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Nonparametric predictive pairwise comparison with competing risks

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ABSTRACT

In reliability, failure data often correspond to competing risks, where several failure modes can cause a unit to fail. This paper presents nonparametric predictive inference (NPI) for pairwise comparison with competing risks data, assuming that the failure modes are independent. These failure modes could be the same or different among the two groups, and these can be both observed and unobserved failure modes. NPI is a statistical approach based on few assumptions, with inferences strongly based on data and with uncertainty quantified via lower and upper probabilities. The focus is on the lower and upper probabilities for the event that the lifetime of a future unit from one group, say Y, is greater than the lifetime of a future unit from the second group, say X. The paper also shows how the two groups can be compared based on particular failure mode(s), and the comparison of the two groups when some of the competing risks are combined is discussed.

1. Introduction

In reliability, failure data often correspond to competing risks [3,28,29], where several failure modes can cause a unit to fail, and where failure occurs due to the first failure event caused by one of the failure modes. Throughout this paper, it is assumed that each unit cannot fail more than once and it is not used any further once it has failed, and that a failure is caused by a single failure mode which, upon observing a failure, is known with certainty. Also we assume throughout that the failure modes are independent, inclusion of assumed dependence would be an interesting topic for future research, but cannot be learned about from the data as considered here, as shown by Tsiatis [31].

Comparison of two groups or treatments with competing risks is a common problem in practice. For example in medical applications, one may want to compare two treatments with multiple competing risks [23], or in reliability one may want to study the effect of the brand of air-conditioning systems which can fail either due to leaks of refrigerant or wear of drive belts [27]. One may wish to compare the two groups either by taking into account all the competing risks or just considering particular competing risks. For example, when studying occurrence of cancer among men and women where cervical cancer (prostate cancer) can cause only women (men) to die and lung cancer can cause both women and men to die, so cervical and prostate cancer each are risks to only one group while lung cancer affects both groups.

In this paper we introduce nonparametric predictive inference (NPI) for comparison of two groups with competing risks. NPI is a statistical method based on Hill's assumption $A_{(n)}$ [16], which gives a direct conditional probability for a future observable random quantity, conditional on observed values of related random quantities [1,5]. $A_{(n)}$ does not assume anything else, and can be interpreted as a post-data assumption related to exchangeability [15], a detailed discussion of $A_{(n)}$ is provided by Hill [17]. Inferences based on $A_{(n)}$ are predictive and nonparametric, and can be considered suitable if there is hardly any knowledge about the random quantity of interest, other than the n observations, or if one does not want to use such information, e.g. to study effects of additional assumptions underlying other statistical methods. $A_{(n)}$ is not sufficient to derive precise probabilities for many events of interest, but it provides bounds for probabilities via the 'fundamental theorem of probability' [15], which are lower and upper probabilities in interval probability theory [1,33–35].

In reliability and survival analysis, data on event times are often affected by right-censoring, where for a specific unit or individual it is only known that the event has not yet taken place at a specific time. Coolen and Yan [10] presented a generalization of $A_{(n)}$, called 'right-censoring $A_{(n)}$' or rc-$A_{(n)}$, which is suitable for right-censored data. In comparison to $A_{(n)}$, rc-$A_{(n)}$ uses the additional assumption that, at the moment of censoring, the residual lifetime of a right-censored unit is exchangeable with the residual lifetimes of all other units that have not yet failed or been censored, see Coolen and Yan [10] for further details of rc-$A_{(n)}$. To formulate the required form of rc-$A_{(n)}$ the concept of M-functions is used [10]. An M-function provides a partial specification of a probability distribution and is mathematically equivalent to Shafer's 'basic probability assignments' [30]. The use of lower and

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upper probabilities to quantify uncertainty has gained increasing attention during the last decade, short and detailed overviews of theories and applications in reliability, together called 'imprecise reliability', are presented by Coolen and Utkin [32,8]. Also, Coolen et al. [7] introduced NPI to some reliability applications, including upper and lower survival functions for the next future observation, illustrated with an application with competing risks data. They illustrated the upper and lower marginal survival functions, so each restricted to a single failure mode. Maturi et al. [26] presented NPI for competing risks data, in particular addressing the question due to which of the competing risks the next item will fail. Coolen-Maturi and Coolen [11] considered the effect of including unobserved, re-defined, unknown or removed competing risks. Recently, Coolen-Maturi and Coolen [14] showed how NPI can be used to learn about specific competing risks by combining information from multiple sources.

