Package ‘randomizeBE’

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Type   Package
Title  Create a Random List for Crossover Studies
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Description Contains a function to randomize subjects, patients in groups of
sequences (treatment sequences).
If a blocksize is given, the randomization will be done within blocks.
The randomization may be controlled by a Wald-Wolfowitz runs test.
Functions to obtain the p-value of that test are included.
The package is mainly intended for randomization of bioequivalence studies
but may be used also for other clinical crossover studies.
Contains two helper functions sequences() and williams() to get the sequences
of commonly used designs in BE studies.

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print.rl4  

S3 method print for class "rl4"

Description

Prints the randomization list including a summary if needed.

Usage

```
## S3 method for class 'rl4'
print(x, sumry=FALSE, ...)
```

Arguments

- `x` Object of class "rl4".
- `sumry` If set to TRUE a summary of the randomization will be shown. This summary contains the p-value of runs test of randomness if 2 sequences are used.
- `...` Additional arguments. None used.

Value

Returns invisible x.

Author(s)

D. Labes

See Also

RL4

Examples

```
# block randomization of 12 subjects for a reference replicate study
# and demonstration of the S3 print method
r1 <- RL4(nsubj=12, blocksize=6, seqs=c("TRR","RTR","RRT"), seed=0)
print(r1, sumry=TRUE)
```
Description

This function calculates the exact cumulative conditional distribution of the Wald-Wolfowitz runs.

Usage

pruns.exact(r, n1, n2, tail = c("2-sided", "lower", "upper"))

Arguments

- **r**: Number of runs observed.
- **n1**: Number of +1 items in the sequence.
- **n2**: Number of -1 items in the sequence.
- **tail**: Tail of the cumulative distribution function.
  Default is the 2-tailed value.

Value

Numeric value of the cumulative distribution function according to the chosen tail.

Note

The 2-sided exact p-value is defined as \( P(\text{abs}(R-E(R)) \geq \text{abs}(r-E(R))) \).
The lower (left) tail p-value is defined as \( P(R \leq r) \).
The upper (right) tail p-value is defined as \( P(R \geq r) \).
\( r \) is the observed value of the random variable \( R \).

Author(s)

D. Labes

Examples

```r
# SPSS "Exact Tests": small sample example, exact p: 0.071
# x <- c(1, 1, 1, 1, 0, 0, 0, 0, 1, 1)
pruns.exact(r=3, n1=4, n2=6)
# 0.07142857
# left tail P(R<=3)=0.04761905
pruns.exact(r=3, n1=4, n2=6, tail="lower")
# right tail P(R>=3)=0.9904762
pruns.exact(r=3, n1=4, n2=6, tail="upper")
# or via runs.pvalue (2-sided)
x <- c(1, 1, 1, 1, 0, 0, 0, 0, 1, 1)
runs.pvalue(x, pmetho"d="ex")
```
(Block) randomization of subjects, patients into sequence groups

Description

This function creates a randomization list of subjects, patients into sequences of treatments.
It is mainly intended for use in crossover studies but may be used also for parallel group designs if
for sequences c("T","R") is used.

Usage

```r
RL4(nsubj, seqs = c("TR", "RT"), blocksize, seed=runif(1,max=1E7),
    randctrl=TRUE, pmethod=c("normal", "exact", "cc"), alpha=0.025)
```

Arguments

- `nsubj`  Number of subjects, patients ... to be randomized.
  Or a vector of the subject numbers (f.i. 1001:1012)
- `seqs`  Character representation of the sequences.
  In BE studies for a 2x2 cross-over usually something like c("TR", "RT").
  If you prefer the ABC notation write down here f.i. c("AB", "BA").
- `blocksize`  Size of the blocks to randomize within.
  If blocksize is missing it defaults to 2*number of sequences.
  blocksize may be a vector of numbers.
  In that case the sizes of the blocks are randomly chosen from that vector.
- `seed`  An integer for the initialisation of the random number generator.
- `randctrl`  Shall the creation of the randomlist controlled by a runs test of randomness?
  Defaults to TRUE.
- `pmethod`  A character string describing the method for the p-value calculation of the runs test.
  "normal" denotes the normal approximation like the function(s) runs.test() of the packages tseries or lawstat.
  "exact" chooses the calculation via exact distribution of the # of runs.
  "cc" chooses the continuity correction to the large sample approximation like in the statistical software SPSS.
  Default is pmethod="normal".
- `alpha`  Critical alpha value for re-creation of the randomlist based on the runs test.
  Recommended is alpha=0.025.
Details
As default the randomization is done as block randomization.
If blocksize is given as a vector of numbers the sizes of the blocks are randomly chosen from that vector.
If blocksize=0 then the randomization takes place in the one block with all subjects.

