ROCnReg: An R Package for Receiver Operating Characteristic Curve Inference with and without Covariate Information

María Xosé Rodríguez-Álvarez  
BCAM - Basque Center for Applied Mathematics  
and IKERBASQUE, Basque Foundation for Science

Vanda Inácio  
University of Edinburgh

Abstract

The receiver operating characteristic (ROC) curve is the most popular tool used to evaluate the discriminatory capability of diagnostic tests/biomarkers measured on a continuous scale when distinguishing between two alternative disease states (e.g., diseased and nondiseased). In some circumstances, the test's performance and its discriminatory ability may vary according to subject-specific characteristics or different test settings. In such cases, information-specific accuracy measures, such as the covariate-specific and the covariate-adjusted ROC curve are needed, as ignoring covariate information may lead to biased or erroneous results. This paper introduces the R package ROCnReg that allows estimating the pooled (unadjusted) ROC curve, the covariate-specific ROC curve, and the covariate-adjusted ROC curve by different methods, both from (semi) parametric and nonparametric perspectives and within Bayesian and frequentist paradigms. From the estimated ROC curve (pooled, covariate-specific or covariate-adjusted), several summary measures of accuracy, such as the (partial) area under the ROC curve and the Youden index, can be obtained. The package also provides functions to obtain ROC-based optimal threshold values using several criteria, namely, the Youden Index criterion and the criterion that sets a target value for the false positive fraction. For the Bayesian methods, we provide tools for assessing model fit via posterior predictive checks, while model choice can be carried out via several information criteria. Numerical and graphical outputs are provided for all methods. The package is illustrated through the analyses of data from an endocrine study where the aim is to assess the capability of the body mass index to detect the presence or absence of cardiovascular disease risk factors. The package is available from the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org/package=ROCnReg.

Keywords: accuracy measures, Bayesian, diagnostic tests, ROC curve, covariate-specific ROC curve, covariate-adjusted ROC curve, optimal thresholds, R.

1. Introduction

Before a diagnostic test is approved for being routinely used in practice, its ability to distinguish, say, diseased from nondiseased individuals, must be narrowly evaluated. Throughout we assume that the true disease status of the individuals is known and the task is, compared to the truth, to quantify how accurate the test being investigated is. Before proceeding, it is worth noting that although our focus is on medical diagnosis, the problem of binary classifi-
cation is a much wider one, finding applications in fields as diverse as biology and finance, to name only two.

The receiver operating characteristic (ROC) curve (Metz 1978) is, unarguably, the most popular tool used for evaluating the discriminatory ability of continuous-outcome diagnostic tests. The ROC curve displays the false positive fraction (FPF) against the true positive fraction (TPF) for all possible threshold values used to dichotomise the test result. The ROC curve thus provides a global description of the trade-off between the FPF and the TPF of the test as the threshold changes. Plenty of parametric and semi/nonparametric methods are available for estimating ROC curves, either from frequentist or Bayesian viewpoints and we refer the interested reader to Pepe (1998, Chapter 5), Zhou, Obuchowski, and McClish (2002, Chapter 4), and Gonçalves, Subtil, Oliveira, and Bermudez (2014), and references therein.

However, it is known that in many situations, a test’s outcome and, by extension, its discriminatory capacity, can be affected by additional information (covariates); Pepe (2003, pp 48–49) provides several examples of covariates that can affect the result of a diagnostic test. For instance, patient characteristics, such as age and gender, are important covariates to be considered as diagnostic accuracy is likely to vary according to them. In these cases, ignoring the information provided by the covariates, by pooling the data without regard their values, may lead to erroneous or, at least, oversimplified conclusions and decisions. Interest should therefore be focused on assessing the accuracy of the test, but taking into account covariate information. Two different ROC-based measures that incorporate covariate information have been proposed: the covariate-specific or conditional ROC curve (see, e.g., Pepe 2003, Chapter 6) and the covariate-adjusted ROC curve (Janes and Pepe 2009). The formal definition of both measures is given in Section 2. In brief, a covariate-specific ROC curve is an ROC curve that conditions on a specific covariate value, thus describing the accuracy of the test in the ‘subpopulation’ defined by that covariate value. On the other hand, the covariate-adjusted ROC curve is a weighted average of covariate-specific ROC curves. Regarding estimation, since the seminal paper of Pepe (1998), a plethora of methods have been proposed in the literature for the estimation of the covariate-specific ROC curve and associated summary measures. Without being exhaustive, we mention the work of Faraggi (2003), Rodríguez-Álvarez, Roca-Pardiñas, and Cadarso-Suárez (2011b,a), Inácio de Carvalho, Jara, Hanson, and de Carvalho (2013), and Inácio de Carvalho, de Carvalho, and Branscum (2017). A detailed review can be found in Rodríguez-Álvarez, Tahoces, Cadarso-Suárez, and Lado (2011c) and Pardo-Fernández, Rodríguez-Álvarez, and van Keilegom (2014). With respect to the covariate-adjusted ROC curve, estimation has been discussed in Janes and Pepe (2009), Rodríguez-Álvarez et al. (2011b), Guan, Qin, and Zhang (2012), and Inácio de Carvalho and Rodríguez-Álvarez (2018).

In a slightly different context, in the machine learning community, the topic of covariate-dependent classification has received much attention recently, being related to the concept of fairness (see, e.g., Hutchinson and Mitchell 2019). As an example, Buolamwini (2017) reports that the evaluation of four gender classifiers revealed that a significant gap exists when comparing gender classification accuracies of females versus males.

There are a few R (R Core Team 2020) packages for ROC curve analysis available on the Comprehensive R Archive Network (CRAN) and, as far as we are aware, all of them implementing frequentist approaches. The package sROC (Wang 2012) contains functions to perform nonparametric, kernel-based, estimation of ROC curves, while pROC (Robin, Turck, Hainard, Tiberti, Lisacek, Sanchez, and Müller 2011) offers a set of tools to visu-
Mariña Xosé Rodríguez-Álvarez, Vanda Inácio

alise, smooth, and compare ROC curves, but covariate information cannot be explicitly taken into account in any of these packages. Packages ROCRegression (available at https://bitbucket.org/mxrodriguez/rocregression) and npROCREgression (Rodríguez-Alvarez and Roca-Pardinas 2017) provide routines to estimate semiparametrically and nonparametrically, under a frequentist framework, the covariate-specific ROC curve. We also mention OptimalCutpoints (López-Ratón, Rodríguez-Álvarez, Cadarso-Suárez, and Gude-Sampedro 2014) and ThresholdROC (Perez Jaume, Skaltsa, Pallarès, and Carrasco Jordan 2017) that provide a collection of functions for point and interval estimation of optimal thresholds for continuous diagnostic tests. To the best of our knowledge, there is no statistical software package implementing Bayesian inference for ROC curves and associated summary indices and optimal thresholds.

To close this gap, in this paper we introduce the ROConReg package that allows conducting Bayesian inference for the (pooled or marginal) ROC curve, the covariate-specific ROC curve, and the covariate-adjusted ROC curve. For the sake of generality, frequentist approaches are also implemented. Specifically, in what concerns estimation of the pooled ROC curve, ROConReg implements the frequentist empirical estimator described in Hsieh and Turnbull (1996), the kernel-based approach proposed of Zou, Hall, and Shapiro (1997), the Bayesian Bootstrap method of Gu, Ghosal, and Roy (2008), and the Bayesian nonparametric method based on a Dirichlet process mixture (DPM) of normal distributions model proposed by Erkanli, Sung, Jane Costello, and Angold (2006). Regarding the covariate-specific ROC curve, ROConReg implements the frequentist normal method of Faraggi (2003) and its semiparametric counterpart as described in Pepe (1998), the kernel-based approach of Rodríguez-Álvarez et al. (2011b), and the Bayesian nonparametric model, based on a single-weights dependent Dirichlet process mixture of normal distributions, proposed by Inácio de Carvalho et al. (2013). As for the covariate-adjusted ROC curve, the ROConReg package allows estimation using the frequentist semiparametric approach of Janes and Pepe (2009), the frequentist nonparametric method discussed in Rodríguez-Álvarez et al. (2011b), and the recently proposed Bayesian nonparametric estimator of Inácio de Carvalho and Rodríguez-Álvarez (2018). Table 1 shows a summary of all methods implemented in the package. In addition, ROConReg also provides functions to obtain ROC-based optimal thresholds to perform the classification/diagnosis using two different criteria, namely, the Youden index and the criterion that sets a target value for the false positive fraction. These are implemented for both the ROC curve, the covariate-specific and the covariate-adjusted ROC curve. A detailed description of the methods is presented in Section 3.

The remainder of the paper is organised as follows. In Section 2 we formally introduce the (pooled or marginal) ROC curve, the covariate-specific ROC curve, and the covariate-adjusted ROC curve. The description of the estimation methods implemented in the ROConReg package is given in Section 3. In Section 4 the usage of the main functions and methods in ROConReg is described and illustrated using a real example. The paper concludes with a discussion in Section 5.

2. Notation and definitions

This section sets out the formal definition of the pooled or marginal ROC curve, the covariate-specific ROC curve, and the covariate-adjusted ROC curve. Also, it describes the most commonly used summary measures of accuracy, namely, the area under the ROC curve (AUC),
ROCnReg: An R Package for ROC Inference

Method Description

**Pooled ROC curve**
- **emp** (Frequentist) empirical estimator (Hsieh and Turnbull 1996).
- **kernel** (Frequentist) kernel-based approach (Zou et al. 1997).
- **BB** Bayesian bootstrap method (Gu et al. 2008).
- **dpm** Nonparametric Bayesian approach based on Dirichlet process mixtures of normal distributions (Erkanli et al. 2006).

**Covariate-specific ROC curve**
- **sp** (Frequentist) parametric and semiparametric induced ROC regression approach (Pepe 1998; Faraggi 2003).
- **kernel** Nonparametric (kernel-based) induced ROC regression approach (Rodríguez-Álvarez et al. 2011b).
- **bnp** Nonparametric Bayesian model based on a single-weights dependent Dirichlet process mixture of normal distributions (Inácio de Carvalho et al. 2013).

**Covariate-adjusted ROC curve**
- **sp** (Frequentist) semiparametric method (Janes and Pepe 2009).
- **kernel** Nonparametric (kernel-based) induced ROC regression approach (Rodríguez-Álvarez et al. 2011b).
- **bnp** Nonparametric Bayesian model based on a single-weights dependent Dirichlet process mixture of normal distributions and the Bayesian bootstrap (Inácio de Carvalho and Rodríguez-Álvarez 2018).

Table 1: Overview of ROC estimation methods included in the ROCnReg package.

---

the partial area under the ROC curve (pAUC), and the Youden Index (YI). For conciseness, we intentionally avoid giving too many details and refer the interested reader to Pepe (2003) (and references therein) for an extensive account of many aspects of ROC curves with and without covariates.

In what follows, we denote as $Y$ the outcome of the diagnostic test and as $D$ the binary variable indicating the presence ($D = 1$) or absence ($D = 0$) of disease. We also assume that along with $Y$ and the true disease status $D$, a covariate vector $X$ is also available, and that it may encompass both continuous and categorical covariates. For ease of notation, the covariate vector $X$ is assumed to be the same in both the diseased ($D = 1$) and nondiseased ($D = 0$) populations, although this is not necessarily the case in practice (e.g. disease stage is, obviously, a disease-specific covariate). By a slight abuse of notation, we use the subscripts $D$ and $\bar{D}$ to denote (random) quantities conditional on, respectively, $D = 1$ and $D = 0$. For example, $Y_D$ and $Y_{\bar{D}}$ denote the test outcomes in the diseased and nondiseased populations.

**2.1. Pooled ROC curve**

In the case of a continuous-outcome diagnostic test, classification is usually made by comparing the test result $Y$ against a threshold $c$. If the outcome is equal or above the threshold, $Y \geq c$, the subject will be considered as diseased. On the other hand, if the test result is below the threshold, $Y < c$, he/she will be classified as nondiseased. The ROC curve is then defined
as the set of all possible false positive fractions, $\text{FPF}(c) = P(Y \geq c \mid D = 0) = P(Y_D \geq c)$, and true positive fractions, $\text{TPF}(c) = P(Y \geq c \mid D = 1) = P(Y_D \geq c)$, which can be obtained by varying the threshold value $c$, i.e.,

$\{(\text{FPF}(c), \text{TPF}(c)) : c \in \mathbb{R}\}$.

