

Permutation Tests for Regression, ANOVA and Comparison of Signals : the permuco Package

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Abstract

Recent methodological researches produced permutation methods to test parameters in presence of nuisance variables in linear models or repeated measures ANOVA. Permutation tests are also particularly useful to overcome the multiple comparisons problem as it is used to test the effect of factors or variables on signals while controlling the family-wise error rate (FWER). This article introduces the **permuco** package which implements several permutation methods. They can all be used jointly with multiple comparisons procedures like the cluster-mass tests or threshold-free cluster enhancement (TFCE). The **permuco** package is designed, first, for univariate permutation tests with nuisance variables, like regression and ANOVA; and secondly, for comparing signals as required, for example, for the analysis of event-related potential (ERP) of experiments using electroencephalography (EEG). This article describes the permutation methods and the multiple comparisons procedures implemented. A tutorial for each of these cases is provided.

Keywords: projections, EEG, ERP, TFCE, cluster-mass statistics, multiple comparisons.

1. Introduction

Permutation tests are exact for simple models like one-way ANOVA and t test (Lehmann and Romano 2008, pp. 176-177). Moreover it has been shown that they have some robust properties under non normality (Lehmann and Romano 2008). However they require the assumption of exchangeability under the null hypothesis to be fulfilled which is not the case in a multifactorial setting. For these more complex designs, Janssen and Pauls (2003), Janssen (2005), Pauly, Brunner, and Konietzschke (2014) and Konietzschke, Bathke, Harrar, and Pauly (2015) show that permutation tests based on non exchangeable data can be exact asymptotically if used with studentized statistics. Another approach to handle multifactorial designs is to transform the data before permuting. Several authors (Draper and Stoneman 1966; Freedman and Lane 1983; Kennedy 1995; Huh and Jhun 2001; Dekker, Krackhardt, and Snijders 2007; Kherad-Pajouh and Renaud 2010; ter Braak 1992) have proposed different types of transformations and Winkler, Ridgway, Webster, Smith, and Nichols (2014) give a simple and unique notation to compare those different methods.

Repeated measures ANOVA including one or more within subject effects are the most widely used models in the field of psychology. In the simplest case of one single random factor, an exact permutation procedure consists in restricting the permutations within the subjects. In more general cases, free permutations in repeated measures ANOVA designs would violate the exchangeability assumption. This is because the random effects associated with subjects and

their interactions with fixed effects imply a complex structure for the (full) covariance matrix of observations. It follows that the second moments are not preserved after permutation. Friedrich, Brunner, and Pauly (2017a) have derived exact asymptotic properties in those designs for a Wald-type statistic and Kherad-Pajouh and Renaud (2015) proposed several methods to transform the data following procedures developed by Kennedy (1995) or Kherad-Pajouh and Renaud (2010).

For linear models, permutation tests are useful when the assumption of normality is violated or when the sample size is too small to apply asymptotic theory. In addition they can be used to control the family wise error rate (FWER) in some multiple comparison settings (Troendle 1995; Maris and Oostenveld 2007; Smith and Nichols 2009). These methods have been successfully applied for the comparison of experimental conditions in both functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) as they take advantage of the spatial and/or temporal correlation of the data.

The aim of the present article is to provide an overview of the use of permutation methods and multiple comparisons procedures using permutation tests and to explain how it can be used in R (Chambers 2009) with the package **permuco**. Note that the presentation and discussion of the available packages that handle permutation tests in related settings is deferred to section 5.1, where all the notions are introduced. Appendix A shows a comparison of the relevant code and outputs. But first, Section 2 focuses on fixed effect models. It explains the model used for ANOVA and regression and the various permutation methods proposed in the literature. Section 3 introduces the methods for repeated measures ANOVA. Section 4 explains the multiple comparisons procedures used for comparing signals between experimental conditions and how permutation tests are applied in this setting. Section 5 describes additional programming details and some of the choices for the default settings in the **permuco** package. Section 6 treats two real data analyses, one from a control trial in psychology and the second from an experiment in neurosciences using EEG.

2. The fixed effects model

2.1. Model and notation

For each hypothesis of interest, the fixed effects model (used for regression or ANOVA) can always be written as

$$y = D\eta + X\beta + \epsilon, \quad (1)$$

where y is the response variable, $\begin{bmatrix} D & X \end{bmatrix}$ is a design matrix split into the nuisance variable(s) D (usually including the intercept) and the variable(s) of interest X associated with the tested hypothesis. D and X may be correlated and we assume without loss of generality that $\begin{bmatrix} D & X \end{bmatrix}$ is a full rank matrix. The parameters of the full model $\begin{bmatrix} \eta^\top & \beta^\top \end{bmatrix}^\top$ are also split into the parameters associated with the nuisance variable(s) η and the one(s) associated with the variable(s) of interest β . ϵ is an error term that follows a distribution

Table 1: Permutation methods in the presence of nuisance variables. See text for explanations of the symbols.

method/Authors	y^*	D^*	X^*
manly (Manly 1991)	Py	D	X
draper_stoneman (Draper and Stoneman 1966)	y	D	PX
dekker (Dekker <i>et al.</i> 2007)	y	D	$PR_D X$
kennedy (Kennedy 1995)	$(PR_D)y$		$R_D X$
huh_jhun (Huh and Jhun 2001)	$(PV_D^\top R_D)y$		$V_D^\top R_D X$
freedman_lane (Freedman and Lane 1983)	$(H_D + PR_D)y$	D	X
terBraak (ter Braak 1992)	$(H_{X,D} + PR_{X,D})y$	D	X

$(0, \sigma^2 I_n)$. The hypothesis tested writes

$$H_0 : \beta = 0 \text{ vs. } H_1 : \beta \neq 0. \quad (2)$$

The permutation test is exact under the null hypothesis for finite samples if the data are exchangeable under the null hypothesis. This assumption is not fulfilled in model (1) as we cannot control the influence of the nuisance term $D\eta$ when permuting. In fact, under the null hypothesis (2), the responses follow a distribution $(D\eta, \sigma^2 I_n)$ which are not exchangeable due to the presence of a unequal first moments. Pauly *et al.* (2014) shows however that permuting the responses and using a Wald-type statistic is an asymptotically exact procedure in factorial designs. Another approach, which is the focus of this paper, is to transform the data prior to the permutation. Those transformation procedures are what will be called permutation methods. They are described in Chapter 2.2 and are implemented in **permuco**.

The permutation of a vector v is defined as Pv and the permutation of the rows of a matrix M as PM where P is a permutation matrix (Gentle 2007, pp. 66-67). For any design matrix M , its corresponding “hat” matrix is $H_M = M(M^\top M)^{-1}M^\top$ and its corresponding “residuals” matrix is $R_M = I - M(M^\top M)^{-1}M^\top$ (Greene 2011, pp. 24-25). The full QR-decomposition is:

$$\begin{bmatrix} M & 0 \\ n \times n & \end{bmatrix} = \begin{bmatrix} Q_M & V_M \\ n \times (n-p) & n \times (n-p) \end{bmatrix} \begin{bmatrix} U_M & 0 \\ 0 & 0 \\ p \times p & \end{bmatrix}, \quad (3)$$

where Q_M and V_M define together an orthonormal basis of \mathbb{R}^n and where U_M is interpreted as M in the subspace of Q_M . An important property of the QR-decomposition is that $H_M = Q_M Q_M^\top$ and $R_M = V_M V_M^\top$ (Seber and Lee 2012, pp. 340-341).

2.2. Permutation methods for linear models and factorial ANOVAs

The discussed permutation methods are functions that transform the data in order to reduce the effect of the nuisance variables. They can be computed for all permutations $P \in \mathcal{P}$ where \mathcal{P} is the set of all n_P distinct permutation matrices of the same size. For any permutation matrix P , a given permutation method will transform the observed data $\{y, D, X\}$ into the permuted data $\{y^*, D^*, X^*\}$. The **permuco** package provides several permutation methods that are summarized in table 1 using a notation inspired by Winkler *et al.* (2014).