Coolen and Yan [9] presented NPI for comparison of two groups of lifetime data including right-censored observations. Coolen-Maturi et al. [13] extended this for comparing more than two groups in order to select the best group, in terms of largest lifetime. Coolen-Maturi et al. [12] considered selection of subsets of the groups according to several criteria. They allowed early termination of the experiment in order to save time and cost, which effectively means that all units in all groups that have not yet failed are right-censored at the time the experiment is ended. Recently, Janurová and Briš [18] applied NPI for mortality analysis, including comparison of two surgery techniques.

Section 2 of this paper presents a brief overview of NPI for the competing risks problem. NPI for pairwise comparison is introduced in Section 3, presenting the NPI lower and upper probabilities for the event that the lifetime of the next future unit from one group is greater than the lifetime of the next future unit from the second group, with different independent competing risks per group. Comparison of two groups based on particular failure mode(s) and after re-defining the competing risks are presented in Sections 4 and 5. Further results related to the concept of 'effect size' are given in Section 6. Our NPI method is illustrated via an example in Section 7. Some concluding remarks are given in Section 8. The paper finishes with appendices including the proofs of main results.

2. NPI for one group with competing risks

In this section, a brief overview of NPI for one group with competing risks is given following the definitions and notations introduced by Maturi et al. [26]. For group X, let us consider the problem of competing risks with J distinct failure modes that can cause a unit to fail. It is assumed that the unit fails due to the first occurrence of a failure mode, and that the unit is withdrawn from further use and observation at that moment. It is further assumed that such failure observations are obtained for n units, and that the failure mode causing a failure is known with certainty. In the case where the unit did not fail it is right-censored.

Let the failure time of a future unit be denoted by X_{n+1}, and let the corresponding notation for the failure time including indication of the actual failure mode, say failure mode j ($j=1,\ldots,J$), be $X_{j,n+1}$. As the different failure modes are assumed to occur independently, the competing risk data per failure mode consist of a number of observed failure times for failures caused by the specific failure mode considered, and right-censoring times for failures caused by other failure modes. It should be emphasized that it is not assumed that each unit considered must actually fail, if a unit does not fail then there will be a right-censored observation recorded for this unit for each failure mode, as it is assumed that the unit will then be withdrawn from the study, or the study ends, at some known time. Hence rc-$A_{(n)}$ can be applied per failure mode j, for inference on $X_{j,n+1}$. Let the number of failures caused by failure mode j be u_j, $x_{j,1}<x_{j,2}<\cdots,<x_{j,u_j}$, and let $n-u_j$ be the number of the right-censored observations, $c_{j,1}<c_{j,2}<\cdots<c_{j,n-u_j}$, corresponding to failure mode j. For notational convenience, let $x_{j,0}=0$ and $x_{j,u_j+1}=\infty$. Suppose further that there are s_{j,i_j} right-censored observations in the interval (x_{j,i_j},x_{j,i_j+1}), denoted by $c^{i_j}_{j,1}<c^{i_j}_{j,2}<\cdots<c^{i_j}_{j,s_{j,i_j}}$, so $\sum_{i_j=0}^{u_j}s_{j,i_j}=n-u_j$. The random quantity representing the failure time of the next unit, with all J failure modes considered, is $X_{n+1}=\min_{1\le j\le J}X_{j,n+1}$. The NPI M-functions for $X_{j,n+1}$ ($j=1,\ldots,J$) are [26]

$$M^j(t^{i_j}_{j,i^*_j},x_{j,i_j+1})=\frac{1}{n+1}(\tilde{n}_{t^{i_j}_{j,i^*_j}})^{\delta^{i_j}_{i^*_j}-1}\prod_{\{r:c_{j,r}<t^{i_j}_{j,i^*_j}\}}\frac{\tilde{n}_{c_{j,r}}+1}{\tilde{n}_{c_{j,r}}} \tag{1}$$