It is common to represent the ROC curve as $\{(p, \text{ROC}(p)) : p \in [0, 1]\}$, where

$$\text{ROC}(p) = 1 - F_D \left\{ F_D^{-1}(1-p) \right\},$$

with $F_D(y) = P(Y_D \geq y)$ and $F_D(y) = P(Y_D \geq y)$ denoting the cumulative distribution function (CDF) of $Y$ in the nondiseased and diseased groups, respectively. Several indices can be used as global summary measures of the accuracy of a test. The most widely used is the area under the ROC curve (AUC), defined as

$$\text{AUC} = \int_0^1 \text{ROC}(p) \, dp. \quad (2)$$

In addition to its geometric definition, the AUC has also a probabilistic interpretation (see, e.g., Pepe 2003, p. 78)

$$\text{AUC} = P(Y_D \geq Y_D), \quad (3)$$

that is, the AUC is the probability that a randomly selected diseased subject has a higher test outcome than that of a randomly selected nondiseased subject. The AUC takes values between 0.5, in the case of an uninformative test that classifies individuals no better than chance, and 1.0 for a perfect test. We note that an AUC below 0.5 simply means that the classification rule should be reversed. As it is clear from its definition, the AUC integrates the ROC curve over the whole range of FPFs. Depending on the circumstances, however, interest might lie only on a relevant interval of FPFs or TPFs, which leads to the notion of partial area under the ROC curve (pAUC). The pAUC over a range of FPFs $(0, u_1)$, where $u_1$ is typically low and represents the largest acceptable FPF, is defined as

$$\text{pAUC}(u_1) = \int_0^{u_1} \text{ROC}(p) \, dp. \quad (4)$$

If, alternatively, one desires to calculate the partial area over the range $(u_1, u_2)$ of FPFs, we can simply do it as

$$\text{pAUC}(u_1, u_2) = \text{pAUC}(u_2) - \text{pAUC}(u_1). \quad (5)$$

On the other hand, the pAUC over a range of TPFs $(v_1, 1)$, where $v_1$ is typically large and represents the lowest acceptable TPF, is defined as

$$\text{pAUC}_{\text{TPF}}(v_1) = \int_{v_1}^1 \text{ROC}_{\text{TNF}}(p) \, dp, \quad (6)$$

where $\text{ROC}_{\text{TNF}}$ is a $270^\circ$ rotation of the ROC curve, which can be expressed as

$$\text{ROC}_{\text{TNF}}(p) = F_D\{F_D^{-1}(1-p)\}. \quad (7)$$

The curve (7) is referred to as the true negative fraction (TNF) ROC curve, since TNF ($= 1 - \text{FPF}$) is plotted on the $y$-axis. Again, $\text{pAUC}_{\text{TPF}}(v_1, v_2) = \text{pAUC}_{\text{TPF}}(v_1) - \text{pAUC}_{\text{TPF}}(v_2)$. 
We shall highlight that the argument \( p \) in the ROC stands for a false positive fraction, whereas in the ROC\(_{\text{TNF}} \) it stands for a true positive fraction.

Another summary index of diagnostic accuracy is the Youden Index (Shapiro 1999; Youden 1950)

\[
YI = \max_c \{ \text{TPF}(c) - \text{FPF}(c) \} 
\]

\[
= \max_c \{ F_D^\top(c) - F_D(c) \} 
\]

\[
= \max_p \{ \text{ROC}(p) - p \} . 
\]

The \( YI \) ranges from 0 to 1, taking the value of 0 in the case of an uninformative test and 1 for a perfect test. As for the AUC, a \( YI \) below 0 means that the classification rule should be reversed. The value \( c^* \) which maximises Equation (8) (or, equivalently, Equation (9)) is frequently used in practice to classify subjects as diseased or nondiseased. It should be noted that this index is equivalent to the Kolmogorov–Smirnov measure of distance between the distributions of \( Y_D \) and \( \bar{Y}_D \) (Pepe 2003, p. 80).

### 2.2. Covariate-specific ROC curve

The conditional or covariate-specific ROC curve, given a covariate value \( x \), is defined as

\[
\text{ROC}(p \mid x) = 1 - F_D(F_D^\top(1 - p \mid x) \mid x), 
\]

where \( F_D(y \mid x) = \mathbf{P}(Y_D \leq y \mid X_D = x) \) and \( F_D^\top(y \mid x) = \mathbf{P}(Y_D \leq y \mid \bar{X}_D = x) \) are the conditional CDFs of the test in the diseased and nondiseased groups, respectively. In this case, a number of possibly different ROC curves (and therefore accuracies) can be obtained for different values of \( x \). Thus, the covariate-specific ROC curve is an important tool that helps to understand and determine the optimal and suboptimal populations where to apply the tests on. Similarly to the unconditional case, the covariate-specific TNF-ROC curve is given by

\[
\text{ROC}_{\text{TNF}}(p \mid x) = F_D(F_D^\top(1 - p \mid x) \mid x), 
\]

and the covariate-specific AUC, \( \text{pAUC} \), and (generalised) Youden index are

\[
\text{AUC}(x) = \int_0^1 \text{ROC}(p \mid x)dp, 
\]

\[
\text{pAUC}(u_1 \mid x) = \int_0^{u_1} \text{ROC}(p \mid x)dp, 
\]

\[
\text{pAUC}_{\text{TPF}}(v_1 \mid x) = \int_{v_1}^1 \text{ROC}_{\text{TNF}}(p \mid x)dp, 
\]

\[
\text{YI}(x) = \max_c |\text{TPF}(c \mid x) - \text{FPF}(c \mid x)| 
\]

\[
= \max_c |F_D(c \mid x) - F_D(c \mid x)| 
\]

\[
= \max_p |\text{ROC}(p \mid x) - p|. 
\]

The value \( c^*_x \) that achieves the maximum in (16) (or (17)) is called the optimal covariate-specific \( YI \) threshold and can be used to classify a subject, with covariate value \( x \), as diseased or nondiseased.
2.3. Covariate-adjusted ROC curve

The covariate-specific ROC curve and associated AUC, pAUCs, and YI described in Section 2.2 depict the accuracy of the test for specific covariate values. However, it would be undoubtedly useful to have a global summary measure that also takes covariate information into account. Such summary measure was developed by Janes and Pepe (2009), who proposed the covariate-adjusted ROC (AROC) curve, defined as

\[
\text{AROC}(p) = \int \text{ROC}(p \mid x) dH_D(x),
\]

(19)

where \( H_D(x) = P(X_D \leq x) \) is the CDF of \( X_D \). That is, the AROC curve is a weighted average of covariate-specific ROC curves, weighted according to the distribution of the covariates in the diseased group. Equivalently, as shown by Janes and Pepe (2009), the AROC curve can also be expressed as

\[
\text{AROC}(p) = P\{Y_D > F_D^{-1}(1 - p \mid X_D)\}
= P\{1 - F_D(Y_D \mid X_D) \leq p\}. 
\]

(20)

As will be seen in Section 3, Expression (20) is very convenient when it comes to estimating the AROC curve. Also, it emphasises that the AROC curve at a FPF of \( p \) is the overall TPF when the thresholds used for defining a positive test result are covariate-specific and chosen to ensure that the FPF is \( p \) in each subpopulation defined by the covariate values.

In contrast to the pooled ROC curve (see Expression (1)) and the covariate-specific ROC curve (see Expression (11)), the AROC is not (and cannot) be expressed in terms of the (conditional) CDFs of the test in each group. This does not, however, preclude the possibility of defining AROC-based summary accuracy measures, yet more care is needed. Thus, for the AROC curve, the area under the AROC, as well as the partial areas and YI are expressed as follows

\[
\text{AAUC} = \int_0^1 \text{AROC}(p) dp, 
\]
(21)

\[
\text{pAAUC}(u_1) = \int_0^{u_1} \text{AROC}(p) dp, 
\]
(22)

\[
\text{pAUC}_{\text{TPF}}(v_1) = \int_{\text{AROC}^{-1}(v_1)}^1 \text{AROC}dp - \{1 - \text{AROC}^{-1}(v_1)\}v_1, 
\]
(23)

\[
\text{YI}_{\text{AROC}} = \max_p \{\text{AROC}(p) - p\}. 
\]
(24)

Note, in particular, that the expressions for both the partial area under the AROC over a range of TPFs and for the YI are defined in terms of the AROC curve. For the YI, once the value that achieves the maximum in (24) is calculated, say \( p^* \), covariate-specific threshold values can be obtained as follows

\[
c_x^* = F_D^{-1}(1 - p^* \mid X_D = x).
\]

Note that, by construction, these threshold values will ensure that the FPF is \( p^* \) in each subpopulation defined by the covariate values, yet the TPF may vary with the covariate values, i.e.,

\[
\text{TPF}(c_x^*) = 1 - F_D(c_x^* \mid X_D = x).
\]
To finish this part, we would like to mention that when the accuracy of a test is not affected by covariates, this does not necessarily mean that the covariate-specific ROC curve (which in this case is the same for all covariate values) coincides with the pooled ROC curve. It does coincide, however, with the AROC curve (see Janes and Pepe 2009; Pardo-Fernández et al. 2014; Inácio de Carvalho and Rodríguez-Álvarez 2018, for more details). As such, in all cases where covariates affect the results of the test, even though they might not affect its discriminatory capacity, inferences based on the pooled ROC curve might be misleading. In such cases, the AROC curve should be used instead. This also applies to the selection of (optimal) threshold values, which might be covariate-specific (i.e., possibly different for different covariate values).

3. Methods

In this section we describe the different methods for ROC inference (with and without covariate information) implemented in the ROCnReg package.

3.1. Pooled ROC curve

Let \( \{y_{Di}\}_{i=1}^{n_D} \) and \( \{y_{Dj}\}_{j=1}^{n_D} \) be two independent random samples of test outcomes from the nondiseased and diseased groups of size \( n_D \) and \( n_D \), respectively.

**Empirical estimator**

The function pooledROC.emp estimates the pooled ROC curve using the empirical estimator proposed by Hsieh and Turnbull (1996), which consists in estimating the CDFs of the test in each group by its empirical counterpart, that is,

\[
\hat{F}_{\overline{D}}(y) = \frac{1}{n_{\overline{D}}} \sum_{i=1}^{n_{\overline{D}}} I(y_{\overline{Di}} \leq y), \quad \hat{F}_{D}(y) = \frac{1}{n_D} \sum_{j=1}^{n_D} I(y_{Dj} \leq y). 
\]

These empirical estimates are then plugged into Equations (1) and (7) to obtain, respectively, an estimate of the ROC and ROC\text{TNF} curves.

In what concerns estimation of the AUC (Expression (3)), pAUC, and pAUC\text{TNF} (Expressions (4) and (6), respectively) these are computed empirically by means of the Mann–Whitney U statistic. With respect to the Youden Index (and associated threshold value), it is obtained by maximising, over a grid of possible threshold values, the expression in (9), with \( F_{\overline{D}} \) and \( F_{D} \) being replaced by their empirical estimators.

**Kernel estimator**

The function pooledROC.kernel estimates the pooled ROC curve using the kernel-based estimator proposed by Zou et al. (1997), which is based on estimating the CDFs of the test as follows

\[
\hat{F}_{\overline{D}}(y) = \frac{1}{n_{\overline{D}}} \sum_{i=1}^{n_{\overline{D}}} \Phi \left( \frac{y - y_{\overline{Di}}}{h_{\overline{D}}} \right), \quad \hat{F}_{D}(y) = \frac{1}{n_D} \sum_{j=1}^{n_D} \Phi \left( \frac{y - y_{Dj}}{h_D} \right),
\]

where \( \Phi(y) \) stands for the standard normal distribution evaluated at \( y \). For the bandwidths, \( h_{\overline{D}} \) and \( h_D \), which control the amount of smoothing, two options are popular. Silverman’s
rule of thumb (Silverman 1986, p. 48), which sets the bandwidth as

\[ h_d = 0.9 \min \{ \text{SD}(\mathbf{y}_d), \text{IQR}(\mathbf{y}_d) / 1.34 \} n_d^{-0.2}, \quad d \in \{ \bar{D}, D \}, \]

where SD(\mathbf{y}_d) and IQR(\mathbf{y}_d) are the standard deviation and interquartile range, respectively, of \( \mathbf{y}_d = (y_{d1}, \ldots, y_{dn_d}) \). Another alternative criterion is to select the bandwidth by using least squares cross-validation (Wand and Jones 1994, Chapter 3).

Here, both the AUC, pAUC, and pAUC_{TNF} (Expressions (2), (4), and (6)) are computed numerically using Simpson’s rule. Regarding the Youden Index (and associated threshold value), it is obtained by maximising, over a grid of possible threshold values, Expression (9), with \( F_D \) and \( F_{\bar{D}} \) being replaced by their kernel estimators.

Uncertainty estimation for both the empirical and kernel estimators is conducted through bootstrap resampling.

**Bayesian bootstrap estimator**

The function pooledROC.bb implements the Bayesian bootstrap (BB) approach proposed by Gu et al. (2008). Their estimator relies on the notion of placement value (Pepe 2003, Chapter 5), which is simply a standardisation of the test outcomes with respect to a reference group. Specifically, \( U_D = 1 - F_{\bar{D}}(Y_D) \) is to be interpreted as a standardisation of a diseased test outcome with respect to the distribution of test results in the nondiseased population. The ROC curve can be regarded as the CDF of \( U_D \)

\[
P(U_D \leq p) = P\{1 - F_{\bar{D}}(Y_D) \leq p\} = 1 - F_D\{F_{\bar{D}}^{-1}(1 - p)\} = \text{ROC}(p), \quad 0 \leq p \leq 1. \tag{25}
\]

This representation in (25) of the ROC curve provided the rationale for the two-step algorithm of Gu et al. (2008), which can be described as follows. Let \( S \) be the number of iterations.

**Step 1: Computation of the placement value based on the BB.**

For \( s = 1, \ldots, S \), let

\[
U^{(s)}_{Dj} = \sum_{i=1}^{n_D} q^{(s)}_{i1} I(y_{Di} \geq y_{Dj}), \quad j = 1, \ldots, n_D,
\]

where \( (q^{(s)}_{11}, \ldots, q^{(s)}_{in_D}) \sim \text{Dirichlet}(n_D; 1, \ldots, 1) \).