The default method of **permuco** is the **freedman_lane** method that works as follows: we first fit the “small” model which only uses the nuisance variables D as predictors. Then, we permute its residuals and add them to the fitted values. These steps produce the permuted response variable y^* which constitutes the “new sample”. It is fitted using the unchanged design D and X . In this procedure, only the residuals are permuted and they are supposed to share the same expectation (of zero) under the null hypothesis. For each permutation, the effect of nuisance variables is hence reduced. Using the above notation, the fitted values of the “small” model can be written as $H_D y$ and its residuals $R_D y$. Its permuted version is pre-multiplied by a permutation matrix, e.g., $PR_D y$. The permuted response variable is therefore simply written as $y^* = H_D y + PR_D y = (H_D + PR_D)y$, as displayed in table 1. The permuted statistics (e.g. t or F statistics) are then computed using y^* and the unchanged design matrices $D^* = D$ and $X^* = X$.

All the remaining permutation methods are also summarized by the transformation of y , D and X into y^* , X^* and D^* and are explained next. The **manly** method simply permutes the response (this method is sometimes called raw permutations). Even if this method does not take into account the nuisance variables, it still has good asymptotic properties when using studentized statistics. **draper_stoneman** permutes the design of interest (note that without nuisance variables permuting the design is equivalent to permuting the response variable). However, this method ignores the correlation between D and X that is typically present in regressions or unbalanced designs. For the **dekker** method, we first orthogonalize X with respect to D , then we permute the design of interest. This transformation reduces the influence of the correlation between D and X and is more appropriate for unbalanced design. The **kennedy** method orthogonalizes all of the elements (y , D and X) with respect to the nuisance variables, removing the nuisance variables in the equation, and then permutes the obtained response. Doing so, all the design matrices lie in the span of X , a sub-space of observed design X and D . However this projection modifies the distribution of the residuals that lose exchangeability ($R_D y \sim (0, R_D \sigma^2)$ for original IID data). The **huh_jhun** method is similar to **kennedy** but it applies a second transformation (V_D^\top) to the data to ensure exchangeability (up to the second moment, $V_D^\top R_D y \sim (0, I_{n-(p-q)} \sigma^2)$). The V_D matrix comes from the Equation 3 and has a dimension of $n \times (n - (p - q))$. It implies that the P ’s matrices for the **huh_jhun** method have smaller dimensions. The **terBraak** method is similar to **freedman_lane** but uses the residuals of the full model. This permutation method creates a new response variable y^* which assumes that the observed value of the estimate $\hat{\beta}|y$ is the true value of β . Computing the statistic using y^* , X , D would not produce a permutation distribution under the null hypothesis. To circumvent this issue, the method changes the null hypothesis when computing the statistics at each permutation to $H_0 : \beta = \hat{\beta}|y = (X^\top R_D X)^{-1} X^\top R_D y|y$. The right part of this new hypothesis corresponds to the observed estimate of the parameters of interest under the full model, and implicitly uses a pivotal assumption. Note that **terBraak** is the only method where the statistic computed with the identity permutation is different from the observed statistic. The notation $R_{D,X}$ means that the residuals matrix is based on the concatenation of the matrices D and X . See section 5.2 for advises on the choice of the method.

For each of the methods presented in Table 1, permutation tests can be computed using different statistics. For univariate or multivariate β parameters, the **permuco** package implemented a F statistic that constitutes a marginal test (or “type III” sum of square) (Searle 2006, pp. 53-54). For a univariate β , one- and two-sided tests (based on a t -statistic) are

1×1

also implemented. We write the F statistic as:

$$F = \frac{y^\top H_{R_D X} y}{y^\top R_{D, X} y} \frac{n-p}{p-q}. \quad (4)$$

When $q = 1$, the t statistic is:

$$t_{St} = \frac{(X^\top R_D X)^{-1} X R_D y}{\sqrt{y^\top R_{D, X} y (X^\top R_D X)^{-1}}} \sqrt{n-p}, \quad (5)$$

where the numerator is the estimate of β under the full model. Note that the statistic can be simplified by a factor of $(X^\top R_D X)^{-1/2}$. The two statistics are function of data. They lead to the general notation $t = t(y, D, X)$ when applied to the observed data and to $t^* = t(y^*, D^*, X^*)$ when applied to the permuted data. The permuted statistics constitute the set \mathcal{T} which contains the t^* for all $P \in \mathcal{P}$. We define the permuted p value as $p = \frac{1}{n_P} \sum_{t^* \in \mathcal{T}} I(|t^*| \geq |t|)$, for a two-tailed t test, $p = \frac{1}{n_P} \sum_{t^* \in \mathcal{T}} I(t^* \geq t)$, for an upper-tailed t test or an F test and finally $p = \frac{1}{n_P} \sum_{t^* \in \mathcal{T}} I(t^* \leq t)$, for a lower-tailed t test, where $I(\cdot)$ is the indicator function.

3. Repeated measures ANOVA

3.1. Model and notation

We write the repeated measures ANOVA model in a linear mixed effects form:

$$y = D\eta + X\beta + E^0\kappa + Z^0\gamma + \epsilon, \quad (6)$$

where y is the response, the fixed part of the design is split into the nuisance variable(s) D and the variable(s) of interest X . The specificity of the repeated measures ANOVA model allows us to split the random part into E^0 and Z^0 which are the random effects associated with D and X respectively (Kherad-Pajouh and Renaud 2015). The fixed parameters are $\begin{bmatrix} \eta^\top & \beta^\top \end{bmatrix}^\top$. The random part is $\begin{bmatrix} \kappa^\top & \gamma^\top \end{bmatrix}^\top \sim (0, \Omega)$ and $\epsilon \sim (0, \sigma^2 I)$. The matrices associated with the random effects E^0 and Z^0 can be computed using:

$$E^0 = (D_{within}^{0'} * Z_\Delta^{0'})^\top \text{ and } Z^0 = (X_{within}^{0'} * Z_\Delta^{0'})^\top, \quad (7)$$

where D_{within}^0 and X_{within}^0 are overparametrized matrices and are associated to the within effects in the design matrices D and X . Z_Δ^0 is the overparametrized design matrix associated to the subjects and $*$ is the column-wise Khatri-Rao product (Khatri and Rao 1968). Since the matrices E^0 and Z^0 are overparametrized, it is not convenient to compute their corresponding

Table 2: Permutation methods in the presence of nuisance variables for repeated measures ANOVA.

method	y^*	D^*	X^*	E^*	Z^*
Rd_keradPajouh_renaud (R_D)	$PR_D y$		$R_D X$		$R_D Z$
Rde_keradPajouh_renaud ($R_{D,E}$)	$PR_{D,E} y$		$R_{D,E} X$		$R_{D,E} Z$

sum of squares. We need versions that are constraint into their respective appropriate subspaces:

$$E = R_{D,X} E^0 \text{ and } Z = R_{D,X} Z^0. \quad (8)$$

The matrices E and Z are respectively of rank $p_2 - q_2$ and q_2 and are the ones used to compute F statistics. Formally, the hypothesis of interest associated with Equation 6 writes:

$$H_0 : \beta = 0 \text{ vs. } H_1 : \beta \neq 0. \quad (9)$$

3.2. Permutation methods for repeated measures ANOVA

Similarly to the fixed effects model, we can test hypotheses using permutation methods (Kherad-Pajouh and Renaud 2015). The ones that are implemented in the **permuco** package are given in Table 2. The two methods are based on a similar idea. By pre-multiplying the design and response variables by R_D or $R_{D,E}$, we orthogonalize the model to the nuisance variables. This procedure can be viewed as an extension of the **kennedy** procedure (see table 1) to repeated measures ANOVA.

The hypothesis in (9) is tested based on the conventional F statistic for repeated measures ANOVA:

$$F = \frac{y^\top H_{R_D X} y}{y^\top H_Z y} \frac{p_2}{p_1}. \quad (10)$$

As for the fixed effects model, the statistic is written as a function of the data $t = t(y, D, X, E, Z)$ and the permuted statistic $t^* = t(y^*, D^*, X^*, E^*, Z^*)$ is a function of the permuted data under the chosen method. The p value is defined as in the fixed effect case.

