trend_beta_vec(form, beta, IP, timepoints)
```

**Arguments**
- `form` character value specifying the type of time trend. Options include 'linear', 'quadratic', 'cubic', 'M', 'W', 'L_up', and 'L_down'.
- `beta` vector specifying the appropriate parameters for functional trend. See details of `mean_trend` for explanation for each form.
- `IP` vector specifying the inflection points. See details of `mean_trend` for explanation for each form.
- `timepoints` numeric vector specifying the points to fit the functional trend.

**Value**
Vector with beta values used to create mean_trend

---

mean_trend_design_mat  
*Create Design Matrix for mean_trend function*

**Description**
By taking in the user specified parameters, we can return a design matrix to use when creating the differential longitudinal abundance.

**Usage**
```r
mean_trend_design_mat(form, beta, IP, timepoints)
```

**Arguments**
- `form` character value specifying the type of time trend. Options include 'linear', 'quadratic', 'cubic', 'M', 'W', 'L_up', and 'L_down'.
- `beta` vector specifying the appropriate parameters for functional trend. See details of `mean_trend` for explanation for each form.
- `IP` vector specifying the inflection points. See details of `mean_trend` for explanation for each form.
- `timepoints` numeric vector specifying the points to fit the functional trend.
**mvrnorm_corr_gen**

Generate Multivariate Random Normal Longitudinal Data

**Description**

For this methodology we assume that we draw a set of $n$ independent each with $q_i$ observations.

**Usage**

```r
mvrnorm_corr_gen(
  n, obs, t, mu, sigma, rho,
  corr_str = c("ar1", "compound", "ind"),
  zero_trunc = TRUE
)
```

**Arguments**

- `n`: integer scalar representing the total number of individuals
- `obs`: vector of length $n$ specifying the number of observations per individual.
- `t`: vector corresponding to the timepoints for each individual.
- `mu`: vector specifying the mean value for individuals.
- `sigma`: scalar specifying the standard deviation for all observations.
- `rho`: numeric scalar value between [0, 1] specifying the amount of correlation between. assumes that the correlation is consistent for all subjects.
- `corr_str`: character value specifying the correlation structure. Currently available methods are \'ar1\', \'compound\', and \'ind\' which correspond to first-order autoregressive, compound or equicorrelation, and independence respectively.
- `zero_trunc`: logical value to specifying whether the generating distribution should come from a multivariate zero truncated normal or an untruncated multivariate normal. by default we assume that zero truncation occurs since this is assumed in our microbiome setting.

**Value**

Numeric matrix with values that will be used to generate functional trends
**Value**

This function returns a list with the following objects:
- **df** - data.frame object with complete outcome \( Y \), subject ID, time, group, and outcome with missing data
- **Y** - vector of complete outcome
- **\( \mu \)** - vector of complete mean specifications used during simulation
- **\( \Sigma \)** - block diagonal symmetric matrix of complete data used during simulation
- **\( N \)** - total number of observations

**Examples**

```r
size <- 15
reps <- 4
N <- size*reps
mvrnorm_corr_gen(n=size, obs=rep(reps, size), t=rep(seq_len(4), size),
mu=rep(1, N), sigma=2, rho=0.9, corr_str="ar1")
```

### Description

This function is used in the `gen_norm_microbiome` call when the user specified the method as `mvrnorm`.

### Usage

```r
mvrnorm_sim(
  n_control,
  n_treat,
  control_mean,
  sigma,
  num_timepoints,
  t_interval,
  rho,
  corr_str = c("ar1", "compound", "ind"),
  func_form = c("linear", "quadratic", "cubic", "M", "W", "L_up", "L_down"),
  beta,
  IP = NULL,
  missing_pct,
  missing_per_subject,
  miss_val = NA,
  dis_plot = FALSE,
  plot_trend = FALSE,
)```
mvrnorm_sim

zero_trunc = TRUE,
asynch_time = FALSE
)

