A RANDOMIZED MOST POWERFUL TEST TO DETECT A CHEATER'S ACTION. APPLICATON TO IDENTIFICATION OF LISTERIOSIS IN LOMBARDY

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Abstract. This article presents a new randomized non-parametric test based on a sample of independent but not identically distributed variables; this test detects if a cheater replaces one of the distributions of the sample with a convex-dominating one. The presented test is the uniformly most powerful, in the sense that it is the most powerful for any change of the cheater. We show that this test may be applied when we have variables with distribution satisfying the monotone likelihood ratio property and we need to check whether a parameter of a variable has been changed.

The application we present concerns the detection of epidemics of listeriosis in Lombardy from 2005 to 2011.

1. Introduction

Let us consider a sample of independent random variables with $(0,1)$-uniform distribution: $Y_1, Y_2, \ldots, Y_n$. We need to discover if a cheater has replaced one of the variables with another r.v. Y defined on $(0,1)$ with a convex cdf F_Y, stochastically dominating the uniform ditribution, i.e. $F(x) \geq x, \forall x \in (0,1)$.

We test the null hypothesis H_0 of equal and uniform distribution of all the variables against the alternative hypothesis H_1 of a cheater's replacement. We choose to observe the statistics $\hat{Y} = \max(Y_1, \ldots, Y_n)$, that we call extreme event. In Theorem 2.8 we present the non-parametric uniformly most powerful (UMP) test, in the sense that it is the most powerful (MP) test for any cheater's choice; in particular, if α is the significance level of the test, we reject H_0 if $\hat{Y} > \sqrt[n]{1-\alpha}$.

This game can be extended to a sample of independent r.v.'s $X_1, X_2, \ldots, X_n$ with cfd $F_{X_1}^0, F_{X_2}^0, \ldots, F_{X_n}^0$ by noting that $Y_i = F_{X_i}^0(X_i) \sim U(0,1)$; if the original distributions are discrete, a randomization can be applied (see Lemma 2.3). In this general framework, we suppose that the cheater changes $F_{X_j}^0$ with another distribution $F_{X_j}^1$: to apply the previous results we should be sure that the randomization of $F_{X_j}^0(X_j)$ is convex when $X_j \sim F_{X_j}^1$. We show that this is the case whenever $F_{X_j}^0$ and $F_{X_j}^1$ have the monotone likelihood ratio property (see Theorem 2.7).

As an example, the result can be applied when we ask ourselves whether the occurrences of a (even rare) disease show evidence of an epidemics. In our case, we apply it to a listeriosis database.

The first important work on epidemics based on spatial analysis is Dr. John Snow's study of London's cholera epidemics [11]. After him, many other researchers have used spatial analysis to study subjects concerning Public Health; a wide collection of these topics, with particular interest to the statistical point of view, is given by Waller and Gotway [?].

In our data, we have a sample of random variables $N_{i,j}$ counting the number of occurrences of a disease in a certain region i at time j that we model with a Poisson distribution, so $F_{i,j}^0 \sim \mathcal{P}(\lambda \cdot p_{i,j})$, i.e. the number $N_{i,j}$ is distributed as a Poisson depending on a parameter λ and on the population $p_{i,j}$ of region i at time j. When an epidemics occurs, the parameter λ of the corresponding $N_{i,j}$ increases: $\lambda_1 > \lambda$. Since the family of Poisson model has the monotone likelihood ratio property, we may apply our test to $(F_{i,j}^0(N_{i,j}))_{i,j}$.

The small number of data is the critical point of the analysis, because usual limit theorems cannot be used; for this reason it is important to find the UMP test.

In Section 2 we present the main result of the article: the UMP test for extreme monotone randomized models. First of all we recall the definition and some properties of the Skorohod representation of a random variable, then in Subsection 2.1 we introduce the randomization of the quantile function for a non-continuous

random variable, then in Subsection 2.2 we define the extreme event of a sample, and finally in 2.3 we present the test and prove the UMP property.