4. Signal and multiple comparisons

In EEG experiments, researchers are often interested in testing the effect of conditions on the event-related potential (ERP). It is a common practice to test the signals at each time point of the ERP. In that kind of experiments, thousands of tests are typically carried out (e.g., one measure every 2ms over 2 seconds) and the basic multiple hypotheses corrections like Bonferroni are useless as their power is too low.

Troendle (1995) proposed a multiple comparisons method that considers the correlation between the resampling data. This method does not specifically use the time-neighborhood

information of a signal but uses wisely the general correlation between the statistics and may be used in more general settings.

Better known, the cluster-mass test (Maris and Oostenveld 2007) has shown to be powerful while controlling the family-wise error rate (FWER) in EEG data analysis. And recently using a similar idea, the threshold-free cluster-enhancement (TFCE) was developed for fMRI data (Smith and Nichols 2009) and EEG data (Pernet, Latinus, Nichols, and Rousselet 2014), but usually presented only with one factor.

All these approaches use permutations and are compatible with the methods displayed in Tables 1 and 2, as shown next.

4.1. Model and notation

We can construct a model at each time point $s \in \{1, \dots, k\}$ for the fixed effects design as:

$$y_s = D\eta_s + X\beta_s + \epsilon_s, \quad (11)$$

where y_s is the response variable for all observations at time s and each of the k models are the same as (1). D and X , the design matrices, are then identical over the k time points. The aim is to test simultaneously all k hypotheses $H_0^s : \beta_s = 0$ vs. $H_1^s : \beta_s \neq 0$ for $s \in \{1, \dots, k\}$ while controlling for the FWER through the k tests. Likewise, the random effects model is written:

$$y_s = D\eta_s + X\beta_s + E^0\kappa_s + Z^0\gamma_s + \epsilon_s, \quad (12)$$

where each of the k models are defined as in (6) and, similarly, we are interested to test the k hypotheses $H_0^s : \beta_s = 0$ vs. $H_1^s : \beta_s \neq 0$ for $s \in \{1, \dots, k\}$.

For both models, we choose one of the permutation methods presented in Tables 1 or 2 and compute the k observed statistics t_s , the k sets of permuted statistics \mathcal{T}_s , which lead to k raw or uncorrected p values.

To correct them, the k sets of permuted statistics \mathcal{T}_s can be analyzed as one set of multivariate statistic. It is done simply by combining the k univariate permutation-based distributions into a single k -variate distribution which maintains the correlation between tests. For each permutation, we simply combine all k univariate permuted statistics t_1^*, \dots, t_k^* into one multivariate permuted statistic $\mathbf{t}^* = [t_1^* \dots t_k^*]^\top$. The three multiple comparison procedures described below are all based on this multivariate distribution and take advantage of the correlation structure between the tests.

4.2. Troendle's step-wise resampling method

The method developed by Troendle (1995) takes advantage of the form of the multivariate resampling distribution of the t_s^* . If we assume that t_s is distributed according to T_s then by ordering the observed statistics t_s we obtain $t_{(1)} \leq \dots \leq t_{(s)} \leq \dots \leq t_{(k)}$ with their corresponding k null hypotheses $H_{(1)} \leq \dots \leq H_{(s)} \leq \dots \leq H_{(k)}$. Then Troendle (1995) use the following arguments. First, for all s , controlling the FWER with $P_{H_{(1)}, \dots, H_{(k)}}(\max_{i \in \{1, \dots, k\}} T_{(i)} \leq t_{(s)}) < \alpha_{FWER}$ is a conservative approach. Secondly, if we reject $H_{(k)}$ and want to test $H_{(k-1)}$, we can safely assume that $H_{(k)}$ is false while controlling the FWER. Either $H_{(k)}$ is a true and we already made a type I error or was wrong and we can go as if $H_{(k)}$ was absent. We can then update

our decision rule for testing $H_{(k-1)}$ by $P_{H_{(1)}, \dots, H_{(k-1)}}(\max_{i \in \{1, \dots, k-1\}} T_{(i)} \leq t_{(k-1)}) < \alpha_{FWER}$. We continue until the first non-significant result and declare all s with a smaller t statistic as non-significant.

This procedure is valide in a general setting and is easily implemented for permutation tests. The permuted sets \mathcal{T}_s is interpreted as a non-parametric distribution of the T_s and based on Troendle (1995), we use the following algorithm to compute the corrected p value:

Algorithm 1 Troendle corrected p value

- 1: Order the k observed statistics t_s into $t_{(1)} \leq \dots \leq t_{(s)} \leq \dots \leq t_{(k)}$
 - 2: **for** $i \in \{1, \dots, k\}$ **do**
 - 3: Define the null distribution $\mathcal{S}_{(k-i+1)}$ for $t_{(k-i+1)}$ by:
 - 4: **for each** $P \in \mathcal{P}$ **do**
 - 5: **Return** the maximum over the $k - i + 1$ first values $t_{(s)}^*$ for $s \in \{1, \dots, k - i + 1\}$
 - 6: Define the corrected p value $p_{(k-i+1)} = \frac{1}{n_P} \sum_{t^* \in \mathcal{S}_{(k-i+1)}} I(t^* \geq t_{(k-i+1)})$
 - 7: Control for a stepwise procedure by:
 - 8: **if** $p_{(k-i+1)} < p_{(k-i+2)}$ **and** $i > 1$ **then** $p_{(k-i+1)} := p_{(k-i+2)}$
-

4.3. Cluster-mass statistic

The method proposed by Maris and Oostenveld (2007) for EEG rely on a continuity argument that implies that an effect will appear into clusters of adjacent timeframes. Based on all time-specific statistics, we form these clusters using a threshold τ as follows (see Figure 1). All the adjacent time points for which the statistics are above this threshold define one cluster C_i for $i \in [1, \dots, n_c]$, where n_c is the number of clusters found in the k statistics. We assign to each time point in the same cluster C_i , the same cluster-mass statistic $m_i = f(C_i)$ where f is a function that aggregates the statistics of the whole cluster into a scalar; typically the sum of the F statistics or the sum of squared of the t statistics. The cluster-mass null distribution \mathcal{M} is computed by repeating the process described above for each permutation. The contribution of a permutation to the cluster-mass null distribution is the maximum over all cluster-masses for this permutation. This process is described in Algorithm 2.

Algorithm 2 Cluster-mass null distribution \mathcal{M}

- 1: **for each** $P \in \mathcal{P}$ **do**
 - 2: Compute the k permuted statistics t_s^* for $s \in \{1, \dots, k\}$.
 - 3: Find the n_c^* clusters C_i^* as the sets of adjacent time points which statistic is above τ .
 - 4: Compute the cluster-mass for each cluster $m_i^* = f(C_i^*)$
 - 5: **Return** the maximum value over the n_c^* values m_i^* .
-

To test the significance of an observed cluster C_i , we compare its cluster-mass $m_i = f(C_i)$ with the cluster-mass null distribution \mathcal{M} . The p value of the effect at each time within a cluster C_i is the p value associated with this cluster, i.e. $p_i = \frac{1}{n_P} \sum_{m^* \in \mathcal{M}} I(m^* \geq m_i)$.

In addition to the theoretical properties of this procedure (Maris and Oostenveld 2007), this method makes sense for EEG data analysis because if a difference of cerebral activity is

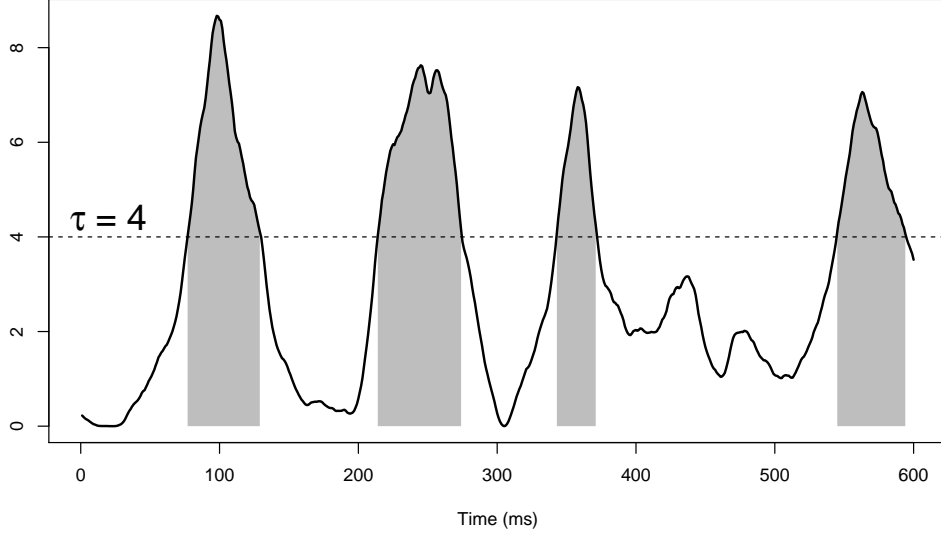


Figure 1: Display of the 600 statistics corresponding to the tests on 600 time points. Here 4 clusters are found using a threshold $\tau = 4$. Using the sum to aggregate the statistics, for each cluster i , the shaded area underneath the curve represents its cluster-mass m_i .

believed to happen at a time s for a given factor, it is very likely that the time $s + 1$ (or $s - 1$) will show this difference too.