where $i_j=0,1,\ldots,u_j$, $i^*_j=0,1,\ldots,s_{j,i_j}$ and

$$\delta^{i_j}_{i^*_j}=\begin{cases}1 & \text{if } i^*_j=0 \qquad \text{i.e. } t^{i_j}_{j,0}=x_{j,i_j} \quad \text{(failure time or time 0)}\\ 0 & \text{if } i^*_j=1,\ldots,s_{j,i_j} \quad \text{i.e. } t^{i_j}_{j,i^*_j}=c^{i_j}_{j,i^*_j} \quad \text{(censoring time)}\end{cases}$$

where $\tilde{n}_{c_r}$ and $\tilde{n}_{t^{i_j}_{j,i^*_j}}$ are the numbers of units in the risk set just prior to times c_r and $t^{i_j}_{j,i^*_j}$, respectively. The corresponding NPI probabilities are

$$P^j(x_{j,i_j},x_{j,i_j+1})=\frac{1}{n+1}\prod_{\{r:c_{j,r}<x_{j,i_j+1}\}}\frac{\tilde{n}_{c_{j,r}}+1}{\tilde{n}_{c_{j,r}}} \tag{2}$$

where x_{j,i_j} and x_{j,i_j+1} are two consecutive observed failure times caused by failure mode j (and $x_{j,0}=0$, $x_{j,u_j+1}=\infty$).

In addition to notation introduced above, let $t^{i_j}_{j,s_{j,i_j}+1}=t^{i_j+1}_{j,0}=x_{j,i_j+1}$ for $i_j=0,1,\ldots,u_j-1$. For a given failure mode j ($j=1,\ldots J$), the NPI lower survival function [26] is, for $t\in[t^{i_j}_{j,a_j},t^{i_j}_{j,a_j+1})$ with $i_j=0,1,\ldots,u_j$ and $a_j=0,1,\ldots,s_{j,i_j}$,

$$\underline{S}_{X_{j,n+1}}(t)=\frac{1}{n+1}\tilde{n}_{t^{i_j}_{j,a_j+1}}\prod_{\{r:c_{j,r}<t^{i_j}_{j,a_j+1}\}}\frac{\tilde{n}_{c_{j,r}}+1}{\tilde{n}_{c_{j,r}}} \tag{3}$$

and the corresponding NPI upper survival function [26] is, for $t\in[x_{i_j},x_{i_j+1})$ with $i_j=0,1,\ldots,u_j$,

$$\overline{S}_{X_{j,n+1}}(t)=\frac{1}{n+1}\tilde{n}_{x_{j,i_j}}\prod_{\{r:c_{j,r}<x_{j,i_j}\}}\frac{\tilde{n}_{c_{j,r}}+1}{\tilde{n}_{c_{j,r}}} \tag{4}$$

Then the lower and upper survival functions for X_{n+1} ($X_{n+1}=\min_{1\le j\le J}X_{j,n+1}$) are given by

$$\underline{S}^{JCR}_{X_{n+1}}(t)=\prod_{j=1}^{J}\underline{S}_{X_{j,n+1}}(t) \quad \text{and} \quad \overline{S}^{JCR}_{X_{n+1}}(t)=\prod_{j=1}^{J}\overline{S}_{X_{j,n+1}}(t) \tag{5}$$

In fact there is a relationship between the above upper survival function in (5) and the upper survival function when all the different failure modes are ignored, that is $\overline{S}^{JCR}_{X_{n+1}}(t)=\overline{S}_{X_{n+1}}(t)$, for more details we refer to Maturi et al. [26].

It is interesting to mention that these NPI lower and upper survival functions bound the well-known Kaplan–Meier estimator [20], which is the nonparametric maximum likelihood estimator of the cause-specific survivor-like functions [19,3], for more details we refer to [10,13].

3. Pairwise comparison with competing risks

Let X and Y be two independent groups (e.g. treatments) with competing risks $j=1,\ldots,J$ and $l=1,\ldots,L$, respectively. These competing risks could be the same (e.g. the lung cancer may affect both men and