Section 3 shows the application of the test to listeriosis. In particular, in Subsection 3.1 we present the data. Then we perform a test to identify the place and time of occurrence of the possible epidemic. This hypothesis test is described in Subsection 3.2 and is based on the UMP test introduced before; in this part of the article we also recall a result to find p-values of a discrete distribution based on the Skorokhod's representation of a random variable [13].

2. A UMP TEST FOR EXTREME MONOTONE RANDOMIZED MODELS

To state the main result, we recall the definition and properties of the Skorohod representation of a random variable [13].

Theorem 2.1. *Let F be a cumulative distribution function; then*

$$N(\omega) = \sup\{y | F(y) < \omega\}$$

with ω from a probability space with uniform probability distribution on $[0, 1]$ is a random variable with cdf F.

Definition 2.2. The random variable defined in the previous theorem is called the **Skorhod representation** of any random variable with distribution F.

The Skorohod representation of a random variable has many properties; we mention two of them:

(1) $F(N(\omega)) \geq \omega$;
(2) $F(z) > \omega \Rightarrow z > N(\omega)$.

We are interested in finding a UMP test for the extreme event on a set of data. In our contest, the highest result we get, the more extreme it is. Therefore, to compare results from different distributions, we use the (randomized) quantile function as an index of "extremeness".

2.1. **Randomization of quantile function.** Assume that we observe the real number x, that is the outcome of a continuous variable X with cumulative function F. Its natural extremal index is $p_x = P(X \leq x) = F(x)$. Unfortunately, it is well known that F is continuous if and only if $F(X)$ is uniformly distributed on $(0, 1)$, and in this case $F(X)$ is the quantile of X. We define now a randomization version of the quantile function which is uniformly distributed on $(0, 1)$, even if the random variable X is not continuous.

Let F be a cumulative function. We define the function $\mathcal{F}_F : \mathbb{R} \times [0, 1] \to [0, 1]$ as

$$(1) \qquad \mathcal{F}_F(x, u) = (1 - u)F(x^-) + uF(x),$$

so that $\mathcal{F}$ has the following properties:

- for any (x, u), $F(x^-) \leq \mathcal{F}_F(x, u) \leq F(x)$, and hence $\mathcal{F}_F(x, u)$ is an extension of the function $F(x)$ when F is not continuous;
- if $F(x) > F(y)$, then $\mathcal{F}_F(x, u) > \mathcal{F}_F(y, v)$ for any $u, v \in (0, 1)$; and hence $\mathcal{F}_F$ preserves the results with higher extremeness;
- as a consequence of Properties 1 and 2 of the Skorhod representation, if U is a $(0, 1)$-uniform random variable independent of X (randomization effect), $\mathcal{F}_F(X, U)$ is always a $(0, 1)$-uniform random variable, as the following lemma states.

Lemma 2.3. *Let N be a random variable with distribution function F and U be a $(0, 1)$-uniform random variable independent of N. Then the random variable*

$$\mathcal{F}_F(N, U) = (1 - U)F(N^-) + UF(N),$$

is a $(0, 1)$-uniform random variable.

2.2. **Extreme randomized event.** A sample size of n independent random variables $N_1, \ldots, N_n$ is given. Under the null hypothesis we assume $\{F_i^0, i = 1, \ldots, n\}$ to be their cumulative functions. Given a set $U_1, \ldots, U_n$ of independent $(0, 1)$-uniform random variables (randomization effects), we may compute the indexes of extremeness

$$(2) \qquad Y_i(N_i, U_i) = \mathcal{F}_{F_i^0}(N_i, U_i) = (1 - U_i)F_i^0(N_i^-) + U_i F_i^0(N_i), \qquad i = 1, \ldots, n.$$

We observe the *extreme event* $\hat{Y} = \max(Y_1, \ldots, Y_n)$. By definition the extreme event is the greatest realization, once the random variables have been randomized and rescaled.