4.4. Threshold-free cluster-enhancement

Although it controls (weakly) the FWER for any a priori choice of threshold, the result of cluster-mass procedure is sensible to this choice. The TFCE (Smith and Nichols 2009) is closely related to the cluster-mass but get rid of this seemingly arbitrary choice. It is defined at each time $s \in [1, \dots, k]$ for the statistics t_s as:

$$u_s = \int_{h=t_0}^{h=t_s} e(h)^E h^H dh, \quad (13)$$

where $e(h)$ is the extend at the height h and it is interpreted as the length of a cluster for a threshold of h . E and H are free parameters named the extend power, and the height power respectively. t_0 is set close to zero. Figure 2 illustrates how the TFCE statistic is computed for a given time point s .

We construct the TFCE null distribution \mathcal{U} by applying the formula in (13) at each time-point of the permuted statistics t_s^* for $s \in \{1, \dots, k\}$ to produce for each permutation, k values u_s^* . Then the contribution of a permutation to \mathcal{U} is the maximum of all k values u_s^* . In practice, the integral in (13) is approximated numerically using small $dh \leq 0.1$, (Smith and Nichols 2009, Pernet *et al.* (2014)).

At time s , the statistic t_s will be modified using the formula in (13). The formula can be viewed as a function of characteristics in the grey area (its area in the special case where both E and H are set to 1).

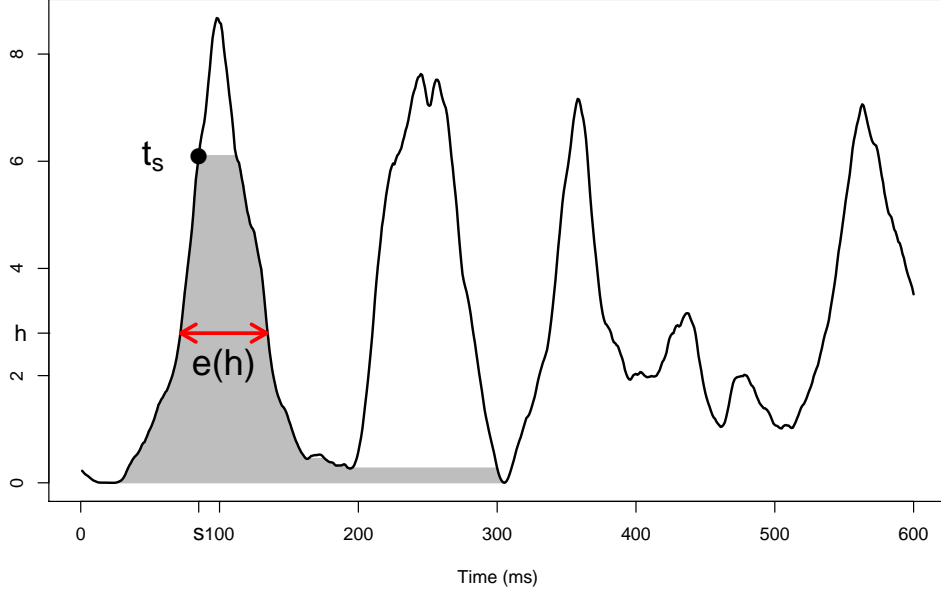


Figure 2: The TFCE transforms the statistic t_s using formula in (13). The extend $e(h)$, in red, is shown for a given height h . The TFCE statistics u_s at s can be viewed as a function of characteristics in the grey area.

Algorithm 3 Threshold-free cluster-enhancement null distribution \mathcal{U}

- 1: **for each** $P \in \mathcal{P}$ **do**
 - 2: Compute the k permuted statistics t_s^* for $s \in \{1, \dots, k\}$
 - 3: Compute the k enhanced statistics u_s^* using a numerical approximation of (13)
 - 4: **Return** the maximum over the k value u_s^*
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To test the significance of a time point s we compare its enhanced statistics u_s with the threshold-free cluster-enhancement null distribution \mathcal{U} . For an F test we define the p value as $p_s = \frac{1}{n_P} \sum_{u^* \in \mathcal{U}} I(u^* \geq u_s)$.

5. Comparison of packages, parameters choice and implementation details

5.1. Comparison of packages

Several packages for permutation tests are available for R in CRAN. Since permutation tests have such a variety of applications, we only review packages (or the part of packages) that handle regression, ANOVA or comparison of signals.

For testing one factor, the **perm** (Fay and Shaw 2010), **wPerm** (Weiss 2015) and **coin** (Hot-horn, Hornik, Van De Wiel, Zeileis, and others 2008) packages produce permutation tests of differences of locations between two or several groups. The latter can also test the difference within groups or block, corresponding to a one within factor ANOVA.

The package **lmPerm** (Wheeler and Torchiano 2016) produces tests for multifactorial ANOVA

and repeated measures ANOVA. It computes sequential (or Type I) and marginal (or Type III) tests for factorial ANOVA and ANCOVA but only the sequential is implemented for repeated measures, even when setting the parameter `seqs = FALSE`. The order of the factors will therefore matter in this case. The permutation method consists in permuting the raw data even in the presence of nuisance variables, which correspond to the `manly` method, see Table 1. For repeated measures designs, data are first projected into the "`Error()`" strata and then permuted, a method that has not been validated (to our knowledge) in any peer-reviewed journal. Additionally, **lmPerm** by default uses a stopping rule based on current p value to define the number of permutations. By default, the permutations are not randomly sampled but modified sequentially merely on a single pair of observations. This speeds up the code but the quality of the obtained p value is not well documented.

The **flip** package (Finos 2014) produces permutation and rotation tests (Langsrud 2005) for fixed effects and handles nuisance variables based on methods similar to the `huh_juhn` method of table 1. It performs tests in designs with random effects only for singular models (e.g. repetition of measures by subjects in each condition) with method based on Basso and Finos (2012) and Finos and Basso (2014) to handle nuisance variables.

The **GFD** package (Friedrich, Konietzschke, and Pauly 2017b) produces marginal permutation tests for pure factorial design (without covariates) with a Wald-type statistic. The permutation method is `manly`. This method has been shown to be asymptotically exact even under heteroscedastic conditions (Pauly *et al.* 2014).

To our knowledge, only the **permuco** provide tests for comparison of signals.

The codes and outputs for packages that perform ANOVA/ANCOVA are given in Appendix A.1 and in Appendix A.2 for repeated measures. For fixed effects, this illustrates that **permuco**, **flip** and **lmPerm** handle covariates and are based on the same statistic (F) whereas **GFD** uses the Wald-type statistic. It also shows that **flip** is testing one factor at a time (main effect of `sex` in this case) whereas the other packages produce directly tests for all the effects. Also, the nuisance variables in **flip** must be carefully implemented using the appropriate coding variables in case of factors. Note that **lmPerm** centers the covariates using the default setting and that it provides both marginal (Type III) or sequential (Type I) tests.

Concerning permutation methods, only the `manly` method is used for both **lmPerm** and **GFD**, the **flip** package uses the `huh_jhun` method, whereas multiple methods can be set by users using the **permuco** package. Note also that different default choices for the V matrix as implemented in **flip** (based on eigendecomposition) and **permuco** (based on QR decomposition) packages lead to slightly different results (see Table 1 for more information on the permutation methods).

