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Recursive partitioning method on survival outcomes for personalized medicine

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Background: A general method to create adjusted recursive partitioning (tree-based) model on survival outcomes is developed. Prognostic survival trees have historically been used to automatically uncover complicated GxG and GxE interactions. However scientists often want to uncover this structure while adjusting for confounding factors that are not of direct interest. Interaction survival trees can automatically identify the best treatment choice for patients and are a promising model to enable personalized medicine, but simulations to assess their performance on the high dimensional data found in personalized medicine have not been conducted.

Methods: We develop a general framework to adjust for confounding factors in prognostic and interaction survival trees. These factors are numerous in practice and can include age, gender, study site in a randomized multicenter clinical trial, and the principal components of ancestry difference to control for population stratification in genetic studies.

Results: Extensive simulations show the performance of our methods under various true tree structures. Our methods are shown to be well controlled under the null with only a 1.4-8.4% chance to build a spurious tree when none should be made. Under the alternative, the power to build the correct tree is robust to the large dimensional covariate space found in personalized medicine, dropping less than 2% when going from 10 to 1,000 potential splits. We applied our adjusted interaction tree on a randomized clinical trial study on head and neck cancer patients. The novel method successfully identify subgroups of head and neck cancer patients that respond positively to having antioxidant vitamins added to their treatment regime. These subgroups are based on the patients' genetic signature and are adjusted for population stratification.

Conclusions: We have demonstrated that our adjusted survival tree method can create prognostic and interaction survival trees that are adjusted for confounders not of direct interest. We have also shown that our adjusted interaction survival trees behave well under the high dimensional covariate space found in personalized medicine.

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