Arguments

n_control integer value specifying the number of control individuals
n_treat integer value specifying the number of treated individuals
control_mean numeric value specifying the mean value for control subjects. All control subjects are assumed to have the same population mean value.
sigma numeric value specifying the global population standard deviation for both control and treated individuals.
num_timepoints either an integer value specifying the number of timepoints per subject or a vector of timepoints for each subject. If supplying a vector the length of the vector must equal the total number of subjects.
t_interval numeric vector of length two specifying the interval of time from which to draw observations \([t_1, t_q]\). Assumed to be equally spaced over the interval unless asynch_time is set to TRUE.
rho value for the correlation parameter. Must be between \([0, 1]\). See mvrnorm_corr_gen for details.
corr_str correlation structure selected. See mvrnorm_corr_gen for details.
func_form character value specifying the functional form for the longitudinal mean trend. See mean_trend for details.
beta vector value specifying the parameters for the differential abundance function. See mean_trend for details.
IP vector specifying any inflection points. Depends on the type of functional form specified. See mean_trend for details. By default this is set to NULL.
missing_pct numeric value that must be between \([0, 1]\) that specifies what percentage of the individuals will have missing values.
missing_per_subject integer value specifying how many observations per subject should be dropped. Note that we assume that all individuals must have baseline value, meaning that the maximum number of missing_per_subject is equal to num_timepoints - 1.
miss_val value used to induce missingness from the simulated data. By default missing values are assumed to be NA but other common choices include 0.
dis_plot logical argument on whether to plot the simulated data or not. By default plotting is turned off.
plot_trend specifies whether to plot the true mean trend. See mean_trend for details.
zero_trunc logical indicator designating whether simulated outcomes should be zero truncated. Default is set to TRUE.
asynch_time logical indicator designed to randomly sample timepoints over a specified interval if set to TRUE. Default is FALSE.
Value

This function returns a list with the following objects:

df - data.frame object with complete outcome Y, subject ID, time, group, and outcome with missing data
Y - vector of complete outcome
Mu - vector of complete mean specifications used during simulation
Sigma - block diagonal symmetric matrix of complete data used during simulation
N - total number of observations
miss_data - data.frame object that lists which ID's and timepoints were randomly selected to induce missingness
Y_obs - vector of outcome with induced missingness

Examples

num_subjects_per_group <- 20
sim_obj <- mvrnorm_sim(n_control=num_subjects_per_group,
n_treat=num_subjects_per_group,
control_mean=5, sigma=1, num_timepoints=5,
t_interval=c(0, 4), rho=0.95, corr_str='ar1',
func_form='linear', beta=c(0, 0.25),
missing_pct=0.6, missing_per_subject=2)

#checking the output
head(sim_obj$df)

#total number of observations is 2(num_subjects_per_group)(num_timepoints)
sim_obj$N

#there should be approximately 60% of the IDs with missing observations
length(unique(sim_obj$miss_data$miss_id))/length(unique(sim_obj$df$ID))

#checking the subject covariance structure
sim_obj$Sigma[seq_len(5), seq_len(5)]

---

mvrnorm_sim_obs Simulate Microbiome Longitudinal Data from Multivariate Random Normal with Observed Data

Description

This function is used in the gen_norm_microbiome_obs call.
Usage

mvrnorm_sim_obs(
  id,
  time,
  group,
  ref,
  control_mean,
  sigma,
  rho,
  corr_str = c("ar1", "compound", "ind"),
  func_form = c("linear", "quadratic", "cubic", "M", "W", "L_up", "L_down"),
  beta,
  IP = NULL,
  dis_plot = FALSE,
  plot_trend = FALSE,
  zero_trunc = TRUE
)

Arguments

id vector of length N that identifies repeated measurements for each unit

time vector of length N that determines when values will be sampled for each unit

group factor vector with two levels indicating the group assignment for each respective id

ref character value identifying which group value to treat as control and which value to treat as treatment

control_mean numeric value specifying the mean value for control subjects. all control subjects are assumed to have the same population mean value.

sigma numeric value specifying the global population standard deviation for both control and treated individuals.

rho value for the correlation parameter. must be between [0, 1]. see mvrnorm_corr_gen for details.

corr_str correlation structure selected. see mvrnorm_corr_gen for details.

func_form character value specifying the functional form for the longitudinal mean trend. see mean_trend for details.

beta vector value specifying the parameters for the differential abundance function. see mean_trend for details.

IP vector specifying any inflection points. depends on the type of functional form specified. see mean_trend for details. by default this is set to NULL.

dis_plot logical argument on whether to plot the simulated data or not. by default plotting is turned off.

plot_trend specifies whether to plot the true mean trend. see mean_trend for details.

zero_trunc logical indicator designating whether simulated outcomes should be zero truncated. default is set to TRUE
Value

This function returns a list with the following objects:

df - data.frame object with complete outcome Y, subject ID, time, group, and outcome with missing data

Y - vector of complete outcome

Mu - vector of complete mean specifications used during simulation

Sigma - block diagonal symmetric matrix of complete data used during simulation

N - total number of observations

Examples

```r
set.seed(011520)
id_list <- lapply(seq_len(30), function(i){
  obs <- sample(seq_len(10), size=1)
  id_rep <- rep(i, obs)
})
time_interval <- c(0, 10)
time_list <- lapply(id_list, function(x){
  time_len <- length(x)
  times <- runif(time_len, min=time_interval[1], max=time_interval[2])
  times <- times[order(times)]
})

# Set up treatment groups

group_list <- lapply(id_list, function(x){
  group_len <- length(x)
  tx_ind <- sample(seq_len(2), 1)
  tx_group <- ifelse(tx_ind==1, "Control", "Treatment")
  groups <- rep(tx_group, group_len)
})

id <- unlist(id_list)
group <- factor(unlist(group_list), levels = c("Control", "Treatment"))
time <- unlist(time_list)

# N=173 total repeated measurements
length(id)

# 15 control and 15 treated subjects
table(group[unique(id)])

# control times
c <- unlist(lapply(unique(id[group=="Control"]), function(x){
  length(id[id==x])
}))

# treatment times
tt <- unlist(lapply(unique(id[group=="Treatment"]), function(x){
  length(id[id==x])
}))
```

