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CALCULATING EXPECTED SURVIVAL FROM HIGH-DIMENSIONAL COX MODELS WITH TREATMENT-BY-BIOMARKER INTERACTIONS IN RANDOMIZED CLINICAL TRIALS

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Abstract:

Calculating expected survival from high-dimensional Cox models with treatment-by-biomarker interactions in randomized clinical trials

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Background. Thanks to the advances in genomics and targeted treatments, an increasing interest is being devoted to develop prediction models with biomarkers or gene signatures to predict how likely patients will benefit from particular treatments. Despite the methodological framework for the development and validation of gene signatures in a high-dimensional setting is quite well established, no clear guidance exists yet on how to estimate expected survival probabilities. We propose a unified framework for developing and validating a high-dimensional Cox model integrating clinical and genomic variables in a randomized clinical trial to estimate the expected absolute treatment effect according to signature values, and to estimate expected survival probabilities for patients with associated confidence intervals.
Methods. Based on a parsimonious selection model in a penalized (lasso or adaptive lasso) high-dimensional Cox model, we investigated several strategies to: estimate the individual survival probabilities at a given timepoint (using single or double cross-validation); construct confidence intervals thereof (analytical or bootstrap); and visualize them graphically (pointwise or spline). We compared these strategies through a simulation study covering null and alternative scenarios and we evaluated them by prediction criteria. We applied the strategies to a large randomized controlled phase III trial in 1574 early breast patients that evaluated the effect of adding trastuzumab to chemotherapy and for which the expression of 462 genes were measured.
Results. Simulation results suggest that a penalized regression model estimated using adaptive lasso estimates the survival probability of new patients with low bias and standard error, and that bootstrapped confidence intervals have empirical coverage probability close to the nominal level across very different scenarios. The double cross-validation allows mimicking internally the prediction performance in absence of external validation data. We also propose a visual representation of the expected survival probabilities using splines. In the breast cancer trial, we identified a prediction model with 4 clinical covariates, the main effect of 98 biomarkers and 24 biomarker-by-treatment interactions. This illustration also highlights the high variability of the expected survival probabilities, with very large confidence intervals.
Conclusion. We propose a unified framework for developing and validating a gene signature in a high-dimensional survival setting in order to calculate expected survival probabilities at a given horizon for future patients, and to visualize the survival predictions. Based on our simulations, the adaptive lasso penalty can be useful to identify a signature and then, to accurately estimate the expected survival probability of future patients.