**Step 2: Generate a realisation of the ROC curve.** Based on (25), generate a realisation of \( \text{ROC}^{(s)}(p) \), the cumulative distribution function of \( (U^{(s)}_{1D}, \ldots, U^{(s)}_{n_D}) \), where

\[
\text{ROC}^{(s)}(p) = \sum_{j=1}^{n_D} q^{(s)}_{2j} I\left( U^{(s)}_{Dj} \leq p \right), \quad (q^{(s)}_{21}, \ldots, q^{(s)}_{2n_D}) \sim \text{Dirichlet}(n_D; 1, \ldots, 1).
\]

The \( S \) posterior samples give rise to an ensemble of ROC curves \( \{ \text{ROC}^{(1)}(p), \ldots, \text{ROC}^{(S)}(p) \} \) from which the posterior mean (or median) can be computed, e.g.,

\[
\hat{\text{ROC}}^{\text{BB}}(p) = \frac{1}{S} \sum_{s=1}^{S} \text{ROC}^{(s)}(p),
\]
and a 95% pointwise credible band can be obtained from the 2.5% and 97.5% percentiles of the same ensemble.

The Bayesian bootstrap estimator leads to closed-form expressions for the AUC and pAUC, which are, respectively, given by

\[
\text{AUC}(s) = \int_0^1 \text{ROC}(s)(p)dp = 1 - \sum_{j=1}^{n_D} q_{2j}^{(s)} U_{Dj}^{(s)},
\]

\[
\text{pAUC}(u_1) = \int_0^{u_1} \text{ROC}(s)(p)dp = u_1 - \sum_{j=1}^{n_D} q_{2j}^{(s)} \min \{u_1, U_{Dj}^{(s)}\}.
\]

It is easy to show that

\[
\text{pAUC}_{\text{TPF}}(v_1) = \int_{v_1}^1 \text{ROC}_{\text{TNF}}(s)(p)dp = \sum_{i=1}^{n_D} q_{1i}^{(s)} \max \{v_1, U_{Di}^{(s)}\} - v_1,
\]

where

\[
U_{Di}^{(s)} = \sum_{j=1}^{n_D} q_{2j}^{(s)} I(y_{Dj} \geq y_{Di}), \quad i = 1, \ldots, n_D,
\]

and it is also easy to demonstrate that the ROC_{TNF} curve is the survival function of the placement value \( U_D = 1 - F_D(Y_D) \). With respect to the Youden Index, it is obtained by maximising, over a grid of possible threshold values, the following expression

\[
YI(s) = \max_c \left\{ F_D^{(s)}(c) - F_D^{(s)}(c) \right\},
\]

where

\[
F_D^{(s)}(c) = \sum_{i=1}^{n_D} q_{1i}^{(s)} I(y_{Di} \leq c) \quad \text{and} \quad F_D^{(s)}(c) = \sum_{j=1}^{n_D} q_{2j}^{(s)} I(y_{Dj} \leq c).
\]

As for the ROC curve, point estimates for the AUC, pAUC, pAUC_{TPF}, YI, and \( c^* \) can be obtained by averaging over the respective ensembles of \( S \) realisations, with credible bands derived from the percentiles of the same ensembles.

**Dirichlet process mixture of normal distributions estimator**

The Bayesian nonparametric approach, based on a Dirichlet process mixture of normal distributions, for estimating the pooled ROC curve (Erkanli et al. 2006) is implemented in the pooledROC.dpm function. In this case, as implicit by the name, the CDFs of the test in each group are estimated via a Dirichlet process mixture of normal distributions, that is, it is assumed that the CDF, say in the diseased group (the one in the nondiseased group follows analogously), is of the form

\[
F_D(y) = \int \Phi(y \mid \mu, \sigma^2)dG_D(\mu, \sigma^2), \quad G_D \sim \text{DP}(\alpha_D, G_D^*),
\]

where \( \Phi(y \mid \mu, \sigma^2) \) denotes the CDF of the normal distribution with mean \( \mu \) and variance \( \sigma^2 \) evaluated at \( y \). Here \( G_D \sim \text{DP}(\alpha_D, G_D^*) \) is used to denote that the mixing distribution \( G_D \) follows a Dirichlet process (DP) (Ferguson 1973) with centring distribution \( G_D^* \), for which \( E(G_D) = G_D^* \), and precision parameter \( \alpha_D \). Larger values of \( \alpha_D \) lead to realisations of \( G_D \)
closer to $G_D^*$, while smaller values lead to realisations of $G_D$ with substantial variation around $G_D$. Usually, due to conjugacy reasons, $G_D^*(\mu, \sigma) \equiv N(\mu \mid m_0, S_0)\Gamma(\sigma^{-2} \mid a_D, b_D)$.

For ease of posterior simulation and because it provides a highly accurate approximation, we make use of the truncated stick-breaking representation of the DP (Ishwaran and James 2001), according to which $G_D$ can be written as

$$G_D(\cdot) = \sum_{l=1}^{L_D} \omega_{Dl} \delta_{(\mu_{Dl}, \sigma_{Dl}^2)}(\cdot),$$

where $(\mu_{Dl}, \sigma_{Dl}^2) \overset{iid}{\sim} G_D^*(\mu, \sigma^2)$, for $l = 1, \ldots, L_D$, and the weights follow the so-called (truncated) stick-breaking construction: $\omega_{D1} = v_{D1}$, $\omega_{Dl} = v_{Dl} \prod_{r<l}(1 - v_{Dr})$, $l = 2, \ldots, L_D$, and $v_{D1}, \ldots, v_{D,L_D-1} \overset{iid}{\sim} \text{Beta}(1, \alpha_D)$. Further, one must set $v_{D,L_D} = 1$ in order to ensure that the weights add up to one. With regard to the parameter $\alpha_D$, it can be either fixed or a priori distribution placed on it. In the latter case, due to conjugacy reasons, a gamma distribution is the most popular choice, $\alpha_D \sim \Gamma(a_{\alpha_D}, b_{\alpha_D})$. The CDF in (26) can therefore be written as

$$F_D(y) = \sum_{l=1}^{L_D} \omega_{Dl} \Phi(y \mid \mu_{Dl}, \sigma_{Dl}^2),$$

where we shall note that $L_D$ is not the exact number of components expected to be observed, but rather an upper bound on it. Some comments are in order regarding how to specify $\alpha_D$ (or $a_{\alpha_D}$ and $b_{\alpha_D}$) and how to set $L_D$. The precision parameter $\alpha_D$ is intrinsically related to the number of occupied mixture components, say $L_D^*$. Using the results shown by Liu (1996) we have that for moderate to large sample sizes, the conditional prior mean and variance of the number of occupied components are, respectively,

$$E(L_D^* \mid \alpha_D) = \alpha_D \log \left( \frac{\alpha_D + n_D}{\alpha_D} \right), \quad \text{var}(L_D^* \mid \alpha_D) = \alpha_D \left\{ \log \left( \frac{\alpha_D + n_D}{\alpha_D} \right) - 1 \right\}.$$

These results can aid in using genuine prior information to derive values for $a_{\alpha_D}$ and $b_{\alpha_D}$. In practice, and in the absence of knowledge about the number of occupied components, it is common to set $\alpha_D = 1$ or to use prior hyperparameters that encourage, a priori, a small number of occupied components (e.g., $a_{\alpha_D} = 1$ and $b_{\alpha_D} = 1$ or $a_{\alpha_D} = 2$ and $b_{\alpha_D} = 2$). The results derived by Liu (1996) can also be used to guide the selection of $L_D$. It might be reasonable to set $L_D > E(L_D^* \mid \alpha_D) + 2\sqrt{\text{var}(L_D^* \mid \alpha_D)}$.

Because the full conditional distributions for all model parameters are available in closed-form, posterior simulation can be easily conducted through Gibbs sampler (see the details, for instance, in Ishwaran and James 2002). At iteration $s$ of the Gibbs sampler procedure, the ROC curve is computed as

$$\text{ROC}^{(s)}(p) = 1 - F_D^{(s)} \left\{ F_D^{-1}(1-p) \right\}, \quad s = 1, \ldots, S,$$

with

$$F_D^{(s)}(y) = \sum_{l=1}^{L_D} \omega_{Dl}^{(s)} \Phi\left( y \mid \mu_{Dl}^{(s)}, \sigma_{Dl}^{2(s)} \right), \quad F_D^{(s)}(y) = \sum_{k=1}^{L_D} \omega_{Dk}^{(s)} \Phi\left( y \mid \mu_{Dk}^{(s)}, \sigma_{Dk}^{2(s)} \right),$$

$$(27)$$
and where the inversion is performed numerically. There is a closed-form expression for the AUC (Erkanli et al. 2006) given by

\[
\text{AUC}(s) = \sum_{k=1}^{L_D} \sum_{l=1}^{L_D} \omega_{Dk} \omega_{Dl} \Phi \left( \frac{b_{kl}^{(s)}}{\sqrt{1 + a_{kl}^{2(s)}}} \right), \quad b_{kl}^{(s)} = \frac{\mu_{Dl}^{(s)} - \mu_{Dk}^{(s)}}{\sigma_{Dl}^{(s)}}, \quad a_{kl}^{(s)} = \frac{\sigma_{Dk}^{(s)}}{\sigma_{Dl}^{(s)}}.
\]

Also, when \(L_D = L_D = 1\), there are closed-form expressions for the pAUC and \(pAUC_{TPF}\) which are used in the package (see Hillis and Metz 2012). For the pAUC/pAUC_{TPF}, when \(L_D > 1\) or \(L_D > 1\), the integrals are approximated numerically using Simpson’s rule. The Youden index/optimal threshold is computed as in the Bayesian bootstrap method, with the obvious difference that here the CDFs are expressed as in (27). At the end of the sampling procedure, we have an ensemble of S ROC curves and AUCs/pAUCs/pAUC_{TPF}/YIs/optimal thresholds which, as before, allows obtaining point and interval estimates.

### 3.2. Covariate-specific ROC curve

We now let \(\{(x_{Di}, y_{Di})\}_{i=1}^{n_D}\) and \(\{(x_{Dj}, y_{Dj})\}_{j=1}^{n_D}\) be two independent random samples of test outcomes and covariates from the nondiseased and diseased groups of size \(n_D\) and \(n_D\), respectively. Further, for all \(i = 1, \ldots, n_D\) and \(j = 1, \ldots, n_D\), let \(x_{Di} = (x_{Di,1}, \ldots, x_{Di,q})'\) and \(x_{Dj} = (x_{Dj,1}, \ldots, x_{Dj,q})'\) be \(q\)-dimensional vectors of covariates, which can be either continuous or categorical.

**Induced semiparametric linear model**

The function \(cRoc.sp\) implements the induced ROC approaches proposed by Faraggi (2003) and Pepe (1998). Both authors assume a location-scale regression model of the following form for the test outcomes in each group

\[
Y_D = X_D' \beta_D + \sigma_D \varepsilon_D, \quad Y_D = \bar{X}_D' \bar{\beta}_D + \sigma_D \varepsilon_D,
\]

where \(X_D' = (1, X_D')'\) and \(\beta_D = (\beta_{D0}, \ldots, \beta_{Dq})'\) is a \((q+1)\)-dimensional vector of (unknown) regression coefficients; \(\bar{X}_D\) and \(\bar{\beta}_D\) are analogously defined. The error terms \(\varepsilon_D\) and \(\varepsilon_D\) have mean zero, variance one, are independent of each other and of the covariate, and have distribution functions given by \(F_{\varepsilon_D}\) and \(F_{\varepsilon_D}\), respectively. Under these assumptions, we have

\[
F_D(y \mid x) = F_{\varepsilon_D} \left( y - \bar{x}' \beta_D \right) / \sigma_D \quad \text{and} \quad F_D(y \mid x) = F_{\varepsilon_D} \left( y - \bar{x}' \bar{\beta}_D \right) / \sigma_D,
\]

with \(\bar{x}' = (1, x')\).

The approaches of Faraggi (2003) and Pepe (1998) differ in the assumptions made about the error terms. More concretely, Faraggi (2003)’s method assumes that the error term in both groups follows a standard normal distribution, i.e., \(F_{\varepsilon_D}(y) = F_{\varepsilon_D}(y) = \Phi(y)\), and can be summarised by the following three steps:

1. Estimate the regression coefficients \(\beta_D\) and \(\beta_D\) by ordinary least squares, on the basis of the samples \(\{(x_{Di}, y_{Di})\}_{i=1}^{n_D}\) and \(\{(x_{Dj}, y_{Dj})\}_{j=1}^{n_D}\), respectively.
2. Estimate $\hat{\sigma}_D^2$ as
\[
\hat{\sigma}_D^2 = \frac{\sum_{j=1}^{n_D} \left( y_{Dj} - \tilde{x}'_{Dj} \hat{\beta}_D \right)^2}{n_D - q - 1},
\]
with $\hat{\sigma}_D^2$ similarly estimated.

3. For a given covariate vector $x$, compute the covariate-specific ROC curve as follows
\[
\hat{\text{ROC}}(p \mid x) = 1 - \Phi \left\{ a(x) + b\Phi^{-1}(1-p) \right\},
\]
where
\[
a(x) = \tilde{x}' \left( \hat{\beta}_D - \hat{\beta} \right), \quad \text{and} \quad b = \frac{\hat{\sigma}_D}{\bar{\sigma}_D}.
\]
Regarding the covariate-specific AUC, pAUC, and pAUC$_{TPF}$ (Expressions (13), (22), and (15)) they admit closed-form expressions (see Hillis and Metz 2012).

