Non-linear Bayesian joint models to estimate direct and indirect treatment effects in oncology clinical trials

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1 Abstract

In oncology clinical trials involving patients with solid tumors, tumor size, described as the sum of the longest diameters (SLD), is measured at regular intervals and can inform disease progression and treatment-related tumor shrinkage. The SLD time trends are typically modeled using nonlinear mixed effects models called tumor growth inhibition (TGI) models. Fitting these models involves estimating the shrinkage rate constant (ks) and the growth rate constant (kg) determining the individual trajectory of SLD observations over time. The association between TGI and survival has been established with joint modeling approaches. To connect the longitudinal and survival parts of the joint model (JM), we explore different link functions (such as the current value of SLD or the time to growth) [Kerioui et al., 2022]. In this project, we focus on the causal effects of a therapeutic intervention on survival mediated by a biomarker (SLD). Le Coënt et al. [2022] and Zheng and Liu [2022] suggested a causal inference framework for the quantification of the natural direct and indirect effects and the resulting estimation of the proportion of the treatment effects (PTE) conveyed by the biomarker. Hence, we provide an estimate of PTE in the context of a TGI-OS JM applied to a real clinical trial in patients with solid tumor treated with immunotherapy. Transposing Zheng et al. framework in a Bayesian setting, we estimate the posterior distribution of the joint model parameters via

Markov chain Monte Carlo. We predict the SLD values and survival outcome based on the posterior samples [Li et al., 2023]. We evaluate the models' goodness of fit and predictive accuracy, we investigate the sensitivity of our results to different priors. Stan is used for the implementation of the joint model. The code will be shared via GitHub.

References

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