# on average the treatment group has one more observation than control
mean(ct)
mean(tt)

mvnorm_sim_obs(id=id, time=time, group=group, ref="Control", control_mean=2, 
sigma=1, rho=0.7, corr_str="compound", func_form="L_up", 
beta=1, IP=5, plot_trend=TRUE, dis_plot=TRUE, zero_trunc=TRUE)

sigma_corr_function

Generating the longitudinal correlation matrix for repeated observations

Description
Generating the longitudinal correlation matrix for repeated observations

Usage

sigma_corr_function(t, sigma, corr_str, rho)

Arguments

t timepoints for repeated observations
sigma the standard deviation parameter for the covariance matrix
corr_str the type of correlatin structure chosen. options currently available include "ar1", "compound", and "ind"
rho the correlation coefficient for non-independent structures

Value
Return the covariance matrix V as a list

simulate2MRexperiment

Convert simulated output to MRexperiment object

Description
In order to allow investigators to more easily incorporate simulated data, this package converts the raw output into an MRexperiment object used in the metagenomeSeq package.

Usage

simulate2MRexperiment(obj, missing = FALSE)
**simulate2phyloseq**

*Convert simulated output to phyloseq object*

**Description**

This function will convert simulated data into a *phyloseq* object.

**Usage**

`simulate2phyloseq(obj, missing = FALSE)`

**Arguments**

- `obj` output from either *gen_norm_microbiome* or *mvrnorm_sim*
- `missing` logical indicator for objects from *mvrnorm_sim*. If `missing = TRUE` then create MRexperiment object with `Y_obs` else use `Y`.

**Value**

A phyloseq object
timepoint_process

Function for processing and checking the inputted timepoints

description

To allow for increased flexibility the user may specify the number of timepoints as either a single value or separately for each individual. There is also an added option about whether to draw the timepoints evenly spaced across the interval of interest or whether to randomly draw them.

usage

timepoint_process(
  num_timepoints,
  t_interval,
  n,
  asynch_time,
  missing_per_subject
)

arguments

num_timepoints either an integer value specifying the number of timepoints per subject or a vector of timepoints for each subject. If supplying a vector the length of the vector must equal the total number of subjects.

t_interval numeric vector of length two specifying the interval of time from which to draw observations \([t_1, t_q]\). Assumed to be equally spaced over the interval unless asynch_time is set to TRUE.

n numeric value representing the total number of observations

asynch_time logical indicator designed to randomly sample timepoints over a specified interval if set to TRUE.
Details

It is assumed that there is a known time interval of interest over which samples will be collected longitudinally on subjects. This interval is specified as \([t_1, t_q]\). All subjects are assumed to have baseline observations, i.e., \(t_1\).

Over this study interval each subject can have a potentially different number of measurements taken. In the most simple case we assume that all subjects will have the same number of measurements and can specify \(\text{num\_timepoints}\) as a single scalar value. Otherwise, we must specify how many timepoints will be collected for each individual. In this latter case \(\text{num\_timepoints}\) must have the same length as the number of subjects.

Finally, we can select whether we want the timepoints to be drawn at equal spaces over our study interval, or whether we want to randomly sample asynchronous timepoints. In the asynchronous case we randomly draw from a uniform distribution over the study interval with the restriction that the first observation must occur at \(t_1\).

Value

Returns a list of the number of timepoints and the times for each unit

\begin{verbatim}
trunc_bugs(Y, N, Mu, Sigma, zero_trunc)
\end{verbatim}

Description

Function for inducing truncation of outcome

Usage

\begin{verbatim}
trunc_bugs(Y, N, Mu, Sigma, zero_trunc)
\end{verbatim}

Arguments

\begin{itemize}
\item \textbf{Y} \hspace{1cm} The original N x 1 vector of simulated multivariate outcomes
\item \textbf{N} \hspace{1cm} Total number of observations equal to sum of repeated measurements for all individuals
\item \textbf{Mu} \hspace{1cm} N x 1 vector representing the mean values
\item \textbf{Sigma} \hspace{1cm} N x N numeric matrix representing the covariance matrix for the feature
\item \textbf{zero_trunc} \hspace{1cm} Logical indicator whether to perform zero-truncation
\end{itemize}

Value

Potentially truncated outcome vector Y
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