As an alternative, Pepe (1998) suggests to estimate the CDF of the errors in each group by the corresponding empirical CDF of the estimated standardised residuals. Therefore, the first two steps of the estimation procedure remain the same, but now we have the following extra step
\[
\hat{F}_{\varepsilon_D}(y) = \frac{1}{n_D} \sum_{j=1}^{n_D} I(\varepsilon_{Dj} \leq y), \quad \varepsilon_{Dj} = \frac{y_{Dj} - \tilde{x}'_{Dj} \hat{\beta}_D}{\hat{\sigma}_D}.
\]
The empirical CDF of the standardised residuals in the nondiseased group is estimated in a similar fashion. The covariate-specific ROC curve is finally computed in an analogous way as for the method of Faraggi (2003) as
\[
\hat{\text{ROC}}(p \mid x) = 1 - \hat{F}_{\varepsilon_D} \left\{ a(x) + b\hat{\sigma}^{-1}_{\varepsilon_D}(1-p) \right\},
\]
where
\[
a^*(x) = \tilde{x}' \left( \hat{\beta}_D - \hat{\beta} \right), \quad \text{and} \quad b^* = \frac{\hat{\sigma}_D}{\bar{\sigma}_D}.
\]
The covariate-specific pAUC$_{TNF}$ (Expression (15)) is then computed numerically using Simpson’s rule based on the previous expressions.

Finally, in pretty much the same way as for the pooled ROC curve, the covariate-specific Youden Index (and associated threshold value) is obtained by maximising, over a grid of possible threshold values, the expression in (17), making use of result (29).

**Induced kernel-based approach**

The kernel-based approach of González-Manteiga, Pardo-Fernández, and van Keilegom (2011) and Rodríguez-Álvarez et al. (2011b) is available in the cROC.kernel. Differently to all the
other estimating approaches for the covariate-specific ROC curve presented in this section, it can only deal with one continuous covariate. Similarly to the approaches of Pepe (1998) and Faraggi (2003), it also assumes a location-scale regression model for the test outcomes in each group, but the effect of the covariate is not assumed to be linear and the variance is allowed to depend on the covariate. Specifically, the models postulated in each group are as follows

\[ Y_D = \mu_D(X_D) + \sigma_D(X_D)\epsilon_D, \quad Y_D = \mu_D(X_D) + \sigma_D(X_D)\epsilon_D, \]  

where \( \mu_D(x) = \mathbb{E}(Y_D \mid X_D = x) \) and \( \sigma^2_D(x) = \text{VAR}(Y_D \mid X_D = x) \) are the regression and variance functions, respectively, with \( \mu_D(x) \) and \( \sigma^2_D(x) \) being analogously defined. The error terms \( \epsilon_D \) and \( \epsilon_D \) have mean zero, variance one, are independent of each other and of the covariate, and have distribution functions given by \( F_{\epsilon_D} \) and \( F_{\epsilon_D} \), respectively.

Both the regression and variance functions are estimated using local polynomial kernel smoothers (Fan and Gijbels 1996). In particular, local constant (Nadaraya–Watson) or local linear estimators are employed for the regression function, whereas for the variance function only local constant estimators are used. Estimation in \texttt{ROCnReg} makes use of the R package \texttt{np} by Hayfield and Racine (2008). We note that estimation proceeds in a sequential manner: 1) the regression function, say in the diseased group and denoted by \( \hat{\mu}_D \), is estimated first on the basis of \( \{(x_{Dj}, y_{Dj})\}_{j=1}^{n_D} \), and 2) the variance function is estimated next on the basis of the sample \( \{(x_{Dj}, [y_{Dj} - \hat{\mu}_D(x_{Dj})]^2)\} \). Both steps involve the selection of a bandwidth parameter which is done via cross-validation. As in the model of Pepe (1998), the CDFs \( F_{\epsilon_D} \) and \( F_{\epsilon_D} \) are estimated via the empirical CDF of the standardised residuals, that is,

\[ \hat{F}_{\epsilon_D}(y) = \frac{1}{n_D}\sum_{j=1}^{n_D} I(\tilde{\epsilon}_{Dj} \leq y), \quad \tilde{\epsilon}_{Dj} = \frac{y_{Dj} - \hat{\mu}_D(x_{Dj})}{\hat{\sigma}_D(x_{Dj})}, \]

with the empirical CDF of the standardised residuals in the nondiseased group estimated analogously. Finally, the covariate-specific ROC curve is computed in an analogous way as before as

\[ \widehat{\text{ROC}}(p \mid x) = 1 - \hat{F}_{\epsilon_D}\left\{a(x) + b(x)\hat{F}_{\epsilon_D}^{-1}(1 - p)\right\}, \]

where

\[ a(x) = \frac{\hat{\mu}_D(x) - \bar{\mu}_D(x)}{\hat{\sigma}_D(x)} \quad \text{and} \quad b(x) = \frac{\bar{\sigma}_D(x)}{\hat{\sigma}_D(x)}. \]

Estimation of the covariate-specific AUC, pAAUC, pAUC\textsubscript{TNF}, and YI follows a similar reasoning as the one described previously for the induced semiparametric linear model when no assumptions are made regarding the distribution of the error terms.

For both the induced semiparametric linear model and the induced kernel approach, uncertainty quantification is done through a bootstrap of the residuals. For further details see, for instance, Rodríguez-Álvarez et al. (2011b).

Bayesian nonparametric approach based on a dependent Dirichlet process mixture of normal distributions

The Bayesian nonparametric approach for conducting inference about the covariate-specific ROC curve of Inácio de Carvalho et al. (2013), which is based on a single-weights dependent Dirichlet process mixture of normal distributions, is implemented in the function \texttt{cROC.rnp}. By opposition to the previously described approaches to ROC regression, this method rests
on directly modelling the CDF of test outcomes separately in the diseased and nondiseased groups. In a single-weights dependent Dirichlet process mixture of normals model (De Iorio, Johnson, Müller, and Rosner 2009), the conditional CDF in the diseased group is modelled as follows

\[ F_D(y_{Dj} \mid X_D = x_{Dj}) = \int \Phi(y_{Dj} \mid \mu_D(x_{Dj}, \beta), \sigma^2) dG_D(\beta, \sigma^2), \quad G_D \sim DP(\alpha_D, G_D^*(\beta, \sigma^2)), \]

with the conditional CDF in the nondiseased group following in an analogous manner. As in the no-covariate case, by making use of Sethuraman’s truncated representation of the DP, we can write the conditional CDF as

\[ F_D(y_{Dj} \mid x_{Dj}) = \sum_{l=1}^{L_D} \omega_{Dl} \Phi(y_{Dj} \mid \mu_{Dl}(x_{Dj}), \sigma^2_{Dl}), \]

\[ \omega_{D1} = v_{D1}, \quad \omega_{Dl} = v_{Dl} \prod_{r<l}(1 - v_{Dr}), \quad l = 2, \ldots, L_D, \]

\[ v_{Dl} \sim Beta(1, \alpha_D), \quad l = 1, \ldots, L_D - 1, \quad v_{DL_D} = 1. \]

It is worth mentioning that although the variance of each component does not depend on covariates, the overall variance of the mixture does depend on covariates,

\[ \text{var}(y_{Dj} \mid x_{Dj}) = \sum_{l=1}^{L_D} \omega_{Dl} \sigma^2_{Dl} + \sum_{l=1}^{L_D} \omega_{Dl} \left\{ \mu^2_{Dl}(x_{Dj}) - \left( \sum_{l=1}^{L_D} \omega_{Dl} \mu_{Dl}(x_{Dj}) \right)^2 \right\}. \]

Note that by assuming that the weights, \( w_{Dl} \), do not vary with covariates, the model might has limited flexibility in practice (MacEachern 2000), but this issue can be largely mitigated by using a flexible formulation for \( \mu_{Dl}(x_{Dj}) \), which is needed not only for the model to be able to recover nonlinear trends, but also to recover flexible shapes that might arise due to a dependence of the weights on the covariates. As such, we model the mean function of each component using an additive smooth structure

\[ \mu_{Dl}(x_{Dj}) = \tilde{\beta}_{Dl0} + f_{l1}(x_{Dj,1}) + \ldots + f_{lq}(x_{Dj,q}), \quad (33) \]

where each smooth function, \( f_{lr} \) (\( r = 1, \ldots, q \)), is approximated using a linear combination of B-splines basis functions. To avoid notational burden we have assumed that all \( q \) covariates are continuous but the function \( cROC.bnp \) cal also deal with categorical covariates and interactions between a (smooth) continuous covariate and a categorical one. For the reasons mentioned before, we recommend that all continuous covariates are modelled as in (33). Nonetheless, posterior predictive checks, as illustrated in Section 4, can also be used to informally validate the fitted model. We write

\[ \mu_{Dl}(x_{Dj}) = \mu_D(x_{Dj}, \beta_D) = z_{Dj}' \beta_D, \quad l = 1, \ldots, L_D, \quad j = 1, \ldots, n_D, \quad (34) \]

where \( z_{Dj} \) is the \( j \)th column of the design matrix that contains the intercept, the cubic B-splines basis representation of the continuous covariates, the categorical covariates (if any), and their interaction(s) with the smoothed continuous covariate(s) (if believed to exist). Also, \( \beta_D \) collects, for the \( l \)th component, the regression coefficients associated with the aforementioned covariates. An important issue is the selection of the number and location of the knots
at which to anchor the basis functions, as this has the potential to impact inferences, more so for the former rather than the latter. The selection of the number of knots can be assisted by a model selection criterion, for example, (the adaptation to the case of mixture models of) the deviance information criterion (DIC) (Celeux, Forbes, Robert, and Titterington 2006), the log pseudo marginal likelihood (LPML) (Geisser and Eddy 1979), and the widely applicable information criterion (WAIC) (Gelman, Hwang, and Vehtari 2014), whereas for the location of the interior knots themselves we follow Rosenberg (1995) and use the quantiles of the prior for the components’ variances can be chosen to represent belief in the variance of the regression model. With regard to the specification of the prior for the components’ variances can be chosen to represent belief in the variance of the regression model. With regard to the specification of $\alpha_D$ and $L_D$, an analogous reason to the DPM model (no-covariate case) can be followed. The blocked Gibbs sampler is used to simulate draws from the posterior distribution and details about it can be found, for instance, in the Supplementary Materials to Inácio de Carvalho et al. (2017).

Similarly to the analogous model for the no covariate case, at iteration $s$ of the Gibbs sampler procedure, the covariate-specific ROC curve is computed as

$$\text{ROC}^{(s)}(p \mid x) = 1 - F^{(s)}_D \left\{ F^{-1(s)}_D(1 - p \mid x) \mid x \right\}, \quad s = 1, \ldots, S,$$

with

$$F^{(s)}_D(y \mid x) = \sum_{l=1}^{L_D} \omega^{(s)}_{Dl} \Phi \left( y \mid \beta^{(s)}_{Dl}, \sigma^{2(s)}_{Dl} \right), \quad F^{(s)}_D(y \mid x) = \sum_{k=1}^{L_D} \omega^{(s)}_{Dk} \Phi \left( y \mid \beta^{(s)}_{Dk}, \sigma^{2(s)}_{Dk} \right),$$

(35)

and where the inversion is performed numerically. A point estimate for $\text{ROC}(p \mid x)$ can be obtained by computing the mean (or the median) of the ensemble $\{\text{ROC}^{(1)}(p \mid x), \ldots, \text{ROC}^{(S)}(p \mid x)\}$, with pointwise credible bands derived from the percentiles of the ensemble.

Although the results presented in Erkanli et al. (2006) can be extended to derive a closed-form expression for the covariate-specific AUC, for computational reasons, in ROCnReg the integral in (13) is approximated using Simpson’s rule, and the same applies for the partial areas. Conditionally on a specific covariate value, the computation of the Youden index and of the optimal threshold proceeds in a similar way as in the DPM model (see Inácio de Carvalho et al. 2017, for details). As for the covariate-specific ROC curve, point and interval estimates can be obtained from the corresponding covariate-specific ensemble of each summary measure.

### 3.3. Covariate-adjusted ROC curve

All estimators for the covariate-adjusted ROC curve make use of Equation (20) and rely on the following three steps

1. Estimation of the conditional distribution of test outcomes in the nondiseased group, $F_D(y_{D1} \mid x_{D1})$. 
2. Computation of the placement value \( U_D = 1 - F_D(Y_D \mid X_D) \) where, by a slight abuse of notation, we are designating it by the same letter used for the unconditional case.

3. Estimation of the cumulative distribution function of \( U_D \).

**Frequentist approaches**

The approaches used for estimation of the AROC curve proposed by Janes and Pepe (2009) and Rodríguez-Álvarez et al. (2011b) only differ in Step 1. Specifically, once one has an estimate of the conditional CDF in the nondiseased group, say \( \hat{F}_D(\cdot \mid x) \), Step 2 in the two approaches consists of trivially computing the diseased placement values as

\[
\hat{U}_{Dj} = 1 - \hat{F}_D(y_{Dj} \mid x_{Dj}), \quad j = 1, \ldots, n_D.
\]

Next, in Step 3, the AROC curve at a false positive fraction of \( p \) is estimated via the empirical distribution function of the placement values calculated in the previous step, \( \{\hat{U}_{Dj}\}_{j=1}^{n_D} \), that is,

\[
\hat{\text{AROC}}(p) = \frac{1}{n_D} \sum_{j=1}^{n_D} I(\hat{U}_{Dj} \leq p).
\]

With regard to Step 1, both authors assume a location-scale regression model for the test outcomes in the nondiseased group and, as such and as explained in the previous section, the conditional CDF of the test results can be written using the CDF of the regression errors, i.e.,

\[
F_D(y \mid x) = F_{\epsilon_D}\left(\frac{y - \mu_D(x)}{\sigma_D(x)}\right).
\]

While Janes and Pepe (2009) assume a location-scale model of the form of (28), Rodríguez-Álvarez et al. (2011b) rely on specification (32). The estimation of the mean and variance functions follow exactly the same procedures as those described in the induced semiparametric linear model (for Janes and Pepe 2009) and induced kernel-based approach (for Rodríguez-Álvarez et al. 2011b) for the covariate specific ROC curve (the only difference being that here we only need to perform the estimation for the nondiseased group). At last, and also as in the estimators for the covariate-specific ROC curve, \( F_{\epsilon_D} \) can be either assumed to be the standard normal distribution or left unspecified and estimated empirically on the basis of the standardised residuals. In both cases, the AAUC and pAAUC can be computed as follows

\[
\hat{\text{AAUC}} = \int_0^1 \text{AROC}(p)dp = 1 - \frac{1}{n_D} \sum_{j=1}^{n_D} \hat{U}_{Dj},
\]

\[
\text{pAAUC}(u_1) = \int_0^{u_1} \text{AROC}(p)dp = u_1 - \frac{1}{n_D} \sum_{j=1}^{n_D} \min\{ u_1, \hat{U}_{Dj} \},
\]

whereas the pAAUC_{TNF} is computed as in Equation (23) using numerical integration methods (function \texttt{integrate} in R package \texttt{stats}).

