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The use of Permutation Tests on Large-Sized Datasets

L'uso dei Test di Permutazione su Grandi Datasets

Massimiliano Giacalone, Agata Zirilli and Angela Alibrandi ¹

Abstract The increasing availability of large-sized datasets produces a growing interest in permutation testing methods. They represent an effective solution for problems concerning the testing of multidimensional hypotheses, difficult to face in a parametric context. In this paper we propose an application of permutation test on a large amount of data in order to show its utility to analyze a big dataset array. The analysis was performed in order to assess the existence of significant differences, with reference to several variables, between two gastrointestinal illnesses.

Abstract La crescente disponibilità di grandi set di dati comporta un notevole interesse per i metodi basati su test di permutazione. Essi rappresentano un'efficace soluzione per problemi inerenti la verifica di ipotesi multidimensionali, difficili da affrontare in un contesto parametrico. Nel presente lavoro proponiamo un'applicazione di tale metodologia ad una elevata numerosità di dati, al fine di dimostrarne l'utilità nell'analisi di un grande dataset. In particolare è stata indagata l'esistenza di differenze significative, in relazione a diverse variabili esaminate, tra due malattie gastrointestinali.

Key words: Large-Sized Datasets, Permutation Tests, Application in Medical Field.

The statistical background of Large-Sized Datasets

In recent years, there is a growing interest in permutation testing methods due to the increasing availability of large-sized datasets and the consequent need to solve

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more and more complex multivariate problems. Actually, permutation tests are essentially exact in a nonparametric conditional framework, where conditioning is on the pooled observed data set; it is generally a set of sufficient statistics in the null hypothesis. Many complex multivariate problems are difficult to handle outside the conditional framework and, in particular, outside the nonparametric combination (NPC) of dependent permutation tests (Arboretti and Brombin, 2014). While permutation tests and bootstraps have very wide-ranging application, both share a common potential drawback: as data-intensive resampling methods, both can be runtime prohibitive when applied to large or even medium-sized datasets. The data explosion over the past few decades has made this a common occurrence and it highlights the increasing need for faster and more efficient permutation tests and bootstrap algorithms (Opdyke, 2013). The permutation test essentially works by combining two important ideas: exchangeability and conditioning. More generally the exchangeability and other sorts of stochastic orders are keys to robust inference on large-sized datasets.

The paper briefly shows an application of NPC test for the analysis of Big Data; since medical data were analyzed, theoretical, methodological and applicative aspects have been fruitfully integrated with specific competences from medicine field (Peek et al., 2014; Rezzani, 2013). We apply a permutation test on a large amount of patients (about 1700) in order to assess the existence of significant differences between patients affected by two gastrointestinal illnesses: Crohn's Disease (CD) and Ulcerative Colitis (UC). Our research showed the utility of the NPC test into analyze a large dataset array.

2. Permutation test

2.1 Methodology

In this context we introduce the theoretical aspects of Non Parametric Combination (NPC) test, based on permutation solution (Pesarin and Salmaso, 2010; Pesarin, 2001; Corain and Salmaso, 2004). Permutation tests represent an effective solution for problems concerning the testing of multidimensional hypotheses, that are difficult to face in a parametric context. This multivariate and multistrata procedure allows to reach effective solutions concerning problems of multidimensional hypotheses verifying within the non parametric permutation inference (Pesarin, 2001); it is used in different application fields that concern verifying of multidimensional hypotheses with a complexity that cannot be managed in parametric context. In comparison to the classical approach, NPC test is characterized by several advantages: it does not request normality and homoschedasticity assumption; it draws any type of variable (Pesarin and Samaso, 2006; Klingenberg et al., 2008); it assumes a good behaviour also in presence of missing data; it is powerful in presence of low sampling size (Brombin and Salmaso, 2009); it resolves multivariate problems without the necessity to specify the structure of dependence among variables; it allows stratified analyses; it allows to test multivariate restricted alternative hypothesis

