A permutation test approach to provide exact inference for incremental gain from nested regression models

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Background: Assessment of the incremental gain and impact of a novel marker to better predict disease risk is an ongoing quest in many clinical disciplines. For binary and time-to-event outcomes, two popular metrics used to assess incremental gain are difference in the C-index or the Area under the ROC curve (dAUC) and Integrated Discrimination Improvement (IDI). However, inference for these two measures are complex for their non-standard distributions, especially, while comparing nested models that are build and evaluated on the same dataset.

Methods and results: We propose an easy-to-implement permutation test for dAUC and IDI to provide exact inference for the incremental gain. Via extensive simulation studies, we show that for small to moderate sample sizes, the type I error rate and power for dAUC and IDI are comparable the type I error rate and power for the likelihood ratio test and Wald test for comparing nested logistic and Cox proportional hazards models. In addition, we also assess the performance of the permutation test for classification trees. We demonstrate the approach in a real dataset where the incremental value of time-to-first cigarette to select ever-smokers for lung cancer was assessed.

Conclusions: We show that permutation test can be used effectively for assessing incremental value of a marker based on nested models. Our work provides an viable solution for assessment of incremental gain for many scientific and clinical scenarios.

Keywords
Incremental value; AUC; IDI; Permutation test; Logistic regression; Cox Proportional Hazards Model