**Bayesian nonparametric approach**

Recently, Inácio de Carvalho and Rodríguez-Álvarez (2018) proposed a Bayesian nonparametric estimator for the AROC curve that combines a dependent Dirichlet process mixture
model and the Bayesian bootstrap. As in the Bayesian nonparametric approach for estimating the covariate-specific ROC curve, in Step 1, rather than assuming a location-scale regression model for the test outcomes in the nondiseased group, the entire conditional distribution is modelled using a single-weights dependent Dirichlet process mixture of normal distributions. Again, here, we also recommend to use cubic B-splines transformations of all continuous covariates. Using the same notation as before, we model the conditional density as

$$F_{D_i}(y_{D_i} | x_{D_i}) = \sum_{l=1}^{L_D} \omega_{D_l} \Phi(y_{D_i} | z'_{D_i} \beta_{D_l}, \sigma_{D_l}^2).$$

Once Step 1 has been completed and given a posterior sample from the parameters of interest, the corresponding realisation of the placement value of a diseased subject in the nondiseased population is easily computed as

$$U_{D_j}^{(s)} = 1 - F_{D_j}(y_{D_j} | x_{D_j}) = \sum_{l=1}^{L_D} \omega_{D_l} \Phi(y_{D_j} | z'_{D_j} \beta_{D_l}^{(s)}, \sigma_{D_l}^{2(s)})$$

Finally, in Step 3, the cumulative distribution function of \( \{U_{D_j}^{(s)}\}_{j=1}^{n_D} \) is estimated through the Bayesian bootstrap

$$\text{AROC}^{(s)}(p) = \sum_{j=1}^{n_D} q_j^{(s)} I \left( U_{D_j}^{(s)} \leq p \right), \quad (q_1^{(s)}, \ldots, q_{n_D}^{(s)}) \sim \text{Dirichlet}(n_D; 1, \ldots, 1).$$

As before, closed-form expressions do exist for the AAUC and pAAUC

\[ \text{AAUC}^{(s)} = \int_0^1 \text{AROC}^{(s)}(p) dp = 1 - \sum_{j=1}^{n_D} q_j^{(s)} U_{D_j}^{(s)}, \]

\[ \text{pAAUC}^{(s)}(u_1) = \int_0^{u_1} \text{AROC}^{(s)}(p) dp = u_1 - \sum_{j=1}^{n_D} q_j^{(s)} \min \left\{ u_1, U_{D_j}^{(s)} \right\}, \]

and the pAAUC_{TNF} is computed using numerical integration methods (Equation (23)). A point estimate for AROC(p) can be obtained by computing the mean (or the median) of the ensemble \{AROC^{(1)}(p), \ldots, AROC^{(S)}(p)\}, that is,

$$\overline{\text{AROC}}(p) = \frac{1}{S} \sum_{s=1}^{S} \text{AROC}^{(s)}(p),$$

and the percentiles of the ensemble can be used to provide pointwise credible bands/credible intervals. The same applies for the AAUC and pAAUC.

### 4. Package Presentation and Illustration

This section describes the main functions in the ROCnReg package and illustrates their usage using endocrine data from a cross-sectional study carried out by the Galician Endocrinology and Nutrition Foundation (FENGA). A detailed description of this dataset can be found in Tomé Martínez de Rituerto, Botana, Cadarso-Suárez, Rego-Iraeta, Fernández-Mariño, Mato,
María Xosé Rodríguez-Álvarez, Vanda Inácio

Solache, and Perez-Fernandez (2009), and it has also been previously analysed in Rodríguez-Álvarez et al. (2011b,a) and Inácio de Carvalho and Rodríguez-Álvarez (2018). For confidentiality reasons, the data used in this paper correspond to a synthetic dataset that was obtained by mimicking the original one. The synthetic dataset can be found in the ROCnReg package under the name endosyn. A summary of the data follows.

```r
R> library(ROCnReg)
R> data("endosyn")
R> summary(endosyn)
```

```
cvd_idf   age    gender    bmi
Min. :0.0000 Min. :18.25 Men :1317 Min. :12.60
1st Qu.:0.0000 1st Qu.:29.57 Women:1523 1st Qu.:23.19
Median :0.0000 Median :39.28 Median :26.24
Mean :0.2433 Mean :41.43 Mean :26.69
3rd Qu.:0.0000 3rd Qu.:50.84 3rd Qu.:29.74
Max. :1.0000  Max. :84.66  Max. :46.20
```

The dataset is comprised of 2840 individuals (1317 Men and 1523 Women, variable gender), with an age range between 18 and 85 years old. Variable bmi contains the body mass index (BMI) values, and cvd_idf is the variable that indicates the presence (1) or absence (0) of two or more cardiovascular disease (CVD) risk factors. Following previous studies, the CVD risk factors considered include raised triglycerides, reduced HDL-cholesterol, raised blood pressure, and raised fasting plasma glucose. Note that from the 2840 individuals, about 24% present two or more CVD risk factors.

Using the ROCnReg package, in the subsequent sections we will illustrate how to ascertain, through the pooled ROC curve, the discriminatory capacity of the BMI (our diagnostic test) in differentiating individuals with two or more CVD risk factors (those belonging to the diseased class D) from those having none or just one CVD risk factor (and that therefore belong to the nondiseased group \(\overline{D}\)). Also, in Section 4.2 we will show how to evaluate, through the covariate-specific ROC curve, the possible modifying effect of age and gender on the discriminatory capacity of the BMI. Finally, Section 4.3 focuses on the covariate-adjusted ROC curve as a global summary measure of the BMI discriminatory ability, when taking the age and gender effects into account.

4.1. Pooled ROC curve

The ROCnReg package allows estimating the pooled ROC curve by means of the four methods described in Section 3. Recall that function pooledROC.emp implements the empirical estimator, pooledROC.kernel the kernel-based approach, and pooledROC.BB and pooledROC.dpm correspond, respectively, to the Bayesian bootstrap estimator and the approach based on Dirichlet process mixtures (of normal distributions). The input arguments in the functions are method-specific (details can be found in the manual accompanying the package), but in all cases numerical and graphical summaries can be obtained by calling the functions print.pooledROC, summary.pooledROC, and plot.pooledROC, which can be abbreviated by print, summary and plot.
By way of example, we present here the syntax using the `pooledROC.dpm` function. Recall that our aim is to ascertain, using the `endosyn` dataset, the discriminatory capacity of the BMI in differentiating individuals with two or more CVD risk factors from those having none or just one CVD risk factor.

```r
R> set.seed(123) # for reproducibility
R> pROC_dpm <- pooledROC.dpm(marker = "bmi", group = "cvd_idf",
+   tag.healthy = 0, data = endosyn,
+   standardise = TRUE, p = seq(0, 1, l = 101),
+   compute.lpm = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
+   pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1),
+   density = densitycontrol(compute = TRUE),
+   prior.h = priorcontrol.dpm(),
+   prior.d = priorcontrol.dpm(),
+   mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1))
```

Before describing in detail the previous call, we first present the control functions that are used. In particular

```
pauccontrol(compute = FALSE, focus = c("FPF", "TPF"), value = 1)
```

can be used to indicate whether the pAUC should be computed (by default it is not computed it), and in case it is computed (i.e., `compute = TRUE`), whether the `focus` should be placed on restricted FPFs (pAUC, see (4)) or on restricted TPFs (pAUC_{TPF}, see (6)). In both cases, the upper bound u_1 (if focus is the FPF) or the lower bound v_1 (if focus is the TPF) should be indicated in `value`. In addition to the pooled ROC curve, AUC and pAUC (if required), the function `pooledROC.dpm` also allows computing the probability density function (PDF) of the test outcomes in both the diseased and nondiseased groups. In order to do so, we use

```
densitycontrol(compute = FALSE, grid.h = NA, grid.d = NA)
```

By default, PDFs are not returned by the function `pooledROC.dpm`, but this can be changed by setting `compute = TRUE`, and through `grid.h` and `grid.d` the user can specify a grid of test results where the PDFs are to be evaluated in, respectively, the nondiseased and diseased groups. Value `NA` signals auto initialisation, with default a vector of length 200 in the range of the test results. Regarding the hyperparameters for the Dirichlet process mixture of normals model (used for the estimation of the PDFs/CDFs of the test outcomes in each group), they can be controlled using

```
priorcontrol.dpm(m0 = NA, SO = NA, a = 2, b = NA, aalpha = 2, balpha = 2, L = 10)
```

A detailed description of these hyperparameters is found in Section 3. Finally, to set the various parameters controlling the Markov chain Monte Carlo (MCMC) procedure (which in our case is simply a Gibbs sampler) we use

```
mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1)
```

Here `nsave` is an integer value with the total number of scans to be saved, `nburn` is the number of burn-in scans, and `nthin` is the thinning interval. Unless due to memory usage
reasons, we recommend not thinning and instead monitoring the effective sample size of the MCMC chain.

Coming back to the `pooledROC.dpm` function, through `marker` the user specifies the name of the variable containing the test results; in our case, these are the values of the BMI. The name of the variable that distinguishes the diseased group (two or more CVD risk factors, $D$) from the nondiseased group (none or one CVD risk factor, $\bar{D}$) is represented by the argument `group`, and the value codifying nondiseased individuals in `group` is specified by `tag.healthy`. The `data` argument is a data frame containing the data and all needed variables. Setting `standardise = TRUE` (the default) will standardise (i.e., subtract the mean and divide by the standard deviation) the test outcomes, which may help improving the MCMC mixing. The set of FPFs at which to estimate the pooled ROC curve is specified in the argument `p`. The log pseudo marginal likelihood (LPML), the widely applicable information criterion (WAIC), and the deviance information criterion (DIC) are computed by setting, respectively, the arguments `compute.lpml`, `compute.WAIC`, and `compute.DIC` to TRUE. Argument `pauc` is an (optional) list of values to replace the default values returned by the function `pauccontrol`. Here, we ask for the pAUC to be computed, with the focus on restricted FPFs and upper bound $u_1 = 0.1$. Similarly, the argument `density` is an (optional) list of values to replace the default values returned by the function `densitycontrol`, as it is the argument `mcmc`. Finally, through `prior.h` and `prior.d` arguments we specify the hyperparameters in the nondiseased and diseased classes, respectively. Again, both arguments are (optional) lists of values to replace the default values returned by the function `priorcontrol.dpm`. Different hyperparameters’ default values are setted depending on whether test outcomes are standardised or not.

A numerical summary of the fitted model can be obtained by calling the function `summary`, that provides, among other information, the estimated AUC (posterior mean) and 95% credible interval and, if required, the LPML, WAIC, and DIC, separately, in the nondiseased (denoted here as healthy) and diseased classes.

```R
R> summary(pROC_dpm)
Call:
pooledROC.dpm(marker = "bmi", group = "cvd_idf", tag.healthy = 0,
data = endosyn, standardise = TRUE, p = seq(0, 1, l = 101),
compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1),
density = densitycontrol(compute = TRUE), prior.h = priorcontrol.dpm(),
prior.d = priorcontrol.dpm(), mcmc = mcmccontrol(nsave = 8000,
nburn = 2000, nskip = 1))

Approach: Pooled ROC curve – Bayesian DPM

Area under the pooled ROC curve: 0.758 (0.738, 0.777)
Partial area under the pooled ROC curve (FPF = 0.1): 0.168 (0.138, 0.199)

Model selection criteria:

|                  | Healthy | Diseased |
|------------------|---------|----------|
| WAIC             | 12490.852 | 4016.597 |
| WAIC (Penalty)   | 6.316   | 4.234    |
```
Sample sizes:

|                   | Healthy | Diseased |
|-------------------|---------|----------|
| Number of observations | 2149    | 691      |
| Number of missing data | 0       | 0        |

To complement these numerical results, the **ROCNReg** package furnishes graphical results that can be used to further explore the fitted model. Specifically, the function `plot` depicts the estimated pooled ROC curve and AUC (posterior means), jointly with 95% credible intervals.

```R
R> plot(pROC_dpm, cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.5)
```

The result of the above code is shown in Figure 1.

![Pooled ROC curve – Bayesian DPM](image)

**Figure 1:** Graphical results as provided by the `plot.pooledROC` function for an object of class `pooledROC.dpm`. Posterior mean and 95% pointwise credible band for the pooled ROC curve and corresponding posterior mean and 95% credible interval for the AUC.