The use of Permutation Tests on Large-Sized Datasets

(allowing the verifying of the directionality for a specific alternative hypothesis); it resolves problems in which observations number is smaller than variables number (Finos and Salmaso, 2006; Basso et al., 2007). All these properties make NPC test very flexible and widely applicable in several fields; in particular we cite recent applications in medical context and in genetics (Zirilli and Alibrandi, 2009; Zirilli and Alibrandi, 2011; Zirilli and Alibrandi, 2012; Bonnini et al., 2006; Arboretti et al., 2005; Salmaso, 2005; Finos et al., 2004; Bonnini et al., 2003; Callegaro et al., 2003; Di Castelnuovo et al., 2000). By means of mentioned procedure it is preliminarily possible to define a set of k one-dimensional permutation test, denominated partial test, through which the marginal contribution of every answer-variable can be examined in the comparison among groups. The partial tests are non-parametrically combined through CMC (Conditional Monte Carlo) procedure in combined tests, using an opportune combination function (generally Fisher, Tippett or Liptak); these tests globally verify the existence of differences among the multivariate distributions of the groups. We supposed that K variables are noticed on N observations (dataset $N \times K$) belonging to C groups and that an appropriate K -dimensional distribution exists. The null hypothesis postulates the equality in distribution of k -dimensional distribution among all C groups (1) against the alternative hypothesis (2):

$$H_0 = \left[\bigcap_{i=1}^k X_{H_i} = \dots = X_{C_i} \right] = \left[\bigcap_{i=1}^k H_{0i} \right] \quad (1) \quad \text{against} \quad H_1 = \bigcup_{i=1}^k H_{1i} \quad (2)$$

Let's assume that, without loss of generality, the partial tests assume real values and they are marginally correct, consistent and significant for great values; the NPC test procedure (based on CMC resampling) develops into the following two-phases algorithm (Fig. 1). The hypotheses systems are verified by the determination of partial tests (1st order) that allow to evaluate the existence of statistically significant differences. The partial tests are combined, in a non parametric way (using a combined function as Fisher, Liptak or Tippett) in a second order test that globally verifies the existence of differences among the multivariate distributions. A procedure of conditioned resampling CMC (Pesarin, 2001) allows to estimate the p-values, associated both to partial tests and to second order tests.

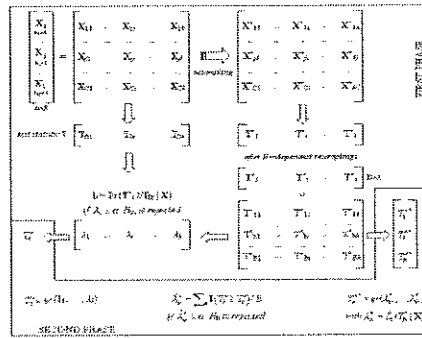


Figure 1: Two Phases Algorithm of NPC Procedure

2.2 Application

In this paper the NPC procedure was applied to a large amount of patients (1722) followed in the gastroenterology unit of the "G.Martino" University Hospital in Messina. The analysis was performed in order to assess the existence of significant differences between two gastrointestinal illnesses: Crohn's Disease (CD) and Ulcerative Colitis (UC). For each patient (in the respect of anonymity) we acquired information about: diagnosis age, gender, smoking habit, use of immunosuppressive therapy and its duration, treatment with biological drugs and its duration, hospitalization, adverse events, infections, cancers, diabetes, hypertension, heart failure, kidney failure, pulmonary failure, neuropathy, liver disease, Charlson Index (the most widely used index to predict the ten-year mortality for a patient who may have comorbid conditions; its score are 1, 2, 3 or 6, depending on the risk of dying), surgery, final exitus and follow-up time. The hypotheses system is the following:

$$H_0 : \left\{ \text{diagnosis_age}_1 \stackrel{d}{=} \text{diagnosis_age}_2 \right\} \cap \dots \cap \left\{ \text{follow-up_time}_1 \stackrel{d}{=} \text{follow-up_time}_2 \right\}$$

$$H_1 : \left\{ \text{diagnosis_age}_1 \stackrel{d}{\neq} \text{diagnosis_age}_2 \right\} \cup \dots \cup \left\{ \text{follow-up_time}_1 \stackrel{d}{\neq} \text{follow-up_time}_2 \right\}$$

where 1 and 2 are the two examined gastrointestinal illnesses (results in Table 1).