Remark 2.4. Note that, where F_i^0 is continuous at N_i, then $Y_i(N_i, U_i) = F_i^0(N_i)$: the randomization in (2) affects only the discrete set of outcomes of N_i with positive probability.

2.3. **Monotone models.** We are interested in testing if the extreme event is coming from its alternative distribution. More precisely, we test

$$H_0 : \{F_i = F_i^0, i = 1, \ldots, n\}, \qquad H_1 : \{F_i = F_i^0, i \neq j\}, F_j = F_j^1.$$

The point of the test is the distribution of the maximum of the variables $\{Y_i, i = 1, \ldots, n\}$. Under the null hypothesis, Lemma 2.3 states that $\{Y_i, i = 1, \ldots, n\}$ are independent $(0, 1)$-uniform random variables. Hence, the density of each Y_i is constant if the distribution function of N_i is F_i^0. The following definition states that in monotone models, the highest results are more and more likely in alternative hypothesis compared to the null one. In other words, Y_i under H_0 is smaller than Y_i under H_1 in the likelihood ratio order.

Definition 2.5. We define the model to be *monotone* if, for any $i = 1, \ldots, n$, F_{Y_i} is convex under the alternative hypothesis.

Remark 2.6. Since every convex function on $[0, 1]$ is differentiable almost everywhere with non-decreasing derivative, then a model is monotone if and only if Y_i has a monotone non-decreasing density under the alternative hypothesis.

Theorem 2.7. *All the families that have the* monotone likelihood ratio (MLR) *property belong to monotone models.*

Proof. Fixed $i \in \{1, \ldots, n\}$, let $F^0 = F_i^0$, $F^1 = F_i^1$ and $Y = Y_i$ as in (2). We denote with $N = N^1$ the fact that the true model is the alternative one H_1. We recall that the MLR property imply the absolute continuity of F^1 with respect to F^0 and viceversa. We divide the proof between continuous and discrete models, since the contribution of U in (2) depends on it.

Absolutely continuous case:: in this case, by definition $Y = F^0(N^1)$, where N^1 has density f^1 and F^0 is the cumulative function with density f_0. By the Change of Variables Formula, we get $f_Y(y) = \frac{f^1(x)}{f^0(x)}$, where $y = F^0(x)$. The thesis is a consequence of the MLR property in continuous case, namely $\frac{f^1(x_1)}{f^0(x_1)} \geq \frac{f^1(x_0)}{f^0(x_0)}$, for any $x_1 > x_0$.

Discrete case:: let $p \in (0, 1)$ be fixed. Then there exists x in the range of N such that $p \in [F^0(x^-), F^0(x))$. By partitioning the space in $N^1 < x$, $N^1 > x$ and $N^1 = x$, we obtain:

$$P(\mathcal{F}_{F^0}(N^1, U) \leq y) = F^1(x^-) + \frac{p^1(x)}{p^0(x)}(y - F^0(x^-)),$$

and hence $f_Y(y) = \frac{p^1(x)}{p^0(x)}$.

Since x is monotone in p, the thesis is a consequence of the MLR property in the continuous case, namely $\frac{p^1(x_1)}{p^0(x_1)} \geq \frac{p^1(x_0)}{p^0(x_0)}$, for any $x_1 > x_0$. $\square$

Theorem 2.8. *With the notations given above, a α-level UMP test for testing the extreme event of a monotone model is of the form*

$$\Phi(N_1, \ldots, N_n) = \begin{cases} 1, & \text{if } M > \sqrt[n]{1 - \alpha}; \\ 0, & \text{if } M \leq \sqrt[n]{1 - \alpha}; \\ 1 - \prod_{j \in R} \frac{\sqrt[n]{1 - \alpha} - F_j^0(N_j^-)}{F_j^0(N_j) - F_j^0(N_j^-)}, & \text{otherwise}; \end{cases}$$

where $M = \max(F_1^0(N_1^-), \ldots, F_n^0(N_n^-))$ *and* $R = \{j \colon F_j^0(N_j^-) < \sqrt[n]{1-\alpha} < F_j^0(N_j)\}$, *or, equivalently,*

$$\Phi(N_1, \ldots, N_n, U_1, \ldots, U_n) = \begin{cases} 1, & \text{if } \max(Y_1, \ldots, Y_n) > \sqrt[n]{1-\alpha}; \\ 0, & \text{otherwise.} \end{cases}$$

Proof. The equivalence of the two definitions of Φ is a simple consequence of (2).