By means of `density = densitycontrol(compute = TRUE)` in the call to the function, we asked for the (estimates of the) PDFs of the BMI in both classes to be returned. This information can be accessed through component `dens` in object `pROC_dpm` (i.e., `pROC_dpm$dens`), which is a list with elements `h` and `d` associated with the nodiseased and diseased groups, respectively. Each of the two elements is itself a list of two components: (1) `grid`, a vector that contains the grid of test results at which the PDFs has been evaluated (estimated); and (2) `dens`, a matrix with the PDFs at each iteration of the MCMC procedure. We can use...
these results to plot, e.g., the posterior mean (and 95% pointwise credible bands) of the PDF of the BMI in the healthy and diseased populations (see Figure 2(a), obtained using the R package `ggplot2` by Wickham 2016). As can be observed, the estimated densities by the DPM method follow very closely the histograms of the data. Also, the estimated densities available in `dens` can be used, as advised by Gelman, Carlin, Stern, Dunson, Vehtari, and Rubin (2013) (p. 553), to monitor convergence of the MCMC chains. The well-known label switching problem often leads to poor mixing of the chains of the component-specific parameters, but this may not impact convergence and mixing of the induced density/distribution of interest. For instance, Figure 3 shows trace plots of the MCMC iterations (after burn-in) of the PDFs of the BMI in the two groups, for different (and randomly selected) values of the BMI, and Figure 4 depicts the corresponding effective sample sizes (obtained using the R package `coda` by Plummer, Best, Cowles, and Vines 2006). Note that both plots give evidence of a good mixing and do not suggest lack of convergence. For conciseness, the R-code for producing Figures 2(a), 3 and 4 is not provided here, but in the R replication code that accompanies this paper.

It is worth noting that the function `pooledROC.dpm` also allows fitting a normal distribution in each group; this is just a particular case (for which \( L_D = L_D = 1 \)) of the more general DPM model. In order to fit such model, one simply needs to set \( L = 1 \) in the `prior.d` and `prior.h` arguments. The code follows.

```r
R> pROC_normal <- pooledROC.dpm(marker = "bmi", group = "cvd_idf", + tag.healthy = 0, data = endosyn, + standardise = TRUE, p = seq(0, 1, l = 101), + compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE, + pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1), + density = densitycontrol(compute = TRUE), + prior.h = priorcontrol.dpm(L = 1), + prior.d = priorcontrol.dpm(L = 1), + mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1))
```

For the sake of space we omit from the summary the call to the function

```r
R> summary(pROC_normal)
```

Call: [...] 

Approach: Pooled ROC curve - Bayesian DPM

Area under the pooled ROC curve: 0.748 (0.728, 0.768)
Partial area under the pooled ROC curve (FPF = 0.1): 0.224 (0.195, 0.254)

Model selection criteria:

|             | Healthy   | Diseased |
|-------------|-----------|----------|
| WAIC        | 12639.978 | 4048.987 |
| WAIC (Penalty) | 2.445     | 2.252    |
| LPML        | -6319.988 | -2024.493|
| DIC         | 12639.517 | 4048.705 |
| DIC (Penalty) | 1.990     | 1.981    |
**ROCnReg**: An *R* Package for ROC Inference

![Histogram of BMI](image)

(a) DPM model with 10 mixture components in each group

(b) Normal model in each group

Figure 2: Histogram of the (observed) BMI and posterior mean jointly along with pointwise 95% pointwise credible bands (red lines) of the PDF of the BMI obtained using (a) a Dirichlet process mixture of normals model (object `pROC_dpm`); and (b) a normal model (object `pROC_normal`). Left: Healthy individuals (none or one CVD risk factor). Right: Diseased individuals (two or more CVD risk factors).

The fit of the DPM and normal models, in each group, can be compared on the basis of the WAIC, DIC, and/or the LPML. Remember that for the LPML, the higher its value, the better the model fit, while for the WAIC and DIC is the other way around. By comparing these values, provided in the summary of each fitted model, we can conclude that the three criteria favour, in both the diseased and (especially in the) nondiseased groups, the more general DPM model. This is also corroborated by the plot of the fitted densities in each group shown in Figure 2(b).

We now estimate the pooled ROC curve using the empirical estimator (function `pooledROC.emp`), and comparisons with the results using the DPM approach are provided.

```r
R> pROC_emp <- pooledROC.emp(marker = "bmi", group = "cvd_idf", +   tag.healthy = 0, data = endosyn,
```

...
Figure 3: Trace plots of the MCMC draws (after burn-in) of the PDFs of the BMI based on model \texttt{pROC\_dpm}. Results are shown separately for the healthy and diseased populations and for different values of the BMI.

Figure 4: Effective sample size of the MCMC chains (after burn-in) of the PDFs of the BMI based on model \texttt{pROC\_dpm} in the healthy and diseased population. In both cases, results are shown along BMI values.

\begin{verbatim}
+ p = seq(0, 1, l = 101),
+ pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1), B = 500)
\end{verbatim}
ROCnReg: An R Package for ROC Inference

```
R> summary(pROC_emp)
```

Call: [...] 

Approach: Pooled ROC curve - Empirical 

Area under the pooled ROC curve: 0.76 (0.741, 0.777) Partial area under the pooled ROC curve (FPF = 0.1): 0.169 (0.14, 0.2)  

Sample sizes:

|                | Healthy | Diseased |
|----------------|---------|----------|
| Number of observations | 2149    | 691      |
| Number of missing data  | 0       | 0        |

Note that the posterior means for the AUC and pAUC obtained using the DPM method (0.758 and 0.167, respectively) are very similar to the point estimates using the empirical estimator (0.760 and 0.169). This can also be observed when plotting the estimated ROC curve using both methods (Figure 5). 

![ROC curve](image)

**Figure 5:** ROC curve estimated using the empirical estimator (black line) and posterior mean (red line) using the DPM method.

We finish this section by showing how to use ROCnReg to obtain an (optimal) threshold value which could be further used to ‘diagnose’ an individual as diseased (two or more CVD risk factors) or healthy/nondiseased (none or one CVD risk factor). To that aim, and for pooledROC objects (i.e., those obtained using functions pooledROC.dpm, pooledROC.BB, pooledROC.emp, and pooledROC.kernel), we use the function compute.threshold.pooledROC. In particular, compute.threshold.pooledROC allows obtaining (optimal) threshold values using two crite-
ria: the YI and the one that sets a target value for the FPF. For illustration, we show here the results using the YI criterion

\begin{verbatim}
R> th_pROC_dmp <- compute.threshold.pooledROC(pROC_dpm, criterion = "YI")
R> th_pROC_dmp

$call
compute.threshold.pooledROC(object = pROC_dpm, criterion = "YI")

$thresholds
   est    ql    qh
26.57007 26.22046 26.93316

$YI
   est    ql    qh
0.4034839 0.3698152 0.4361766

$FPF
   est    ql    qh
0.3720433 0.3406711 0.4048674

$TPF

# TODO #

As can be observed, the function returns the posterior mean (est) and 95% credible interval (lower bound: ql, upper bound: qh) for the YI and associated threshold value, as well as for the FPF and TPF linked to this cutoff value. For our example, the (posterior mean of the) YI is 0.40 and the YI-based threshold value is a BMI value of 26.6, which falls in the nutritional status defined as pre-obesity by the World Health Organization (WHO). By using this YI-based threshold value, we would have a FPF of 0.37 and a TPF of 0.78.

4.2. Covariate-specific ROC curve

We now turn our attention to the inclusion of covariates into the ROC analysis. As shown in Table 1 and Section 3, with \texttt{ROCnReg} the user can estimate the covariate-specific ROC curve by means of three approaches: function \texttt{cROC.sp} implements the frequentist parametric and semiparametric induced ROC regression estimator, \texttt{cROC.kernel} corresponds to the nonparametric, kernel-based, counterpart of \texttt{cROC.sp}, and \texttt{cROC.bnp} stands for the Bayesian approach based on a single-weights dependent Dirichlet process mixture of normal distributions. As for the functions in \texttt{ROCnReg} for estimating the pooled ROC curve, the input arguments are method-specific, and we refer the reader to the manual for details. For all methods, numerical and graphical summaries are obtained using functions \texttt{print.cROC}, \texttt{summary.cROC} and \texttt{plot.cROC}. Also, for objects of class \texttt{cROC.bnp}, \texttt{ROCnReg} provides the function \texttt{predictive.ckecks}, which implements tools for assessing model fit via posterior predictive checks.

Recall that, when including covariate information into the ROC analysis, interest is in evaluating if and how the discriminatory capacity of the test varies with such covariates. In
particular, in our endocrine study we aim at evaluating the possible effect of both age and gender in the discriminatory capacity of the BMI. In what follows, we do that using the cROC.bnp function, and two different models are fitted. One which considers a normal distribution in each group and that incorporates the age effect in a linear way, and a second one which capped the maximum number of mixture components, in each group, at 10 (i.e., \(L_D = L_D = 10\)) and that models the age effect using cubic B-splines (and thus allows for a nonlinear effect of age). Following Rodriguez-Álvarez et al. (2011b,a), both models consider the interaction between age and gender. For clarity, we first focus on the code when modeling age effect in a linear way, and use it to describe in detail the different arguments of the cROC.bnp function.

```R
R> # Dataframe for predictions
R> agep <- seq(22, 80, l = 30)
R> endopred <- data.frame(age = rep(agep,2),
+   gender = factor(rep(c("Women", "Men"), each = length(agep))))

R> set.seed(123) # for reproducibility
R> cROC_bp <- cROC.bnp(formula.healthy = bmi ~ gender*age,
+   formula.diseased = bmi ~ gender*age,
+   group = "cvd_idf",
+   tag.healthy = 0,
+   data = endosyn,
+   newdata = endopred,
+   standardise = TRUE,
+   p = seq(0, 1, len = 101),
+   compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
+   pauc = pauccontrol(compute = FALSE),
+   prior.h = priorcontrol.bnp(L = 1),
+   prior.d = priorcontrol.bnp(L = 1),
+   density = densitycontrol(compute = TRUE),
+   mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1))
```

As can be seen, many arguments coincide with those of the function pooledROC.dpm (described in Section 4.1). We thus focus here on those that are specific to cROC.bnp. The arguments formula.healthy and formula.diseased are formula objects specifying the model for the regression functions (see Equation (34)) in, respectively, the nondiseased and diseased classes. They are similar to the formula used with the glm function, except that nonlinear functions (modelled by means of cubic B-splines) can be added using function \(f\) (an example will follow). Note that in both cases, the left-hand side of the formulas should include the name of the test (in our case bmi). In our application, and for both groups, the model for the component’s means includes, in addition to the linear effect of age and gender, the (linear) interaction between the two (i.e., \(gender+age \equiv gender + age + gender:age\)). Through newdata the user can specify a new data frame containing the values of the covariates at which the covariate-specific ROC curve and AUC (and also pAUC and PDFs, if required) are to be computed. Finally, prior.h (the same holds for prior.d) is an (optional) list of values to replace the defaults returned by priorcontrol.bnp
priorcontrol.bnp(m0 = NA, S0 = NA, nu = NA, psi = NA, a = 2, b = NA,
aalpha = 2, balpha = 2, L = 10)

which allows setting the hyperparameters for the dependent Dirichlet process mixture of normals model (see Section 3). In our example, we only modified the upper bound for the number of components in the mixture model (by default $L = 10$) and set it to 1. With this configuration, the model for the covariate-specific ROC curve can be regarded as a Bayesian counterpart of the induced ROC approach proposed by Faraggi (2003) and we denote it as the Bayesian normal linear model.

In this case, the **summary** of the fitted model provides the following information.

\[
\begin{align*}
R & \text{> summary(cROC_bp)} \\
\text{Call: [...]}
\end{align*}
\]

**Approach:** Conditional ROC curve – Bayesian nonparametric

Parametric coefficients

|            | Healthy          |           |           |
|------------|------------------|-----------|-----------|
|            | Post. mean       | Post. quantile 2.5% | Post. quantile 97.5% |
| (Intercept)| 26.14497         | 25.87325  | 26.41554  |
| genderWomen| -0.91824         | -1.27527  | -0.55899  |
| age        | 1.19345          | 0.91068   | 1.47484   |
| genderWomen:age | 1.19561 | 0.83890   | 1.56203   |

Diseased:

|            |           |           |           |
|------------|-----------|-----------|-----------|
|            | Post. mean       | Post. quantile 2.5% | Post. quantile 97.5% |
| (Intercept)| 29.18996         | 28.75918  | 29.61591  |
| genderWomen| 2.07963          | 1.38729   | 2.75586   |
| age        | 0.66089          | 0.20842   | 1.09862   |
| genderWomen:age | -0.77379 | -1.45333  | -0.08315  |

ROC curve:

|            |           |           |           |
|------------|-----------|-----------|-----------|
|            | Post. mean       | Post. quantile 2.5% | Post. quantile 97.5% |
| (Intercept)| -0.69570         | -0.81690  | -0.57313  |
| genderWomen| -0.68491         | -0.86589  | -0.50254  |
| age        | 0.12168          | 0.00351   | 0.24315   |
| genderWomen:age | 0.44995 | 0.27100   | 0.63188   |
| b          | 0.93815          | 0.88238   | 0.99487   |

Model selection criteria:

|        | Healthy | Diseased |
|--------|---------|----------|
| WAIC   | 12175.108 | 4008.079 |
Sample sizes:

|                          | Healthy | Diseased |
|--------------------------|---------|----------|
| Number of observations   | 2149    | 691      |
| Number of missing data   | 0       | 0        |