The randomization is in the default settings controlled by a Wald-Wolfowitz runs test of randomness, i.e. if this test shows significant deviation from randomness (p-value<0.025 as default) the randomization list is recreated.
This behavior may be switched off by setting randctrl=FALSE if you don’t see any needfulness for such a control.
The reason for such a control was originally to avoid randomlists with only 'alternating' sequences f.i. "TR" "RT" "TR" "RT" ...
See http://forum.bebac.at/mix_entry.php?id=8745

In its original form the runs test is only defined for dichotomous outcomes (i.e if 2 sequences are used).
If more than 2 sequences are used the runs test is modified by dichotomizing the sample of sequence numbers into cases < median and > median.
See package lawstat or http://de.wikipedia.org/wiki/Run-Test for this.

Value
Returns a list of class "rl4". This list has the components

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>rl</td>
<td>A data.frame with the random list.</td>
</tr>
<tr>
<td>seed</td>
<td>The used seed.</td>
</tr>
<tr>
<td>blocksize</td>
<td>The used blocksize.</td>
</tr>
<tr>
<td>ninseqs</td>
<td>A named vector containing the number of subjects in the sequence groups.</td>
</tr>
<tr>
<td>runs.pvalue</td>
<td>The p-value of a runs test of randomness.</td>
</tr>
<tr>
<td>date</td>
<td>Date and time of creation.</td>
</tr>
</tbody>
</table>

The class rl4 has the S3 method print.rl4.

Note
The blocksize(s) should be a multiple of the used # of sequences. If this is not the case it (they) will be adjusted accordingly.
The number of subjects should be a multiple of the used # of sequences. If this is not the case a warning is thrown that the design is not balanced.
The default for pmethod is the calculation via standard normal approximation. This has shown the 'best' potential in rejecting the randomness for alternating random lists.
The randomness control does not work properly if more than 2 sequences are used. In that case a test of repeated patterns of sequences in blocks of length=nseq is done additionally to the runs test.
Example (seqno) 1 2 3 1 2 3 ...
Author(s)

D. Labes
Part of the code for using the runs test for randomness according to a suggestion by Helmut Schuetz.

See Also

print.rl4, runs.pvalue

Examples

```r
# block randomization of 12 subjects for a 2x2 cross-over using the defaults
# seqs = c("TR", "RT"), blocksize=4 and seed from Sys.time()
RL4(nsubj=12)

# block randomization of a full replicate design with randomly
# chosen blocksizes 2 or 4
rl <- RL4(nsubj=12, blocksize=c(2, 4), seqs=c("TRRT","RTTR"))
print(rl)

# randomization of 12 subjects for a 2x2 cross-over
# where the original random list don't pass the runs test
# watch the message.
RL4(nsubj=12, blocksize=0, seed=10)
#if you don't worry about some 'extreme' lists
RL4(nsubj=12, blocksize=0, seed=10, randctrl=FALSE)

# randomness control doesn't work that good in case of more
# than 2 sequences: 3x3 latin square example
rl <- RL4(nsubj=12, seq <- c("ABC","BCA","CAB"), blocksize=3, seed=5125)
print(rl, sumry=TRUE)
# gives runs p.value=0.2502
```

---

`runs.pvalue` 2-sided p-value of the runs test

Description

The function calculates the 2-sided p-value of the Wald-Wolfowitz runs test after dichotomizing the input vector.

Usage

```r
runs.pvalue(y, pmethod = c("exact", "normal", "cc"))
```
Arguments

- **y**: Numeric vector of data values.
- **pmethod**: A character string describing the method for the p-value calculation of the runs test.
  - "exact" chooses the calculation via exact distribution of the # of runs.
  - "normal" denotes the normal approximation like the function(s) `runs.test()` of the packages `lawstat` or `tseries`.
  - "cc" chooses the continuity correction to the large sample approximation like in the statistical software SPSS.

Details

This function calculates the 2-sided p-value of the runs.test. The large sample approximations are an adaption from the codes for `runs.test()` found in the R-packages `lawstat` and `tseries`. The aim of this own was to avoid the heavy footprint of both packages for this small package.

The user can choose the application of a continuity correction to the normal approximation like a SAS implementation [http://support.sas.com/kb/33/092.html](http://support.sas.com/kb/33/092.html) uses or like SPSS if n<50.

The exact distribution of runs and the p-value based on it are described in the manual of SPSS "Exact tests" to be found f.i. [http://www.sussex.ac.uk/its/pdfs/SPSS_Exact_Tests_21.pdf](http://www.sussex.ac.uk/its/pdfs/SPSS_Exact_Tests_21.pdf). If pmethod="exact" is chosen and n>30 and n1>12 and n2>12 (see `pruns.exact`) the continuity corrected version of the normal approximation is used to save time and memory.