Finally, concerning repeated measures designs, **flip** cannot handle cases where measures are not repeated in each condition for each subject, and therefore cannot be compared in Appendix A.2. As already said, **lmPerm** produces sequential tests in repeated measures designs and **permuco** produces marginal tests. This explains why, with unbalanced data, only the last interaction term in each strata produces the same statistic.

5.2. Permutation methods

For the fixed effects model, simulations (Kherad-Pajouh and Renaud 2010; Winkler *et al.* 2014) show that the method `freedman_lane`, `dekker`, `huh_jhun` and `terBraak` perform well, whereas `manly`, `draper_stoneman` and `kennedy` can be either liberal or conservative. More-

over [Kherad-Pajouh and Renaud \(2010\)](#) provide a proof for an exact test of the `huh_jhun` method under sphericity. Note that `huh_jhun` will reduce the dimensionality of the data and if $n - (p - q) \leq 7$ the number of permutations may be too low. Based on all the above literature the default method for the *permuco* package is set to `freedman_lane`.

For the random effects model, [Kherad-Pajouh and Renaud \(2015\)](#) show that a more secure approach is to choose the `Rde_keradPajouh_renaud` method.

All $n!$ permutations are not feasible already for moderate sized datasets. A large subset of permutation is used instead, and it can be tuned with the `np` argument. The default value is `np = 5000`. [Winkler, Ridgway, Douaud, Nichols, and Smith \(2016\)](#) recall that with `np = 5000` the 0.95% confidence interval around $p = 0.05$ is relatively small: $[0.0443; 0.0564]$. For replicability purpose, the `P` argument can be used instead of the `np` argument. The `P` argument needs a `Pmat` object which stores all permutations. For small datasets, if the `np` argument is greater than the number of possible permutations ($n!$), the tests will be done on all permutations. This can be also be selected manually by setting `type = "unique"` in the `Pmat` functions.

Given the inequality sign in the formulas for the p value described at the end of section 2.2, the minimal p value is $1/\text{np}$, which is a good practice for permutation tests. Moreover this implies that the sum of the two one-sided p values is slightly greater than 1.

The `huh_jhun` method is based on a random rotation that can be set by a random $n \times n$ matrix in the `rnd_rotation` argument. This random matrix will be orthogonalized by a QR decomposition to produce the proper rotation. Note that the random rotation in the `huh_jhun` method allows us to test the intercept, which is not available for the other methods.

5.3. Multiple comparisons

The `multcomp` argument can be set to `"bonferroni"` for the Bonferroni correction, to `"holm"` for the Holm correction ([Holm 1979](#)), `"benjamini_hochberg"` for the Benjamini-Hochberg method ([Benjamini and Hochberg 1995](#)), to `"troendle"`, see chapter 4.2, to `"clustermass"`, see chapter 4.3 and to `"tfce"`, see chapter 4.4. Note that in the *permuco* package, these 6 methods are available in conjunction with permutation, although the first 3 methods are general procedures that could also be used in a parametric setting.

For the `"clustermass"` method, the `threshold` parameter of the cluster-mass statistic is usually chosen by default at the 0.95 quantile of the corresponding univariate parametric distribution; but the FWER is preserved for any a priori value of the `threshold` that the user may set. The mass function is specified by the `aggr_FUN` argument. It is set by default to the sum of squares for a t statistic and the sum for an F . It should be a function that returns a positive scalar which will be large for an uncommon event under the null hypothesis (e.g., use the sum of absolute value of t statistics instead of the sum). It can be tuned depending on the expected signal. For the t statistic, typically, the sum of squares will detect more efficiently high peaks and the sum of absolute values will detect more efficiently wider clusters.

For the `"tfce"` method, the default value for the extend parameter is $E = 0.5$ and for the height $H = 2$ for t tests and, for F test, it is $E = 0.5$ and $H = 1$ following the recommendations of [Smith and Nichols \(2009\)](#) and [Pernet et al. \(2014\)](#). The `ndh` parameter controls the number of steps used in the approximation of the integral in (13) and is set to 500 by default.

The argument `return_distribution` is set by default to `FALSE` but can be set to `TRUE` to

return the large matrices ($n_P \times k$) with the value of the permuted statistics.

The algorithm and formula presented in the previous sections may not be efficient for very large size of data. When available, they are implemented in a more efficient way in **permuco**. For example, to reduce the computing time, the permuted statistics are computed through a QR decomposition using the `qr`, `qr.fitted`, `qr.resid` or `qr.coef` functions.

6. Tutorial

To load the **permuco** package:

```
R> install.packages("permuco")
R> library("permuco")
```

6.1. Fixed effects model

The **emergencycost** dataset contains information from 176 patients from an emergency service (Heritier, Cantoni, Copt, and Victoria-Feser 2009). The variables are the sex, the age (in years), the type of insurance (private/semiprivate or public), the length of the stay (LOS) and the cost. These observational data allow us to test which variables influence the cost of the stay of the patients. In this example, we will investigate the effect of the sex and of the type of insurance on the cost and we will control those effects by the length of the stay. To this end, we perform an ANCOVA and need to center the covariate.

```
R> emergencycost$LOSc <- scale(emergencycost$LOS, scale = F)
```

The permutation tests are obtained with the `aovperm` function. The `np` argument sets the number of permutations. We choose to set a high number of permutations (`np = 100000`) to reduce the variability of the permutation p values so that they can safely be compared to the parametric ones. The `aovperm` function automatically converts the coding of factors with the `contr.sum` which allows us to test the main effects of factors and their interactions.

```
R> mod_cost_0 <- aovperm(cost ~ LOSc * sex * insurance, data = emergencycost,
R>                               np = 100000)
R> mod_cost_0
```

Anova Table

Permutation test using `freedman_lane` to handle nuisance variables and 1e+05 permutations.

	SS	df	F parametric	P(>F)
LOSc	2.162e+09	1	483.4422	0.0000
sex	1.463e+07	1	3.2714	0.0723
insurance	6.184e+05	1	0.1383	0.7105
LOSc:sex	8.241e+06	1	1.8427	0.1765
LOSc:insurance	2.911e+07	1	6.5084	0.0116

sex:insurance	1.239e+05	1	0.0277	0.8680
LOSc:sex:insurance	1.346e+07	1	3.0091	0.0846
Residuals	7.514e+08	168		
	permutation P(>F)			
LOSc			0.0000	
sex			0.0763	
insurance			0.6794	
LOSc:sex			0.1576	
LOSc:insurance			0.0233	
sex:insurance			0.8537	
LOSc:sex:insurance			0.0847	
Residuals				

The interaction LOSc:insurance is significant both using the parametric p value 0.0116 and the permutation one 0.0233 using a 5% level. However, the difference between these 2 p values is 0.0117 which is high enough to lead to different conclusions e.g., in case of correction for multiple tests or a smaller α level.

If we are interested in the difference between the groups for a high value of the covariate, we center the covariate to the third quantile (14 days) and re-run the analysis.

```
R> emergencycost$LOS14 <- emergencycost$LOS - 14
R> mod_cost_14 <- aovperm(cost ~ LOS14 * sex * insurance, data = emergencycost,
R>                               np = 100000)
R>
R> mod_cost_14
```

Anova Table

Permutation test using freedman_lane to handle nuisance variables and 1e+05 permutations.

	SS	df	F	parametric P(>F)
LOS14	2.162e+09	1	483.4422	0.0000
sex	2.760e+07	1	6.1703	0.0140
insurance	9.864e+05	1	0.2206	0.6392
LOS14:sex	8.241e+06	1	1.8427	0.1765
LOS14:insurance	2.911e+07	1	6.5084	0.0116
sex:insurance	7.722e+05	1	0.1727	0.6783
LOS14:sex:insurance	1.346e+07	1	3.0091	0.0846
Residuals	7.514e+08	168		
	permutation P(>F)			
LOS14			0.0000	
sex			0.0224	
insurance			0.6082	
LOS14:sex			0.1576	
LOS14:insurance			0.0233	
sex:insurance			0.6540	

```
LOS14:sex:insurance      0.0847
Residuals
```

For a long length of stay, the effect of sex is significant using the parametric p value $p = 0.014$ and the permutation one $p = 0.0224$.