The first thing to note is that, in this case, the `summary` function does not provide the estimated AUC as there is one (possibly different) AUC for each combination of covariate values. Also, given that: (1) only one component has been considered for modelling the CDFs of tests results in the diseased and nodiseased groups, and (2) covariate effects have been modelled in a linear way, the `summary` function provides the posterior mean (and quantiles) of the (parametric) coefficients associated with the regression functions (see Equation (28)) and with the covariate-specific ROC curve (see Equation (31)). We note that since in the call to the function we have specified `standardise = TRUE` (and consequently both the test outcomes and covariates are standardised), the regression coefficients are on the scale of the standardised covariates. If we focus on the coefficients for the covariate-specific ROC curve, there seems that the discriminatory capacity of the BMI decreases with age, with the decrease being more pronounced in women (note that the expression of the covariate-specific ROC curve in (30) implies that positive coefficients correspond with a decrease in discriminatory capacity). These results are possibly better judged by plotting the estimated covariate-specific ROC curves and associated AUCs. This can be done using the `plot` function. For the covariate-specific ROC curve, the depicted graphics will depend on the number and nature of the covariates included in the analyses. In particular, for our application, we obtain, separately for men and women, the covariate-specific ROC curves (and AUCs) along age. These are shown in Figure 6, obtained using the code.

```R
R> op <- par(mfrow = c(2,2))
R> plot(cROC_sp, ask = FALSE)
R> par(op)
```

In this example we have modelled the `age` effect linearly and only one mixture component was considered. However, `ROCNReg` also allows for modelling the effect of continuous covariates in a nonlinear way, either using kernel-based smoothers (via the function `cROC.kernel`) or cubic B-spline basis expansions (through the function `cROC.bnp`). Also, as noted before, using only one mixture component for the dependent Dirichlet process mixture of normals model (function `cROC.bnp`) is equivalent to consider a (Bayesian) normal model, which might be too restrictive for most data applications. In what follows, we provide more flexibility to the model for the covariate-specific ROC curve by means of (a) increasing the number of mixture components, and (b) modelling the `age` effect in a nonlinear way (recall our considerations in Section 4 about the lack of flexibility of the single-weights dependent Dirichlet process mixture of normals when covariates effects on the components’ means are modelled linearly). The former is done by modifying the value of `L` in the arguments `prior.h` and `prior.d`,
Figure 6: Graphical results as provided by the `plot.cROC` function for an object of class `cROC.bnp`. Results for the model that includes the linear interaction between `age` and `gender` and one mixture component. Top row: Posterior mean of the covariate-specific ROC curve along `age`, separately for men and women. Bottom row: Posterior mean and 95% pointwise credible band for the covariate-specific AUC along `age`, separately for men and women.

with 10 being the default value. Regarding the latter, this is done by making use of the function `f` when specifying the component’s mean functions through `formula.healthy` and `formula.diseased`. In particular, in our application we are interested in modelling the factor-by-curve interaction between `age` and `gender` (i.e., we model `age` effect “separately” for men and women). This is done using, e.g., `bmi ~ gender + f(age, by = gender, K = c(3,5))`. Though argument `K` we indicate the number of internal knots for constructing the cubic B-spline basis that is used to approximate the nonlinear effect of `age` (with the quantiles of `age` used for their location). Note that we can specify a different number of internal knots for men and women (`K = c(3,5)`), where the order of vector `K` should match the ordering
of the levels of the factor gender. When using cubic B-spline basis, one is faced with the
decision about the number of knots (in ROCnReg the location is always based on quantiles).
Here, the task of selecting the number of interior knots is assisted by the WAIC, DIC, and/or
LPML, i.e., we fit the model for different number of internal knots and consider the model
that provided the lowest WAIC/DIC or the highest LPML (this is done in both the healthy
and diseased populations and we remark that the number of knots does not need to be the
same in the two). The final model is shown below.

```r
R> # Levels of gender, and its ordering.
R> # Needed if we want to specify different
R> # number of knots for men and women
R> levels(endosyn$gender) ####### TODO
[1] "Men"  "Women"

R> set.seed(123) # for reproducibility
R> cROC_bnp <- cROC.bnp(
+   formula.healthy = bmi ~ gender + f(age, by = gender, K = c(0,0)),
+   formula.diseased = bmi ~ gender + f(age, by = gender, K = c(3,3)),
+   group = "cvd_idf",
+   tag.healthy = 0,
+   data = endosyn,
+   newdata = endopred,
+   standardise = TRUE,
+   p = seq(0, 1, len = 101),
+   compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
+   pauc = pauccontrol(compute = FALSE),
+   prior.h = priorcontrol.bnp(),
+   prior.d = priorcontrol.bnp(),
+   density = densitycontrol(compute = TRUE),
+   mcmc = mcmccontrol(nsave = 20000, nburn = 8000, nskip = 1))
R> summary(cROC_bnp)

Call: [...] 

Approach: Conditional ROC curve - Bayesian nonparametric

Model selection criteria:

|              | Healthy  | Diseased |
|--------------|----------|----------|
| WAIC         | 11832.688| 3916.557 |
| WAIC (Penalty)| 28.278  | 33.897   |
| LPML         | -5916.370| -1958.513|
| DIC          | 11830.206| 3912.840 |
| DIC (Penalty)| 27.037  | 32.039   |
```
Sample sizes:

| Healthy | Diseased |
|---------|----------|
| 2149    | 691      |

The graphical results are shown in Figure 7. Note that, especially for women, age displays a marked nonlinear effect. Recall that for objects of class `cROCs.bnp`, and if required in the call to the function, the `summary` function provides, separately for the diseased and nondiseased/healthy groups, the WAIC, LPML, and DIC. Note that, in both cases, the three criteria support the use of the more flexible model that uses B-splines and 10 mixture components for modelling the distribution of the BMI (model `cROCs_bnp`) over the more restrictive Bayesian normal linear model (model `cROCs_bp`). Since WAIC, LPML, and DIC are relative criteria, posterior predictive checks were also implemented in `ROCnReg` through the function `predictive.checks`. Specifically, the function generates replicated datasets from the posterior predictive distribution in both class $D$ and $\bar{D}$ and compares them to the test values (BMI values in our application) using specific statistics. For the choice of such statistics we follow Gabry, Simpson, Vehtari, Betancourt, and Gelman (2019), who suggest choosing statistics that are ‘orthogonal’ to the model parameters. Since we are using a location-scale mixture of normals model, we use here the skewness and kurtosis and check how well the posterior predictive distribution captures these two quantities.

Results are shown in Figure 8. As can be seen, the model that includes the factor-by-curve interaction between age and gender and 10 mixture components performs quite well in capturing both quantities, while the Bayesian normal linear model fails to do so. Also shown in Figure 8 (and provided by function `predictive.checks`) are the kernel density estimates of 500 randomly selected datasets drawn from the posterior predictive distribution, in each group, compared to the kernel density estimate of the observed BMI (in each group). Again, the more flexible model, as opposed to the Bayesian normal linear model, is able to simulate data that are very much similar to the observed BMI values.

As for the pooled ROC curve (Section 4.1), `ROCnReg` also provides a function that allows obtaining (optimal) threshold values for the covariate-specific ROC curve. For illustration, instead of the threshold values based on the Youden Index, we now use the criterion that sets
**ROCnReg: An R Package for ROC Inference**

Figure 7: Graphical results as provided by the `plot.cROC` function for an object of class `cROC.bnp`. Results for the model that includes the factor-by-curve interaction between `age` and `gender` and 10 mixture components. Top row: Posterior mean of the covariate-specific ROC curve along age, separately for men and women. Bottom row: Posterior mean and 95% pointwise credible band for the covariate-specific AUC along age, separately for men and women.

A target value for the FPF. The code for model `cROC_bnp`, when setting the FPF = 0.3, is as follows.

```r
R> th_fpf_cROC_bnp <- compute.threshold.cROC(cROC_bnp, + criterion = "FPF", FPF = 0.3, newdata = endopred)
R> names(th_fpf_cROC_bnp)

[1] "newdata" "thresholds" "TPF" "FPF" "call"
```
Figure 8: Graphical results as provided by the `predictive.checks` function for an object of class `cROC.bnp`. Histograms of the statistics `skewness` and `kurtosis` computed from 8000 draws from the posterior predictive distribution in the diseased and nondiseased group. The red line is the estimated statistic from the observed BMI values. The right-hand side plots show the kernel density estimate of the observed BMI (solid black line), jointly with the kernel density estimates for 500 simulated datasets drawn from the posterior predictive distributions.

In addition to the data frame `newdata` containing the covariate values at which the thresholds are computed, function `compute.threshold.cROC` returns the covariate-specific thresholds corresponding to the specified FPF (posterior mean and 95% pointwise credible intervals).
as well as the covariate-specific TPF (posterior mean and 95% pointwise credible intervals) attached to these thresholds. Although ROCnReg does not provide a function for plotting the results obtained using `compute.threshold.cROC`, graphical results can be easily obtained. For simplicity, we only show here the code for the covariate-specific threshold values (`thresholds`), but a similar code can be used to plot the covariate-specific TPFs (TPF). Both plots are shown in Figure 9. As can be observed, for a FPF of 0.3, the BMI age-specific thresholds tend to increase with age both for men and women, although for the latter there is a slight decrease after an age of about 70 years old. The age-specific TPFs corresponding to the thresholds for which the FPF is 0.3 show a nonlinear behaviour and these are in general higher for women than for me (of the same age).

```r
df <- data.frame(age = th_fpf_cROC_bnp$newdata$age, 
+                  gender = th_fpf_cROC_bnp$newdata$gender, 
+                  y = th_fpf_cROC_bnp$thresholds[[1]]$"est", 
+                  ql = th_fpf_cROC_bnp$thresholds[[1]]$"ql"), 
+                  qh = th_fpf_cROC_bnp$thresholds[[1]]$"qh")) $#### TODO

R> g0 <- ggplot(df, aes(x = age, y = y, ymin = ql, ymax = qh)) + 
+     geom_line() + 
+     geom_ribbon(alpha = 0.2) + 
+     labs(title = "Covariate-specific thresholds for a FPF = 0.3", 
+           x = "Age (years)", y = "BMI") + 
+     theme(strip.text.x = element_text(size = 20), 
+           plot.title = element_text(hjust = 0.5, size = 20), 
+           axis.title = element_text(size = 20), 
+           axis.title = element_text(size = 20)) + 
+     facet_wrap(~gender)
R> print(g0)
```

Finally, we mention that for conciseness we have not shown here how to perform convergence diagnostics of the MCMC chains for models fitted using `cROC.bnp`. In very much the same way as shown in Section 4.1 for the object `pROC_dpm`, using the information contained in component `dens` in the list of returned values (if required), one can produce trace plots of the conditional densities at some sampled values, as well as, obtain the corresponding effective sample sizes.

### 4.3. Covariate-adjusted ROC curve

In this last section we illustrate how to conduct inference about the covariate-adjusted ROC curve using ROCnReg. Similarly to the covariate-specific ROC curve, three approaches are available, namely, function `AROC.sp` implements the frequentist approaches that postulate that test outcomes in the nondiseased group follow a linear model with the CDF of the error term being either normally distributed or estimated via the empirical CDF of the standardised residuals, `AROC.kernel` corresponds to the kernel-based counterpart, and `AROC.bnp` implements the Bayesian (nonparametric) approach based on a single-weights dependent Dirichlet process mixture of normal distributions and the Bayesian bootstrap.

Recall that the AROC curve is a global summary measure of diagnostic accuracy that takes covariate information into account. In the context of our endocrine application we seek to
study the overall discriminatory capacity of the BMI for detecting the presence of CVD risk factors when adjusting for age and gender. Here we focus on how to estimate the AROC curve using the \texttt{AROC.bnp} function. The function syntax is exactly similar to the one of \texttt{cROC.bnp}, with the only difference being that we only need to specify the formula for the components’ means in the nondiseased population. The code and respective summary follow.