Value

Numeric p-value of the 2-sided test.

Author(s)

D. Labes
adapted from `runs.test()` package lawstat
Authors: Wallace Hui, Yulia R. Gel, Joseph L. Gastwirth, Weiwen Miao
and from `runs.test()` package tseries
Author: A. Trapletti

See Also

`pruns.exact`

Examples

```
# alternating sequence 1,2,1,2 ...
# maybe seen as numeric representation of 'TR','RT' ...
# and is used in that way here in this package
x <- rep(c(1, 2), 6)
runs.pvalue(x, pmethod="normal")
```
sequences

Obtain sequences for BE study designs

Description

The function is intended as helper function to get the sequences for commonly used designs in BE studies. These sequences may then subsequently used in function rl4().

Usage

sequences(design, tmts = NULL)

Arguments

design A character value describing the study design. For crossover studies it is “tmts x sequences x periods” without space. F.i. "2x2x2" is the standard 2-treatments-2-sequence-2-period crossover. The designs "2x2x2", "3x3x3", "4x4x4" may be abbreviated to "2x2", "3x3", "4x4".
tmts A character vector with the codes of the treatments.

Details

This function was implemented because I couldn’t remember f.i. all the six sequences of a "3x6x3" design if had to be coded by T1,T2 and R. The sequences are primarily build within the ABC... notation. If treatment codes are given the "AB..." in the sequences are replaced by these codes.

The following designs are implemented:
"parallel" = 2-group parallel design
"2x2" = classical 2-treatments-2-sequence-2-period crossover
"3x3" = 3-treatments-3-sequence-3-period crossover (Latin square)
"3x6x3" = 3-treatments-6-sequence-3-period crossover (Williams design)
sequences

"4x4" = 4-treatments-4-sequence-4-period crossover (Latin square)
"2x2x3" = 2-sequence-3-period replicate crossover
"2x2x4" = 2-sequence-4-period full replicate crossover
"2x4x4" = 4-sequence-4-period full replicate crossover
"2x3x3" = 3-sequence-3-period partial (reference) replicate crossover
"2x4x2" = 4-sequence-2-period replicate crossover, Baalams design.

The sequences for the "3x3" and "4x4" designs are randomly derived from the standard Latin squares (in ABC notation)
ABC, BCA, CAB
or in case of the "4x4" design from
ABCD, BDAC, CADB, DCBA.

Value

Returns a character vector with the sequences.

Note

For the higher order designs (designs with more than 2 treatments or replicate crossover designs, respectively) only a selection of possible designs are covered.
The design sequences for "4x4" are not guaranteed to be a Williams design. If need a Williams design use function williams() instead.

Author(s)

Detlew Labes

References


See Also

williams, RL4

Examples

# classical 2x2 crossover in TR notation (simple enough to remember
sequences("2x2", tmts=c("T","R"))
# 3-treatment-6-sequence-3-period Williams design in ABC notation
sequences("3x6x3")
# 3-treatment-3-sequence-3-period design with one Test and two References
sequences("3x3", tmts=c("T","R1","R2"))
# 4-treatment-4-period in TxRy notation, two Test and two Reference
sequences("4x4", tmts=c("T1","T2","R1","R2"))
williams Construct sequences of a Williams design

Description
The function constructs the sequences of a Williams design via the algorithm given by Sheehe and Bross.

Usage
williams(ntmt = 4, tmts = NULL)

Arguments
- ntmt: Number of treatments. Must be an integer >1.
- tmts: NULL or a vector of treatment codes.

Details
A Williams design is a crossover design in which each subject receives each treatment. The design is balanced over periods. The design has additionally the further feature that every treatment follows every other treatment the same number of times. It is said that these designs are balanced for first order carry over effects.
For an even number of treatments the design is a Latin square. For an odd number the design is a combination of two Latin squares.

Although the balance to first order carry over effects is not absolutely necessary in well planned BE studies with sufficient washout the Williams designs were traditionally used in "3x6x3" "4x4" crossover studies.

The sequences are created originally within the ABC... notation. If tmts are given the sequences are returned based on these treatment codes.

Value
Returns a character vector of the sequences.

Note
If ntmt>3 the design returned is randomly chosen from the possible designs.

A similar but simpler function was contained in the package crossdes. But this package was removed from the CRAN repository.

Author(s)
D. Labes
References


See Also

sequences, RL4

Examples

# Williams design for 4 treatments in ABC... notation
williams()

# The 6 sequences of the Williams design for 3 treatments
# same as sequences(design="3x6x3") except the ordering
williams(ntmt=3)
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