Statistica Sinica **33** (2023), 1-22
doi:https://doi.org/10.5705/ss.202021.0020

INTERVAL ESTIMATION FOR OPERATING CHARACTERISTIC OF CONTINUOUS BIOMARKERS WITH CONTROLLED SENSITIVITY OR SPECIFICITY

Yijian Huang[1], Isaac Parakati[2], Dattatraya H. Patil[1] and Martin G. Sanda[1]

[1]*Emory University and*
[2]*Ann & Robert H. Lurie Children's Hospital of Chicago*

Abstract: The receiver operating characteristic (ROC) curve provides a comprehensive performance assessment of a continuous biomarker over the full threshold spectrum. Nevertheless, a medical test often dictates operating at a certain high level of sensitivity or specificity. A diagnostic accuracy metric directly targeting clinical utility is specificity at the controlled sensitivity level, or vice versa. While the empirical point estimation is readily adopted in practice, the nonparametric interval estimation is difficult because the variance involves density functions, owing to the estimated threshold. In addition, even with a fixed threshold, many standard confidence intervals for the binomial proportion, including the Wald interval, can exhibit erratic behaviors. This study is motivated by the superior performance of the score interval for binomial proportion, and we propose a novel extension for the biomarker problem. We also develop an exact bootstrap procedure and establish the consistency of the bootstrap variance estimator. Both single-biomarker evaluation and two-biomarker comparison are investigated. Extensive simulation studies demonstrated competitive performance of our proposals. An application to aggressive prostate cancer diagnosis is also provided.

Key words and phrases: Diagnostic test, exact bootstrap, score confidence interval, sensitivity at controlled specificity, specificity at controlled sensitivity.

1. Introduction

Fueled by rapid recent advances in the scientific knowledge of molecular biology and high-throughput omics technologies, a large number of candidate biomarkers are being identified for disease diagnosis and prognosis, and the prediction of response to specific therapeutic interventions. Biomarker evaluation and comparison has become especially important for their validation and further clinical translation to ultimately improve and advance clinical practice (e.g., Tzoulaki, Siontis and Ioannidis (2011); Ioannidis and Panagiotou (2011)). Many

Corresponding author: Yijian Huang, Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA 30322, USA. E-mail: yhuang5@emory.edu.