If the researcher has an a priori oriented alternative hypothesis $H_A : \beta_{sex=M} > \beta_{sex=F}$, the `lmperm` function produces one-sided t tests. To run the same models as previously, we first need to set the coding of the factors with the `contr.sum` function before running the permutation tests.

```
R> contrasts(emergencycost$insurance) <- contr.sum
R> contrasts(emergencycost$insurance)
```

```
      [,1]
public      1
semi_private -1
```

```
R> contrasts(emergencycost$sex) <- contr.sum
R> contrasts(emergencycost$sex)
```

```
      [,1]
F      1
M     -1
```

```
R> modlm_cost_14 <- lmperm(cost ~ LOS14 * sex * insurance,
R>                        data = emergencycost, np = 100000)
R>
R> modlm_cost_14
```

Table of marginal t-test of the betas

Permutation test using `freedman_lane` to handle nuisance variables and 100000 permutations.

	Estimate	Std. Error	t value	parametric	Pr(> t)
(Intercept)	14217.0	360.17	39.4730		0.0000
LOS14	845.5	38.45	21.9873		0.0000
sex1	-894.7	360.17	-2.4840		0.0140
insurance1	169.1	360.17	0.4696		0.6392
LOS14:sex1	-52.2	38.45	-1.3575		0.1765
LOS14:insurance1	98.1	38.45	2.5512		0.0116
sex1:insurance1	-149.7	360.17	-0.4155		0.6783
LOS14:sex1:insurance1	-66.7	38.45	-1.7347		0.0846
				permutation	Pr(<t) permutation Pr(>t)
(Intercept)					
LOS14		1.0000			0.0000
sex1		0.0152			0.9848

insurance1	0.6823	0.3177
LOS14:sex1	0.0796	0.9204
LOS14:insurance1	0.9868	0.0132
sex1:insurance1	0.3337	0.6663
LOS14:sex1:insurance1	0.0395	0.9605

permutation $\Pr(>|t|)$

(Intercept)	
LOS14	0.0000
sex1	0.0224
insurance1	0.6082
LOS14:sex1	0.1576
LOS14:insurance1	0.0233
sex1:insurance1	0.6540
LOS14:sex1:insurance1	0.0847

The effect sex1 is significant for both the parametric one-sided p value $p = 0.007$ and the permutation one-sided p value $p = 0.0152$. It indicates that when the length of the stay is high, men have a shorter cost than women.

To test the effect of the sex within the public insured persons (called simple effect), we change the coding of the factors inside the `data.frame` using the `contr.treatment` function and disable the automatic recoding using the argument `coding_sum = FALSE`.

```
R> contrasts(emergencycost$insurance) <- contr.treatment
R> emergencycost$insurance <- relevel(emergencycost$insurance, ref = "public")
R> contrasts(emergencycost$insurance)
```

	semi_private
public	0
semi_private	1

```
R> contrasts(emergencycost$sex) <- contr.sum
R> contrasts(emergencycost$sex)
```

	[,1]
F	1
M	-1

```
R> mod_cost_se <- aovperm(cost ~ LOSc * sex * insurance, data = emergencycost,
R>                          np = 100000, coding_sum = FALSE)
R> mod_cost_se
```

Anova Table

Permutation test using `freedman_lane` to handle nuisance variables and $1e+05$ permutations.

	SS	df	F	parametric	P(>F)
L0Sc	9.512e+09	1	2126.7539		0.0000
sex	6.092e+07	1	13.6210		0.0003
insurance	6.184e+05	1	0.1383		0.7105
L0Sc:sex	1.510e+08	1	33.7708		0.0000
L0Sc:insurance	2.911e+07	1	6.5084		0.0116
sex:insurance	1.239e+05	1	0.0277		0.8680
L0Sc:sex:insurance	1.346e+07	1	3.0091		0.0846
Residuals	7.514e+08	168			
	permutation P(>F)				
L0Sc		0.0000			
sex		0.0004			
insurance		0.6794			
L0Sc:sex		0.0000			
L0Sc:insurance		0.0233			
sex:insurance		0.8537			
L0Sc:sex:insurance		0.0847			
Residuals					

The sex row can be interpreted as the effect of sex for the `public` insured persons for an average length of stay. Both the parametric $p = 0.0003$ and permutation p value $p = 0.0004$ show significant effect of sex within the public insured persons.

Given the skewness of the data for each case where the permutation test differs from the parametric result, we tend to put more faith on the permutation result since it does not rely on assumption of normality.

6.2. Repeated measures ANCOVA

The `jpah2016` dataset contains a subset of a control trial in impulsive approach tendencies toward physical activity or sedentary behaviors. It contains several predictors like the body mass index, the age, the sex, and the experimental conditions. For the latter, the subjects were asked to perform different tasks: to approach physical activity and avoid sedentary behavior (`ApSB_AvPA`), to approach sedentary behavior and avoid physical activity (`ApPA_AvSB`) and a control task. The dependent variables are measures of impulsive approach toward physical activity (`iapa`) or sedentary behavior (`iasb`). See [Cheval, Sarrazin, Pelletier, and Friese \(2016\)](#) for details on the experiment. We will analyze here only a part of the data.

```
R> jpah2016$bmic <- scale(jpah2016$bmi, scale = F)
```

We perform the permutation tests by running the `aovperm` function. The within subject factors should be written using `+ Error(...)` similarly to the `aov` function from the `stats` package:

```
R> mod_jpah2016 <- aovperm(iapa ~ bmic * condition * time + Error(id/(time)),
R>                          data = jpah2016, method = "Rd_kheradPajouh_renaud")
```

The results are shown in an ANOVA table by printing the object:

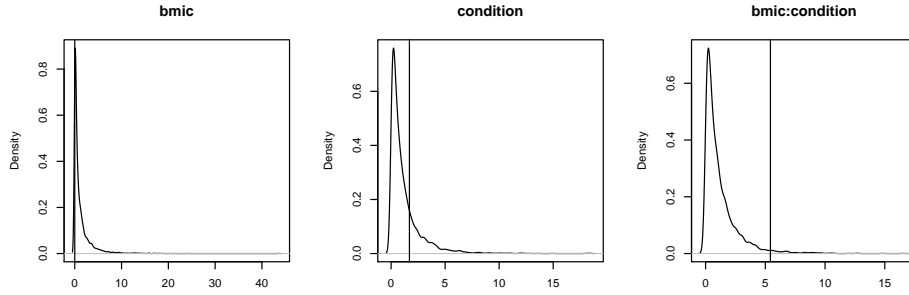


Figure 3: The permutation distributions of the F statistics for the effects **bmic**, **condition** and **bmic:condition**. The vertical lines indicate the observed statistics.

```
R> mod_jpah2016
```

Permutation test using `Rd_kheradPajouh_renaud` to handle nuisance variables and 5000 permutations.

	SSn	dfn	SSd	dfd	MSEn	MSEd
bmic	18.6817	1	106883.5	13	18.6817	8221.808
condition	27878.1976	2	106883.5	13	13939.0988	8221.808
bmic:condition	89238.4780	2	106883.5	13	44619.2390	8221.808
time	268.8368	1	167304.9	13	268.8368	12869.607
bmic:time	366.4888	1	167304.9	13	366.4888	12869.607
condition:time	21159.7735	2	167304.9	13	10579.8867	12869.607
bmic:condition:time	29145.7201	2	167304.9	13	14572.8601	12869.607
	F parametric		P(>F) permutation		P(>F)	
bmic	0.0023		0.9627		0.9646	
condition	1.6954		0.2217		0.2180	
bmic:condition	5.4269		0.0193		0.0230	
time	0.0209		0.8873		0.8808	
bmic:time	0.0285		0.8686		0.8594	
condition:time	0.8221		0.4611		0.4520	
bmic:condition:time	1.1323		0.3521		0.3412	

This analysis reveals a significant p value for the effect of the interaction **bmic:condition** with a statistic $F = 5.4269$, which lead to a permutation p value $p = 0.023$ not far from the parametric one. For this example, the permutation tests backs the parametric analysis. The permutation distributions can be viewed using the `plot` function like in Figure 3.

```
R> plot(mod_jpah2016, effect = c("bmic", "condition", "bmic:condition"))
```

6.3. EEG experiment in attention shifting

Table 3: Variables in the `attentionshifting_design` dataset.