To use Neyman-Pearson lemma applied to the extreme event $\hat{Y} = \max(Y_1, \ldots, Y_n)$, we first note that, under H_0, $\{Y_i, i = 1, \ldots, n\}$ are independent $(0,1)$-uniform random variables, and hence $f_{\hat{Y}}^0(x) = nx^{n-1}$ for any $x \in (0,1)$, and moreover,

$$E^0(\Phi(N_1, \ldots, N_n, U_1, \ldots, U_n)) = 1 - (\sqrt[n]{1-\alpha})^n = \alpha.$$

Under the null hypothesis H_0, setting $\tau_j = P(\hat{Y} = Y_j)$, we get

$$P_{H_1}(\hat{Y} \le x) = \sum_j P_{H_1}(\hat{Y} \le x | \hat{Y} = Y_j) P(\hat{Y} = Y_j) = \sum_j x^{n-1} F_{Y_j}^1(x) \tau_j;$$

and hence

$$\frac{f_{\hat{Y}}^1(x)}{f_{\hat{Y}}^0(x)} = \frac{\sum_j (x^{n-1} f_{Y_j}^1(x) + (n-1)x^{n-2} F_{Y_j}^1(x)) \tau_j}{nx^{n-1}} =$$

$$= \sum_j \frac{f_{Y_j}^1(x)}{n} \tau_j + \frac{n-1}{n} \sum_j \frac{\int_0^x f_{Y_j}^1(y)\, dy}{x} \tau_j,$$

and, by definition of monotone model, both the terms are convex combination of monotone non-decreasing functions, the second being the integral mean of a monotone and non-negative function. Therefore, $\frac{f_{\hat{Y}}^1(x)}{f_{\hat{Y}}^0(x)}$ is monotone in x, and the thesis is proved.   □

3. Application to listeriosis

Invasive listeriosis is a rare severe disease with low annual incidence ($< 1/100\,000$). It typically includes long incubation periods (7-60 days), usually resulting in hospitalization (85% to 90%) and has a high fatality rate (20-50%). Persons with specific immunocompromising conditions, pregnant women and newborns appear to be particularly susceptible to invasive listeriosis, and most reported cases occur in these specific risk groups. The identification of outbreaks is difficult because of the long incubation period of the invasive forms (even several weeks) and of the probable large number of asymptomatic or paucisymptomatic infections even in people exposed to the same infection vehicle [1, 8].

3.1. **The data: listeriosis in Lombardy.** The data we have collected and analyzed consist of detailed information about the persons who have contracted listeriosis in Lombardy between years 2005 and 2011. This region accounts for 16% of the Italian population ($\sim 10\,000\,000$ inhabitants), but for 55% of the notified listeriosis cases in the entire country. These cases have been identified through a laboratory-based surveillance system enhanced in the latest years [7]. We have focused our attention on some variables, such as the date of identification of the disease and the province of residence of the patient, so that we are able to analyze the spatiotemporal location of cases. We notice that the data increase in the latest years; this fact is due to an improvement in the transmission of information: since 2008 the process has become more systematic. Hence we have decided to limit our statistical tests to the cases individuated from 2008 on.

Another important variable of the data is the molecular type of each *L.monocytogenes* isolate, which has been identified through a laboratory analysis based on MLST (MultiLocus Sequence Typing) [9]. Thanks to this laboratory work, it has been possible to concentrate our statistical study on a single sequence type (ST). In fact possible confirmations of the presence of epidemics would make sense only if the cases refer to a unique type [10].

