Designing clinical trials based on quantiles with right-censored data
Master 2 internship in Statistics

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Context

In clinical studies it is common that data suffer from right-censoring due to dropout (some patients might leave the study before its end) or end of follow-up (some patients will never develop the outcome during the follow-up). Taking into account right-censoring is a statistical challenge and the analysis of such data needs dedicated tools. Classical methods include the Kaplan-Meier estimator to estimate the survival function in a non-parametric way and the Cox model to model the hazard function given a set covariates. See for instance Kalbfleisch & Prentice (2002) for a thorough presentation of the subject.

In Randomized Clinical Trials (RCT), standard methods already exist to determine the sample size when the estimand is a hazard ratio (typically the hazard ratio for comparing the effect of two treatments) based on either the log-rank test (see Schoenfeld, 1981) or the Cox model (see Schoenfeld, 1983). However, in cancer studies, some treatments may have a late effect and the proportional hazard assumption imposed by the Cox model is no longer verified. This is the case for instance when comparing the effect of immunotherapy to chemotherapy and it was previously showed that the quantile regression was relevant for estimating the benefit of immunotherapy as compared to chemotherapy on a range of quantiles (see for instance Mboup et al., 2021). Therefore, the difference in quantile of failure times is an estimand of major interest for the following two reasons:

(i) it allows for varying treatment effects (across quantiles) which corresponds to the heterogeneity of treatment effect

(ii) quantile regression can accommodate for non-proportional hazards (related to the late effects of immunotherapy).

Goal of the internship

The main aim of the internship is to review the existing literature on statistical tests that have been developed to test the equality of a given quantile between two independent groups from censored data. Among others, the current proposals include the works from Brookmeyer & Crowley (1982), Rahbar et al. (2012), and Ahn & Mendolia (2014). However, all those proposed approaches exhibit a small power in simulation experiments which will impose to use a very large sample size in a RCT in order to use those tests at a high-power value. Also, in the aforementioned papers the authors did not consider heavy tailed distributions. Since a major goal in cancer studies is to detect long-term treatment effect, it is therefore important to assess the performance of those tests in this setting. Finally, a promising method was also developed in Kosorok (1999) which has not yet been compared to the other proposals. Therefore the intern will study more deeply the performances of the existing approaches through extensive simulations, including scenarios with heavy tailed distributions.

There are several possible extensions to this work and for this reason, the work performed during the internship is intended to be continued during a PhD thesis. In particular, the selection of a relevant quantile is a big challenge in practice. It might therefore be of interest to select few quantiles of interest and develop a method that allows for interim analysis in a clinical trial. Also, the existing approaches do not seem to be able to account for clustered data except the one in Ahn & Mendolia (2014). The development of such method would of great interest in practice in order to take into account data from several clinical trials.

Required profile

We are seeking candidates with a strong mathematical background and a keen interest in medical applications. Skills in the R software are also required.

Practical details

The internship will take place within the 2 partner teams of MAP5 (O. Bouaziz, Université de Paris) and the Statistics team for precision medicine of Inserm U900 unit (A. Latouche, Cnam and Institut Curie).

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