Variable name	Description	Levels
<code>id</code>	number of identification	15 subjects
<code>visibility</code>	time that the image is shown	16ms 166ms
<code>emotion</code>	emotion of the shown faces	angry, neutral
<code>direction</code>	position of the faces on the screen	left, right
<code>laterality_id</code>	measure of the laterality of the subjects	scale from 25 to 100
<code>age</code>	age of the subjects	from 18 to 25
<code>sex</code>	sex of the subjects	male, female
<code>STAIS_state</code>	state anxiety score of the subjects	
<code>STAIS_trait</code>	trait anxiety score of the subjects	

`attentionshifting_signal` and `attentionshifting_design` are data provided in the **permuco** package. They come from an EEG recording of 15 participants watching images of either neutral or angry faces (Tipura, Renaud, and Pegna 2017). Those faces were shown at a different visibility: subliminal (16ms) and supraliminal (166ms) and were displayed to the left or to the right of a screen. The recording is at 1024Hz for 800ms. Time 0 is when the image appears (event-related potential or ERP). The `attentionshifting_signal` dataset contains the ERP of the electrode O1. The design of experiment is given in the `attentionshifting_design` dataset along with the laterality, sex, age, and 2 measures of anxiety of each subjects, see Table 3.

As almost any ERP experiment, the data is designed for a repeated measures ANOVA. Using the **permuco** package, we test each time points of the ERP for the main effects and the interactions of the variables `visibility`, `emotion` and `direction` while controlling for the FWER. We perform F tests using a threshold at the 95% quantile, the sum as a cluster-mass statistics and 5000 permutations. We handle nuisance variables with the method `Rd_kheradPajouh_renaud`:

```
R> electrod_01 <-
R>   clusterlm(attentionshifting_signal ~ visibility * emotion * direction
R>           + Error(id/(visibility * emotion * direction)),
R>           data = attentionshifting_design)
```

The `plot` method produced a graphical representation of the tests that allows us to see quickly the significant time frames corrected by `clustermass`. The results are shown in Figure 4.

```
R> plot(electrod_01)
```

Only one significant result appears for the main effect of visibility. This cluster is corrected using the `clustermass` method. Printing the `clusterlm` object gives more information about all clusters for the main effect of visibility, whether they are significant or not:

```
R> print(electrod_01, effect = "visibility")
```

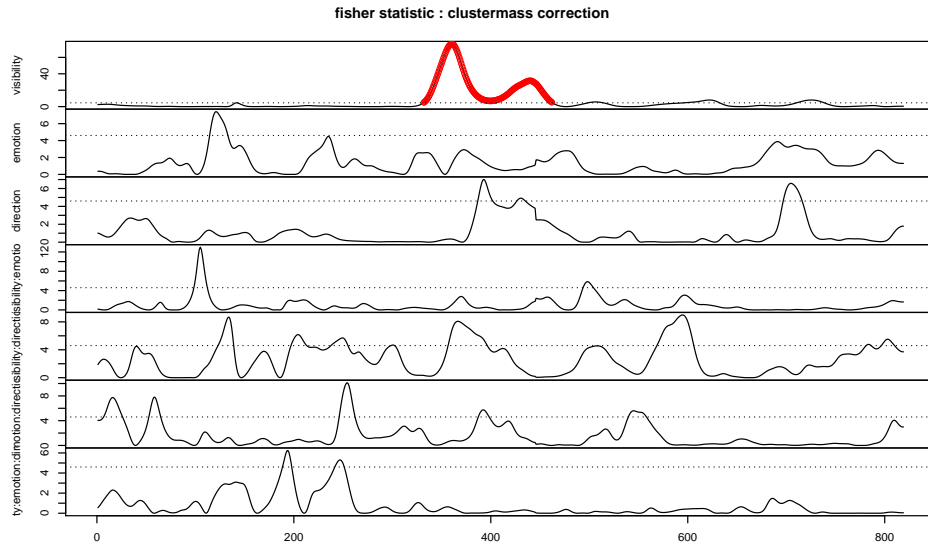


Figure 4: The `plot` method on a `clusterlm` object displays the observed statistics of the three main effects and their interactions. The dotted horizontal line represents the threshold which is set by default to the 95% percentile of the statistic. For this dataset, one cluster is significant for the main effect of visibility using the `clustermass` method, as shown by the red part. The `print` method gives more details.

Cluster fisher test using `Rd_kheradPajouh_renaud` to handle nuisance variables with 5000 permutations and the `sum` as mass function.

Alternative Hypothesis : `two.sided`.

```
visibility, threshold = 4.60011.
  start end cluster mass P(>mass)
1   142 142     4.634852  0.5048
2   332 462   3559.149739  0.0018
3   499 514    85.019645  0.4060
4   596 632   234.877913  0.2290
5   711 738   191.576178  0.2680
```

The only significant effect appears between the measures 332 and 462 that correspond to the 123.7ms and 250.9ms after the event. The cluster-mass statistic is 3559.1 with a p value of 0.0018. The threshold is set to 4.60011 which is the 95% percentile of the F statistic. If we want to use other multiple comparisons procedures, we use `multcomp` argument:

```
R> full_electrod_01 <-
R>   clusterlm(attentionshifting_signal ~ visibility * emotion * direction
R>             + Error(id/(visibility * emotion * direction)),
R>             data = attentionshifting_design, P = electrod_01[["P"]])
```

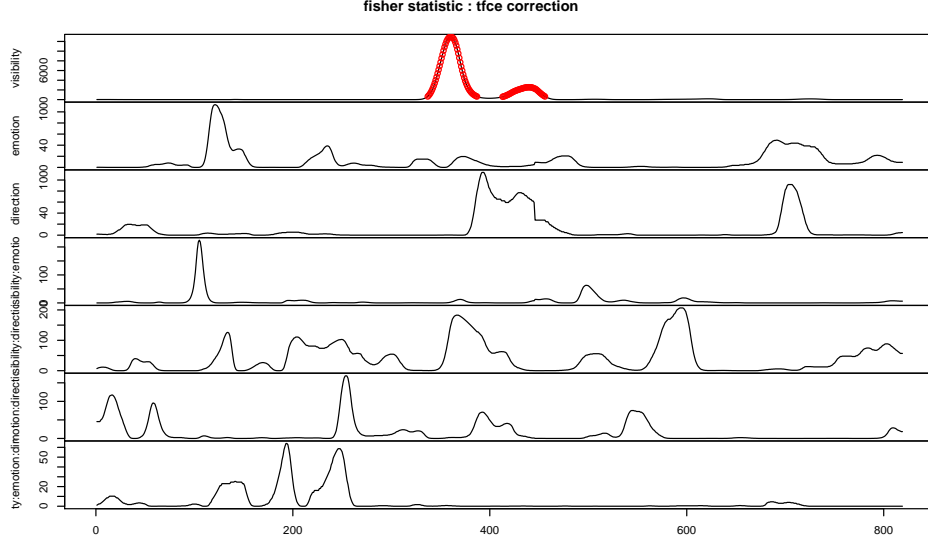


Figure 5: Setting the `multcomp` to "tfce" in the `plot` function will display the TFCE p values. The argument `enhanced_stat = TRUE` shows the TFCE statistics u_s of equation 13.

```
R> method = "Rde_kheradPajouh_renaud",
R> multcomp = c("troendle", "tfce", "clustermass",
R>               "bonferroni", "holm", "benjaminin_hochberg"))
```

Note that we retrieve the very same permutations as previous model by using the `P` argument. The computation time for those tests is reasonable: it takes less than 12 minutes on a desktop computer (i7 3770CPU 3.4GHz, 8Go RAM) to compute the 7 permutation tests with all the multiple comparison procedures available. To see quickly the results of the threshold-free cluster-enhancement procedure, we set the `multcomp` argument of `plot` to "tfce" as shown in Figure 5.

```
R> plot(full_electrod_01, multcomp = "tfce", enhanced_stat = TRUE)
```

This procedure gets approximately a similar significant period for the same effect. However we get two smaller and separated significant periods rather than one longer. If the curves in the TFCE plot happen to show some small steps (which is not the case in Figure 5) it may be because of a too small number of terms in the approximation of the integral of the `tfce` statistics of equation 13. In that case it would be reasonable to increase the value of the parameter `ndh`.