The statistic tests we have performed consider only the data referred to isolates belonging to ST38, which is the most numerous one. In fact the database contains information about 180 cases, of which 139 are notified since 2008; since this year there are 36 strains belonging to ST38, whereas the second most numerous is ST1, with only 18 cases.

TABLE 1. Number of cases $n_{i,j}$ in each province and year

		BG	BS	CO	CR	LC	LO	MB	MI	PV	VA
					Province						
Year	2008	0	0	0	0	0	0	0	0	0	1
	2009	2	1	0	1	1	1	1	3	0	0
	2010	8	1	1	0	0	0	0	4	0	1
	2011	4	0	0	0	0	0	0	4	1	0

3.2. **Identification of epidemics in space and time.** We ask ourselves if there is evidence of epidemics in our data. We test the null hypothesis of absence of epidemics (H_0) against the alternative hypothesis of presence of epidemics (H_1). In particular, if in a certain spatiotemporal region an epidemic occurs, the number of detected cases increases.

Let $N_{i,j}$ be the number of detected cases in region i at time j; we cannot use the statistics $\max N_{i,j}$ because these random variables are not identically distributed. In fact under the null hypothesis we suppose that the number of detected cases is distributed as a Poisson variable with intensity $\lambda \cdot p_{i,j}$ depending on the population of regions i at times j, and hence we test this hypothesis with the UMP test given in Theorem 2.8. We use a conservative estimate of λ ($\hat{\lambda} \approx 9.703 \cdot 10^{-7}$).

Each case belonging to ST38 has been provided with a spatial variable defining the province of residence of the patient. We point out that the provinces of Sondrio and Mantova have not communicated any case of listeriosis and so they have been excluded from the analysis: R is then a set describing Lombardy without the territories of these two provinces. Besides, we have to specify that province Monza e Brianza was born during the considered period of time, so we have decided to attribute label "MB" to any patient living in places belonging to this province in 2011, even if the case of listeriosis was detected before the birth of the province. The time interval T has been partitioned through 4 years: $2008, \ldots, 2011$. Table 1 shows the values of $n_{i,j}$ for any $1 \le i \le 10, 1 \le j \le 4$.

The values of $p_{i,j}$ are given by ISTAT [6]; for each year we have chosen the data referring to December 31st. As concerns years 2008 and 2009, we have chosen as population of Monza e Brianza the same population of January 1st 2010, and this value has been subtracted to the population of Milano.

We define
$$Y_{i,j} := \mathcal{F}_{F^0_{i,j}}(N_{i,j}, U_{i,j}) = (1 - U_{i,j})F_{F^0_{i,j}}(N^-_{i,j}) + U_{i,j}F_{F^0_{i,j}}(N_{i,j})$$
for any $1 \le i \le 10, 1 \le j \le 4$. By Theorem 2.8, we focus on the statistics $M := \max_{i,j} Y_{i,j}$. To find the p-value of our test, our aim is to calculate an upper and lower bound in terms of the observed $F^0_{i,j}(N_{i,j})$ for
$$P(\max_{i,j} Y_{i,j} > \max_{i,j} \mathcal{F}_{F^0_{i,j}}(n_{i,j}, u_{i,j})) = P(M > m).$$
If this probability is lower than the confidence level of our test, then we can reject the null hypothesis.

By definition of $\mathcal{F}_F$, and since $N_{i,j}$ is integer-valued ($N^-_{i,j} = N_{i,j} - 1$), we trivially have
$$F_{F^0_{i,j}}(N_{i,j} - 1) \le Y_{i,j} \le F_{F^0_{i,j}}(N_{i,j}), \forall i, j$$
and hence
(3) $$\underline{M} := \max_{i,j} F_{F^0_{i,j}}(N_{i,j} - 1) \le M \le \max_{i,j} F_{F^0_{i,j}}(N_{i,j}) =: \overline{M}.$$
If we define
$$\underline{m} := \max_{i,j} F_{F^0_{i,j}}(n_{i,j} - 1), \qquad \overline{m} = \max_{i,j} F_{F^0_{i,j}}(n_{i,j}).$$
then, by (3), under H_0 we get
$$1 - \overline{m}^{i \cdot j} = P(M > \overline{m}) \le P(M > m) \le P(M > \underline{m}) = 1 - \underline{m}^{i \cdot j},$$
i.e., $1 - \overline{m}^{i \cdot j} \le p \le 1 - \underline{m}^{i \cdot j}$, where p is the p-value of our UMP test.

