ARTICLE IN PRESS

Computational Statistics and Data Analysis ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Computational Statistics and Data Analysis

journal homepage: www.elsevier.com/locate/csda

Joint inference about sensitivity and specificity at the optimal cut-off point associated with Youden index

Jingjing Yin, Lili Tian *

Department of Biostatistics, University at Buffalo, Buffalo, NY 14214, USA

ARTICLE INFO

Article history:
Received 18 March 2013
Received in revised form 29 January 2014
Accepted 30 January 2014
Available online xxxx

Keywords:
Sensitivity
Specificity
Youden index
Optimal cut-off point
Confidence region
Generalized inference
Smooth bootstrap

ABSTRACT

In diagnostic studies, both sensitivity and specificity depend on cut-off point and they are well-known measures for diagnostic accuracy. The diagnostic cut-off point is mostly unknown and needs to be determined by some optimization criteria out of which the one based on the Youden index has been widely adopted in practice. The estimation of the optimal cut-off point associated with Youden index depends on both diseased and healthy samples, henceforth, sensitivity and specificity at the estimated cut-off point are correlated. Therefore, it is desirable to make joint inference on both sensitivity and specificity at the estimated cut-off point. Several parametric and non-parametric approaches are proposed to estimate the joint confidence region of sensitivity and specificity at the cut-off point determined by the Youden index. A real data set is analyzed using the proposed approaches.

1. Introduction

For the purpose of making a diagnosis, i.e., classifying a subject as either diseased or healthy, a diagnostic cut-off point c is needed. Let Y_1 and Y_2 denote the marker values for diseased and healthy subjects, respectively. Without loss of generality, larger marker values indicate greater severity of the disease. Sensitivity is the probability of a diseased subject being diagnosed as diseased (i.e. $P(Y_1 > c)$) and specificity is the probability of a healthy subject being diagnosed as non-diseased (i.e. $P(Y_2 \leq c)$). The Receiver Operating Characteristic (ROC) curve, a graph of true positive rate (sensitivity) versus false positive rate (1-specificity), is very useful in diagnostic studies for the purpose of evaluating the discriminatory ability of biomarkers or diagnostic tests. Extensive statistical research has been done in this field. For excellent reviews of statistical methods involving ROC curves; see Shapiro (1999), Zhou et al. (2009), Pepe (2004) and Zou et al. (2010).

In practical settings, the value of the cut-off point c is usually unknown and needs to be determined. There exist several estimation methods for the cut-off point c. For example, c can be determined by the northwest corner method (Karve et al., 2009) (i.e., by minimizing the distance of the ROC curve to the point (0, 1) on the ROC plot), by Youden index (defined as $J = \max_c\{\text{Sensitivity}(c) + \text{Specificity}(c) - 1\}$ Youden, 1950) Verniquet and Kakel (2012), Gnjidic et al. (2012), Pan et al. (2012) and many other methods (Zou et al., 2013; Sokolova et al., 2006). Among all the existing cut-off point estimation methods, the one based on Youden index has been most widely used in practice due to the fact that it is a direct measure of the diagnostic accuracy at the optimal cut-off point, i.e., the maximum of overall correct classification rate a marker can achieve. The optimal cut-off point is determined at where the maximum of Sensitivity(c) + Specificity(c) is achieved (Youden, 1950). It is obvious that markers with the same Youden index can have very different sensitivity and specificity at the optimal cut-off point. For example, in Fig. 1, all three markers have the same Youden index at the respective optimal

* Correspondence to: Department of Biostatistics, 717 Kimball Tower, 3435 Main St. Bldg. 26 Buffalo, NY 14214-3000, USA. Tel.: +1 716 829 2715.
E-mail address: ltian@buffalo.edu (L. Tian).