7. Conclusion

This article presents recent methodological advances in permutations tests and their implementation in the **permuco** package. Hypotheses in linear models framework or repeated measures ANOVA are tested using several methods to handle nuisance variables. Moreover

permutations tests can solve the multiple comparisons problem and control the FWER through cluster-mass tests or TFCE, and the `clusterlm` function implements those procedures for the analysis of signals, like EEG data. Section 6 illustrates some real data example of tests that can be performed for regression, repeated measures ANCOVA and ERP signals comparison.

We hope that further developments of **permuco** expand cluster-mass tests to multidimensional adjacency (space and time) to handle full scalp ERP tests that control the FWER over all electrodes. Another evolution will concern permutation procedures for mixed effects models to allow researchers to perform tests in models containing participants and stimuli specific random effects.

Acknowledgement

We are particularly grateful for the assistance given by Eda Tipura that greatly improved this manuscript. She provided original EEG data, as well as many comments coming from her extended reading of the paper; although any errors are our own.

A. Comparisons of existing packages

A.1. ANOVA and ANCOVA

```
R> install.packages("lmPerm")
R> install.packages("flip")
R> install.packages("GFD")
R> library("lmPerm")
R> library("flip")
R> library("GFD")

R> emergencycost$LOSc <- scale(emergencycost$LOS, scale = FALSE)
R> contrasts(emergencycost$sex) <- contr.sum
R> contrasts(emergencycost$insurance) <- contr.sum
R>
R> X <- model.matrix( ~ sex+insurance, data = emergencycost)[, -1]
R> colnames(X) <- c("sex_num", "insurance_num")
R> emergencycost <- data.frame(emergencycost,X)
R>
R> anova_permuco <- aovperm(cost ~ sex * insurance, data = emergencycost)
R> anova_GFD <- GFD(cost ~ sex * insurance, data = emergencycost,
R>                  CI.method = "perm", nperm = 5000)
R>
R>
R> ancova_permuco <- aovperm(cost ~ LOSc * sex * insurance, data = emergencycost,
R>                          method = "huh_jhun")
R> ancova_flip <- flip(cost ~ 1, X = ~ sex_num, Z = ~ LOSc * insurance_num * sex_num
R>                  - sex_num, data = emergencycost, statTest = "ANOVA",
```



```
R>                                perms = 5000)
R> ancova_lmPerm <- aovp(cost ~ LOS * sex * insurance, data = emergencycost,
R>                                seqs = FALSE, nCycle = 1)
```

```
R> anova_permuco
```

Anova Table

Permutation test using freedman_lane to handle nuisance variables and 5000 permutations.

	SS	df	F	parametric	P(>F)
sex	60470803	1	0.7193		0.3975
insurance	598973609	1	7.1249		0.0083
sex:insurance	334349436	1	3.9771		0.0477
Residuals	14459666504	172			

	permutation	P(>F)
sex		0.3978
insurance		0.0120
sex:insurance		0.0508
Residuals		

```
R> anova_GFD
```

Call:

```
cost ~ sex * insurance
```

Wald-Type Statistic (WTS):

	Test statistic	df	p-value	p-value	WTPS
sex	0.6397413	1	0.42380448		0.4662
insurance	6.3367469	1	0.01182616		0.0584
sex:insurance	3.5371972	1	0.06000678		0.0730

ANOVA-Type Statistic (ATS):

	Test statistic	df1	df2	p-value
sex	0.6397413	1	5.743756	0.4556003
insurance	6.3367469	1	5.743756	0.0471947
sex:insurance	3.5371972	1	5.743756	0.1112178

```
R> ancova_permuco
```

Anova Table

Permutation test using huh_jhun to handle nuisance variables and 5000, 5000, 5000, 5000, 5000, 5000, 5000 permutations.

	SS	df	F	parametric	P(>F)
LOSc	2162110751	1	483.4422		0.0000

```

sex          14630732    1    3.2714          0.0723
insurance    618366     1    0.1383          0.7105
LOSc:sex     8241073    1    1.8427          0.1765
LOSc:insurance 29107536  1    6.5084          0.0116
sex:insurance 123892    1    0.0277          0.8680
LOSc:sex:insurance 13457877 1    3.0091          0.0846
Residuals    751350616 168

```

permutation P(>F)

```

LOSc          0.0002
sex           0.0736
insurance     0.7224
LOSc:sex      0.1756
LOSc:insurance 0.0102
sex:insurance 0.8704
LOSc:sex:insurance 0.0820
Residuals

```

```
R> summary(ancova_lmPerm)
```

Component 1 :

	Df	R Sum Sq	R Mean Sq	Iter	Pr(Prob)
LOS	1	2162110751	2162110751	5000	<0.0000000000000002
sex	1	14630732	14630732	4159	0.0236
LOS:sex	1	8241073	8241073	1525	0.0616
insurance	1	618366	618366	94	0.5213
LOS:insurance	1	29107536	29107536	5000	0.0010
sex:insurance	1	123892	123892	80	0.5625
LOS:sex:insurance	1	13457877	13457877	2238	0.0429
Residuals	168	751350616	4472325		

```

LOS          ***
sex          *
LOS:sex      .
insurance
LOS:insurance ***
sex:insurance
LOS:sex:insurance *
Residuals
---

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```
R> ancova_flip
```

```

      Test Stat tail p-value
cost   F 3.271   > 0.0724

```

A.2. Repeated measures ANOVA

```
R> jpah2016$id = as.factor(jpah2016$id)
R> jpah2016$bmic = scale(jpah2016$bmi, scale = FALSE)
R>
R> rancova_permuco <- aovperm(iapa ~ bmic * condition * time + Error(id/(time)),
R>                               data = jpah2016)
R> rancova_lmPerm <- aovp(iapa ~ bmic * condition * time + Error(id/(time)),
R>                               data = jpah2016, nCycle = 1, seqs = FALSE)
```

```
R> rancova_permuco
```

Permutation test using Rd_kheradPajouh_renaud to handle nuisance variables and 5000 permutations.

	SSn	dfn	SSd	dfd	MSEn	MSEd
bmic	18.6817	1	106883.5	13	18.6817	8221.808
condition	27878.1976	2	106883.5	13	13939.0988	8221.808
bmic:condition	89238.4780	2	106883.5	13	44619.2390	8221.808
time	268.8368	1	167304.9	13	268.8368	12869.607
bmic:time	366.4888	1	167304.9	13	366.4888	12869.607
condition:time	21159.7735	2	167304.9	13	10579.8867	12869.607
bmic:condition:time	29145.7201	2	167304.9	13	14572.8601	12869.607

	F	parametric P(>F)	permutation P(>F)
bmic	0.0023	0.9627	0.9660
condition	1.6954	0.2217	0.2180
bmic:condition	5.4269	0.0193	0.0248
time	0.0209	0.8873	0.8856
bmic:time	0.0285	0.8686	0.8666
condition:time	0.8221	0.4611	0.4392
bmic:condition:time	1.1323	0.3521	0.3528

```
R> summary(rancova_lmPerm)
```

Error: id

Component 1 :

	Df	R	Sum Sq	R	Mean Sq	Iter	Pr(Prob)
bmic	1		3270		3270	51	0.8824
condition	2		20000		10000	801	0.3009
bmic:condition	2		89238		44619	4863	0.0255 *
Residuals	13		106884		8222		

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Error: id:time

Component 1 :

	Df	R	Sum Sq	R	Mean Sq	Iter	Pr(Prob)
time	1		1047		1047.4	51	0.9412
bmic:time	1		31		31.5	51	0.8039
condition:time	2		29793		14896.4	320	0.3875
bmic:condition:time	2		29146		14572.9	419	0.3914
Residuals	13		167305		12869.6		

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