\begin{verbatim}
R > AROC_bnp <- AROC.bnp(
  +   formula.healthy = bmi ~ gender + f(age, by = gender, K = c(0,0)),
  +   group = "cvd_idf",
  +   tag.healthy = 0,
  +   data = endosyn,
  +   standardise = TRUE,
)  
\end{verbatim}
`ROCnReg`: An R Package for ROC Inference

```r
+ p = seq(0, 1, len = 101),
+ compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
+ pauc = pauccontrol(compute = FALSE),
+ prior = priorcontrol.bnp(),
+ density = densitycontrol.aroc(compute = FALSE),
+ mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1))

R > summary(AROC_bnp)

Call: [...]  

Approach: AROC Bayesian nonparametric  

Area under the covariate-adjusted ROC curve: 0.656 (0.628, 0.685)

Model selection criteria:  

| Healthy      |    |
|--------------|----|
| WAIC         | 11832.688 |
| WAIC (Penalty)| 28.278  |
| LPML         | -5916.370 |
| DIC          | 11830.206 |
| DIC (Penalty)| 27.037  |

Sample sizes:  

| Healthy | Diseased |
|---------|----------|
| Number of observations | 2149 | 691 |
| Number of missing data | 0 | 0 |

The area under the AROC curve (posterior mean) is 0.655 (95% credible interval: (0.627, 0.683)) thus revealing a reasonable good ability of the BMI to detect the presence of CVD risk factors, when teasing out the age and gender effects. As for the pooled ROC curve and the covariate-specific ROC curve, a plot function is also available (result in Figure 10(a)).

R> plot(AROC_bnp, cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.3)

We finish with a comparison of the AROC curve with the pooled ROC curve that was obtained earlier by using a DPM model with 10 components in each group. In Figure 10(b) we show the plots of the two curves and, can be noticed, the pooled ROC curve lies well above the AROC curve, thus evidencing the need for incorporating covariate information into the analysis.

R> plot(AROC_bnp$p, AROC_bnp$ROC[,1],
+ type = "l", xlim = c(0,1), ylim = c(0,1),
+ xlab = "FPF", ylab = "TPF",
+ main = "Pooled ROC curve vs AROC curve",
+ cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.5)
R> lines(AROC_bnp$p, AROC_bnp$ROC[,2], col = 1, lty = 2)
5. Summary and future plans

In this paper we have introduced the capabilities of the R package \texttt{ROCnReg} for conducting inference about the pooled ROC curve, the covariate-specific ROC curve, and the covariate-adjusted ROC curve and their associated summary indices. As we have illustrated, the current version of the package provides several options for estimating ROC curves, both under frequentist and Bayesian paradigms, either parametrically, semiparametrically, or nonparametrically. To the best of our knowledge, this is the first software package implementing Bayesian inference for ROC curves. Several additions/extensions are planned in the future and these, among others, include:

- Make the MCMC algorithm faster by implementing its time-consuming parts in C++.
- Incorporate methods for non-binary disease status (e.g., no disease, mild disease, severe disease). That is, implement ROC surface models.
• Implement new (optimal) threshold criteria (e.g., YI including costs).

Computational details

The results in this paper were obtained using R 3.6.3 with the ROCnReg 1.0 package. The ROCnReg package has multiple dependencies: `stats`, `graphics`, `grDevices`, `splines`, `moments` (Komsta and Novomestky 2015), `nor1mix` (Maechler 2019), `Matrix` (Bates and Maechler 2019), `spatstat` (Baddeley and Turner 2005), `np` (Hayfield and Racine 2008), `lattice` (Sarkar 2008), `MASS` (Venables and Ripley 2002) and `pbivnorm` (Genz and Kenkel 2015). R itself and all packages used are available from the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org/.

Acknowledgments

MX Rodríguez-Álvarez was funded by project MTM2017-82379-R (AEI/FEDER, UE), by the Basque Government through the BERC 2018-2021 program and by the Spanish Ministry of Science, Innovation, and Universities (BCAM Severo Ochoa accreditation SEV-2017-0718). The work of V Inácio was partially supported by FCT (Fundação para a Ciência e a Tecnologia, Portugal), through the projects PTDC/MAT-STA/28649/2017 and UID/MAT/00006/2020.

References

Baddeley A, Turner R (2005). “spatstat: An R Package for Analyzing Spatial Point Patterns.” Journal of Statistical Software, 12(6), 1–42. URL http://www.jstatsoft.org/v12/i06/.

Bates D, Maechler M (2019). Matrix: Sparse and Dense Matrix Classes and Methods. R package version 1.2-17, URL https://CRAN.R-project.org/package=Matrix.

Buolamwini JA (2017). Gender shades: intersectional phenotypic and demographic evaluation of face datasets and gender classifiers. Ph.D. thesis, Massachusetts Institute of Technology, School of Architecture and Planning, Program in Media Arts and Sciences.

Celeux G, Forbes F, Robert CP, Titterington DM (2006). “Deviance information criteria for missing data models.” Bayesian Analysis, 1(4), 651–673.

De Iorio M, Johnson WO, Müller P, Rosner GL (2009). “Bayesian nonparametric nonproportional hazards survival modeling.” Biometrics, 65(3), 762–771.

Erkanli A, Sung M, Jane Costello E, Angold A (2006). “Bayesian semi-parametric ROC analysis.” Statistics in Medicine, 25(22), 3905–3928.

Fan J, Gijbels I (1996). Local Polynomial Modelling and Its Applications. Monographs on Statistics and Applied Probability. Chapman & Hall/CRC.

Faraggi D (2003). “Adjusting receiver operating characteristic curves and related indices for covariates.” The Statistician, 52(2), 179–192.
Ferguson TS (1973). “A Bayesian analysis of some nonparametric problems.” The Annals of Statistics, 1(2), 209–230.

Gabry J, Simpson D, Vehtari A, Betancourt M, Gelman A (2019). “Visualization in Bayesian workflow.” Journal of the Royal Statistical Society: Series A, 182(2), 389–402.

Geisser S, Eddy WF (1979). “A predictive approach to model selection.” Journal of the American Statistical Association, 74(365), 153–160.

Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB (2013). Bayesian Data Analysis. Chapman and Hall/CRC.

Gelman A, Hwang J, Vehtari A (2014). “Understanding predictive information criteria for Bayesian models.” Statistics and Computing, 24(6), 997–1016.

Genz A, Kenkel B (2015). pbivnorm: Vectorized Bivariate Normal CDF. R package version 0.6.0, URL https://CRAN.R-project.org/package=pbivnorm.

Gonçalves L, Subtil A, Oliveira MR, Bermudez P (2014). “ROC curve estimation: an overview.” REVSTAT–Statistical Journal, 12(1), 1–20.

González-Manteiga W, Pardo-Fernández JC, van Keilegom I (2011). “ROC curves in non-parametric location-scale regression models.” Scandinavian Journal of Statistics, 38(1), 169–184.

Gu J, Ghosal S, Roy A (2008). “Bayesian bootstrap estimation of ROC curve.” Statistics in Medicine, 27, 5407–5420.

Guan Z, Qin J, Zhang B (2012). “Information borrowing methods for covariate-adjusted ROC curve.” Canadian Journal of Statistics, 40(3), 569–587.

Hayfield T, Racine JS (2008). “Nonparametric Econometrics: The np Package.” Journal of Statistical Software, 27(5). URL http://www.jstatsoft.org/v27/i05/.

Hillis SL, Metz CE (2012). “An Analytic Expression for the Binormal Partial Area under the ROC Curve.” Academic Radiology, 19(12), 1491 – 1498.

Hsieh F, Turnbull BW (1996). “Nonparametric and semiparametric estimation of the receiver operating characteristic curve.” The Annals of Statistics, 24(1), 25–40.

Hutchinson B, Mitchell M (2019). “50 Years of Test (Un)Fairness: Lessons for Machine Learning.” In Proceedings of the Conference on Fairness, Accountability, and Transparency, FAT* ’19, pp. 49–58. ACM, New York, NY, USA. ISBN 978-1-4503-6125-5.

Inácio de Carvalho V, de Carvalho M, Branscum AJ (2017). “Nonparametric Bayesian covariate-adjusted estimation of the Youden index.” Biometrics, 73(4), 1279–1288.

Inácio de Carvalho V, Jara A, Hanso TE, de Carvalho M (2013). “Bayesian Nonparametric ROC Regression Modeling.” Bayesian Analysis, 8(3), 623–646.

Inácio de Carvalho V, Rodríguez-Álvarez MX (2018). “Bayesian nonparametric inference for the covariate-adjusted ROC curve.” 1806.00473.
Ishwaran H, James LF (2001). “Gibbs sampling methods for stick-breaking priors.” *Journal of the American Statistical Association, 96*(453), 161–173.

Ishwaran H, James LF (2002). “Approximate Dirichlet process computing in finite normal mixtures: smoothing and prior information.” *Journal of Computational and Graphical Statistics, 11*(3), 508–532.

Janes H, Pepe MS (2009). “Adjusting for covariate effects on classification accuracy using the covariate-adjusted receiver operating characteristic curve.” *Biometrika, 96*(2), 371–382.

Komsta L, Novomestky F (2015). *moments: Moments, cumulants, skewness, kurtosis and related tests*. R package version 0.14, URL https://CRAN.R-project.org/package=moments.

Liu JS (1996). “Nonparametric hierarchical Bayes via sequential imputations.” *The Annals of Statistics, 24*(3), 911–930.

López-Ratón M, Rodríguez-Álvarez MX, Cadarso-Suárez C, Gude-Sampedro F (2014). “OptimalCutpoints: an R package for selecting optimal cutpoints in diagnostic tests.” *Journal of Statistical Software, 61*(8), 1–36.

MacEachern SN (2000). “Dependent dirichlet processes.” *Unpublished manuscript, Department of Statistics, The Ohio State University*, pp. 1–40.

Maechler M (2019). *nor1mix: Normal aka Gaussian (1-d) Mixture Models (S3 Classes and Methods)*. R package version 1.3-0, URL https://CRAN.R-project.org/package=nor1mix.

Metz CE (1978). “Basic principles of ROC analysis.” *Seminars in Nuclear Medicine, 8*(4), 283 – 298.

Pardo-Fernández JC, Rodríguez-Álvarez MX, van Keilegom I (2014). “A review on ROC curves in the presence of covariates.” *REVSTAT-Statistical Journal, 12*(1), 21–41.

Pepe MS (1998). “Three Approaches to Regression Analysis of Receiver Operating Characteristic Curves for Continuous Test Results.” *Biometrics, 54*(1), 124–135.

Pepe MS (2003). *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford Statistical Sciences Series. Oxford University Press, New York.

Perez Jaume S, Skaltsa K, Pallarès N, Carrasco Jordan JL (2017). “ThresholdROC: optimum threshold estimation tools for continuous diagnostic tests in R.” *Journal of Statistical Software, 82*(4), 1–21.

Plummer M, Best N, Cowles K, Vines K (2006). “CODA: Convergence Diagnosis and Output Analysis for MCMC.” *R News, 6*(1), 7–11. URL https://journal.r-project.org/archive/.

R Core Team (2020). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
Robin X, Turek N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Müller M (2011). “pROC: an open-source package for R and S+ to analyze and compare ROC curves.” *BMC Bioinformatics, 12*, 77.

Rodríguez-Alvarez MX, Roca-Pardiñas J (2017). **npROCRegression**: Kernel-Based Non-parametric ROC Regression Modelling. R package version 1.0-5, URL [https://CRAN.R-project.org/package=npROCRegression](https://CRAN.R-project.org/package=npROCRegression).

Rodríguez-Álvarez MX, Roca-Pardiñas J, Cadarso-Suárez C (2011a). “A new flexible direct ROC regression model: Application to the detection of cardiovascular risk factors by anthropometric measures.” *Computational Statistics & Data Analysis, 55*(12), 3257–3270.

Rodríguez-Álvarez MX, Roca-Pardiñas J, Cadarso-Suárez C (2011b). “ROC curve and covariates: extending induced methodology to the non-parametric framework.” *Statistics and Computing, 21*(4), 483–499.

Rodríguez-Álvarez MX, Tahoces PG, Cadarso-Suárez C, Lado MJ (2011c). “Comparative study of ROC regression techniques – Applications for the computer-aided diagnostic system in breast cancer detection.” *Computational Statistics & Data Analysis, 55*(1), 888–902.

Rosenberg PS (1995). “Hazard function estimation using B-splines.” *Biometrics, 51*(3), 874–887.

Sarkar D (2008). **Lattice**: Multivariate Data Visualization with R. Springer, New York. ISBN 978-0-387-75968-5, URL [http://lmdvr.r-forge.r-project.org](http://lmdvr.r-forge.r-project.org).

Shapiro DE (1999). “The interpretation of diagnostic tests.” *Statistical Methods in Medical Research, 8*(2), 113–134.

Silverman BW (1986). *Density Estimation for Statistics and Data Analysis*. Chapman & Hall/CRC.

Tomé Martínez de Rituerto MA, Botana MA, Cadarso-Suárez C, Rego-Iraeta A, Fernández-Mariño A, Mato JA, Solache I, Perez-Fernandez R (2009). “Prevalence of metabolic syndrome in Galicia (NW Spain) on four alternative definitions and association with insulin resistance.” *Journal of Endocrinological Investigation, 32*(6), 505–511.

Venables WN, Ripley BD (2002). *Modern Applied Statistics with S*. Fourth edition. Springer, New York. ISBN 0-387-95457-0, URL [http://www.stats.ox.ac.uk/pub/MASS4](http://www.stats.ox.ac.uk/pub/MASS4).

Wand MP, Jones MC (1994). **Kernel Smoothing**. Chapman & Hall/CRC.

Wang XF (2012). **sROC**: Nonparametric Smooth ROC Curves for Continuous Data. R package version 0.1-2, URL [https://CRAN.R-project.org/package=sROC](https://CRAN.R-project.org/package=sROC).

Wickham H (2016). **ggplot2**: Elegant Graphics for Data Analysis. Springer-Verlag New York. ISBN 978-3-319-24277-4. URL [https://ggplot2.tidyverse.org](https://ggplot2.tidyverse.org).

Youden WJ (1950). “Index for rating diagnostic tests.” *Cancer, 3*(1), 32–35.

Zhou XH, Obuchowski NA, McClish DK (2002). *Statistical Methods in Diagnostic Medicine*. Wiley: New York.
Zou KH, Hall WJ, Shapiro DE (1997). “Smooth non-parametric receiver operating characteristic (ROC) curves for continuous diagnostic tests.” *Statistics in Medicine, 16*(19), 2143–2156.

**Affiliation:**
Maria Xosé Rodríguez-Álvarez  
BCAM - Basque Center for Applied Mathematics  
and  
IKERBASQUE, Basque Foundation for Science  
Alameda de Mazarredo, 14  
E-48009 Bilbao, Basque Country, Spain  
E-mail: mxrodriguez@bcamath.org

Vanda Inácio  
School of Mathematics  
University of Edinburgh  
James Clerk Maxwell Building, The King’s Buildings, Peter Guthrie Tait Road  
EH9 3FD Edinburgh, Scotland, United Kingdom  
E-mail: vanda.inacio@ed.ac.uk