http://dx.doi.org/10.1016/j.csda.2014.01.021
0167-9473/

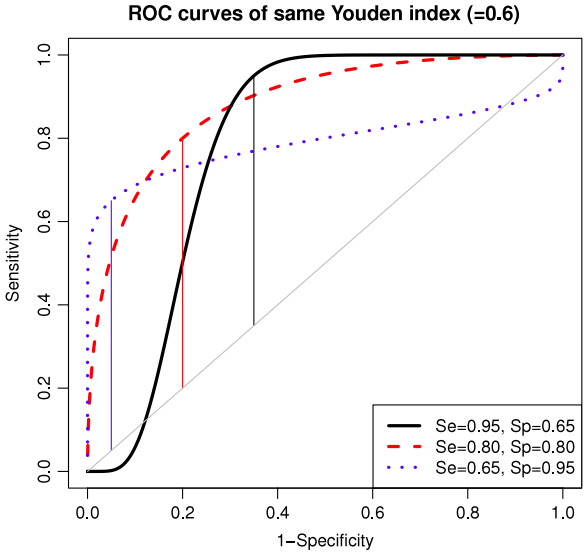

Fig. 1. Examples of *ROC* curves of same Youden index and different sensitivity and specificity at optimal cut-off point. The vertical distance between the *ROC* curve and the diagonal line represents the value of the Youden index.

cut-off points, however, their corresponding sensitivity and specificity differ greatly. Therefore, at the optimal cut-off point, it is important to consider both sensitivity and specificity simultaneously.

Since the optimal cut-off point is estimated based on data of both diseased and healthy samples, sensitivity and specificity at the estimated cut-off point are correlated. Therefore, joint inference of the correlated sensitivity and specificity provides a more comprehensive view than the marginal/individual confidence intervals. Hence, it is desirable to estimate the joint confidence region of sensitivity and specificity at the estimated optimal cut-off point.

There exist some research papers about joint inference methods in the *ROC* analysis. Yin and Tian (2013) proposed several parametric and non-parametric joint confidence regions of *AUC* and Youden index. Adimari and Chiogna (2010) applied empirical likelihood method to estimate the joint confidence region for any pair of (sensitivity, specificity, cut-off point) given the third value is fixed, hence it can be used to make joint inference of sensitivity and specificity at any known or selected cut-off point. However, usually in practice, the cut-off point is unknown and needs to be estimated.

Therefore, the joint confidence region of sensitivity and specificity at the estimated optimal cut-off point associated with Youden index is proposed in this paper. The joint confidence region of sensitivity and specificity at the estimated cut-off point defines an elliptical area around the point estimates of sensitivity and specificity at $100(1-\alpha)\%$ confidence level. The proposed elliptical joint confidence region allows clinicians to have a thorough understanding about a biomarker's diagnostic ability in terms of sensitivity and specificity simultaneously at the optimal cut-off point and hence better judgments can be made.

The rest is organized as follows. Notations and preliminaries are covered in Section 2. In Section 3, the parametric joint confidence region for sensitivity and specificity at the optimal cut-off point is discussed. In Section 4, the non-parametric joint confidence regions are presented. Section 5 contains simulation results. In Section 6, a real data example is analyzed. Section 7 provides summary and discussion.

2. Preliminaries

Let Y_1 and Y_2 denote the marker measurements for diseased and healthy subjects, respectively, and $F_{Y_1}(.)$ and $F_{Y_2}(.)$ denote the corresponding cumulative distribution functions (cdfs). Note that Y_1 and Y_2 are independent. Henceforth, let $\boldsymbol{\eta} = (P_1, P_2)^T$ denote the vector of true values of sensitivity (P_1) and specificity (P_2), and c denote any given/known cut-off point. Sensitivity (P_1) and specificity (P_2) at cut-off point (c) are

$$P_1(c) = 1 - F_{Y_1}(c) \quad \text{and} \quad P_2(c) = F_{Y_2}(c),$$

and the corresponding estimates are

$$\hat{P}_1(c) = 1 - \hat{F}_{Y_1}(c) \quad \text{and} \quad \hat{P}_2(c) = \hat{F}_{Y_2}(c),$$

where $\hat{F}_{Y_1}(.)$ and $\hat{F}_{Y_2}(.)$ are the estimated cdfs of diseased and healthy samples, respectively.

The cut-off point c is generally unknown and is estimated by some optimization methods such as the Youden index method. Denote the optimal cut-off point determined by Youden index as c_o as follows

$$c_o = \{c : \max_c(P_1(c) + P_2(c) - 1) = \max_c(F_{Y_2}(c) - F_{Y_1}(c))\}.$$

Please cite this article in press as: Yin, J., Tian, L., Joint inference about sensitivity and specificity at the optimal cut-off point associated with Youden index. Computational Statistics and Data Analysis (2014), http://dx.doi.org/10.1016/j.csda.2014.01.021