Table 1: NPC test for comparisons between CD and UC

VARIABLES	CD	UC	p-value
Diagnosis age	43.80±21.59	45.87±20.83	0.028
Gender (M% / F%)	49.3 / 50.7	57.7 / 42.3	0.001
Smoking habit (yes % / no %)	43.9 / 56.1	35.2 / 64.8	0.000
Immunosuppressive therapy (yes % / no %)	38.4 / 61.6	26.4 / 73.6	0.000
Duration of immunosuppressive therapy	12.27±8.67	14.92±9.84	0.003
Biological drugs (yes % / no %)	18.4 / 81.6	8.7 / 91.3	0.000
Duration of treat. with biological drugs	12.23±7.33	16.03±9.41	0.005
Hospitalization (yes % / no %)	45.6 / 54.4	27.8 / 72.2	0.000
Adverse events (yes % / no %)	17.9 / 82.1	9.2 / 90.8	0.000
Infections (yes % / no %)	7.0 / 93.0	7.6 / 92.4	0.627
Cancers (yes % / no %)	3.6 / 96.4	2.5 / 97.5	0.275
Diabetes (yes % / no %)	5.6 / 94.4	10.6 / 89.4	0.000
Hypertension (yes % / no %)	20.3 / 79.7	19.6 / 80.4	0.737
Heart failure (yes % / no %)	5.7 / 94.3	5.7 / 94.3	0.985
Kidney failure (yes % / no %)	2.1 / 97.9	2.6 / 97.4	0.507
Pulmonary failure (yes % / no %)	3.6 / 96.4	5.1 / 94.9	0.155
Neuropathy (yes % / no %)	1.7 / 98.3	1.6 / 98.4	0.885
Liver disease (yes % / no %)	1.6 / 98.4	1.3 / 98.7	0.607
Charlson (%) * score 0	87.6	93.6	0.012
scores 1 / 2 / 3	8.6 / 2.9 / 1	12.8 / 3.3 / 0.3	
Surgery (yes % / no %)	19.7 / 80.3	5.3 / 94.7	0.000
Final exitus (S / D)	97.9 / 2.1	97.6 / 2.4	0.664
Follow-up time	34.57±4.54	34.92±4.16	0.056
COMBINED p-value			0.000

* No patient has Charlson score equal to 6

3 Results and Final Remarks

In this paper we want to show as the permutation tests are very helpful for large-sized data analysis in many applicative contexts. In large data sets consisting of 1000 observations, performance of the permutation test appears equivalent to that of the asymptotic test (Potter, 2005); on the other hand, the NPC test, based on permutation solution, can be appropriately applied when the assumption for asymptotic tests are fulfilled (Ludbrook and Dudley, 1998). In addition, unlike the classical non parametric tests, the NPC method entails testing a global null hypothesis consisting of the intersection of $K > 1$ partial sub-hypotheses. In essence, the global null states that all of its constituent sub-hypotheses are true. The global alternative hypothesis is the union of K sub-alternatives (Pesarin and Salmaso, 2010). In this way NPC provides in multivariate context the combined p-value, by means of an adequate combining function. From the applicative point of view, we have great interest in evaluating this combined p-value because it provides a result that takes into account the contribution of all examined variables; on the other hand, no other non-parametric test provides the advantage of a combined p-value. This particular feature justifies our choice of the NPC test as methodically appropriate solution. In particular we applied permutation tests to perform comparison between a large number of patients affected by Crohn's Disease and Ulcerative Colitis. Both of these illness are inflammatory bowel diseases, involving more than 100,000 people in Italy; they often arise in young people, go on for a lifetime and manifest alterations of the intestinal canal, causing relationship and working problems. Examining the results achieved by applying NPC tests, we have to notice the high significance of the combined test, that provides guarantee affirming that patients with CD and UC significantly differ between them, in relation to the set of examined variables. Focusing our attention on partial tests, we can see that some variables significantly discriminate the two different subpopulations; in particular the UC patients, in comparison with the CD patients, have a higher diagnosis age, do not show a marked smoking status, the proportion of patients treated with immunosuppressants or with biological drugs is lower than the CD patients, even if the duration of such therapies is longer. CD patients have a higher rate of hospitalization; probably it is related to the significant greater occurrence of adverse events (rather than UC). Diabetes is more present in the sub-population of UC patients. Analyzing the Charlson score we can highlight that UC patients have a more severe clinical situation than CD patients. Finally, the CD patients are more frequently subjected to surgery compared to UC.

Until a few years ago the use of Big Data was not received particular attention from researchers. Today the conspicuous availability of large amounts of data and the need of their analysis required an adjustment of data processing methodologies, with careful attention to all the sources of variation in data. In this context, the non-parametric procedures, such as permutation tests, are widely applicable in virtue of the numerous optimal properties of which they are characterized.

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