If $1 - \underline{m}^{i \cdot j}$ is smaller than our significance level, we can reject the null hypothesis and state that an epidemic occurred ($\Phi = 1$ in Theorem 2.8); if $1 - \overline{m}^{i \cdot j}$ is greater than the significance level, the null hypothesis cannot be rejected ($\Phi = 0$ in Theorem 2.8); if only the first value is smaller than the significance level, a randomized

test has to be carried on ($0 < \Phi < 1$ in Theorem 2.8). With our sample we find that $1 - \overline{m}^{i \cdot j} = 0.00006$ and $1 - \underline{m}^{i \cdot j} = 0.00053$. These values force us to reject the null hypothesis, and hence the number of cases of listeriosis with isolates belonging to ST38 detected in the province and year corresponding to the maximum is significantly higher than expected under non-epidemic conditions. Hence we can statistically conclude that an epidemic has occurred in Bergamo in 2010.

We have also continued the analysis by asking ourselves whether in some other provinces and years we could find some epidemics. To this aim we have repeated the spatiotemporal test excluding from the sample the datum that refers to Bergamo cases in 2010. This analysis has not given any result, because in no case we have obtained sufficiently small values to reject the null hypothesis. This conclusion does not mean that we exclude the possibility of existence of other epidemics, but just that further analyses have to be carried on.

REFERENCES

[1] Bortolussi R. Listeriosis: a primer. *CMAJ* 2008; **179** (8): 795-7.
[2] Brown EN, Barbieri R, Ventura V, et al. The time-rescaling theorem and its application to neural spike train data analysis. *Neural computation* 2002; **14**(2): 325-346.
[3] Cox DR and Isham V. *Point Processes*. London: Chapman & Hall, 1980.
[4] Cressie NAC. *Statistics for Spatial Data*. New York: John Wiley & Sons, Wiley Series in Probability and Mathematical Statistics: Applied Probability and Statistics, 1993.
[5] Fromont M, Laurent B and Reynaud-Bouret P. Adaptive tests of homogeneity for a Poisson process. *Ann Inst Henri Poincaré Probab Stat* 2011; **47**(1): 176-213.
[6] ISTAT - Direzione centrale per le statistiche e le indagini sulle istituzioni sociali. Demographic tables, http://demo.istat.it/archivio.html.
[7] Mammina C, Parisi A, Guaita A, et al. Enhanced surveillance of invasive listeriosis in the Lombardy region, Italy, in the years 2006-2010 reveals major clones and an increase in serotype 1/2a. *BMC Infect Dis* 2013; **13**: 152.
[8] Ramaswamy V, Cresence VM, Rejitha JS, et al. Listeria - review of epidemiology and pathogenesis.*J Microbiol Immunol Infect* 2007; **40** (1): 4-13.
[9] Salcedo C, Arreaza L, Alcalá B, et al. Development of a multilocus sequence typing method for analysis of Listeria monocytogenes clones. *J Clin Microbiol* 2003; **41** (2): 757-62.
[10] Sauders BD, Fortes ED, Morse DL, et al. Molecular subtyping to detect human listeriosis clusters. *Emerg Infect Dis* 2003; **9** (6): 672-80.
[11] Snow J. *On the Mode of Communication of Cholera*. London: John Churchill, 1855.
[12] Waller LA, Gotway CA. *Applied Spatial Statistics for Public Health Data*. Hoboken: Wiley-Interscience, Wiley Series in Probability and Statistics, 2004.
[13] Williams D. *Probability with Martingales*. Cambride: Cambridge University Press, 1997.

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