Generalizations of the Receiver Operating Characteristic (ROC) Curve

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Talk overview

1. ROC curve overview
   - Definition
   - Empirical non-parametric estimator
   - Asymptotic properties
   - Area under the ROC curve
2. ROC curve generalization
   - Motivation and definition
   - Non-parametric estimator
   - Asymptotic properties
   - Area under the ROC curve
3. Real data applications
   - Leukocyte count and mortality risk in critically ill children
   - Response to the OnabotulinumtoxinA treatment for the chronic migraine headaches and the CGRP levels in women
4. Future work
5. Conclusions

ROC curve overview. Definition

The well-known receiver operating characteristic (**ROC**) curve (Green and Swets, 1966) is a very useful instrument to measure how well a (bio)marker is able to distinguish two populations (frequently healthy vs. diseased) from each other.

It displays in a plot the sensitivity (S_E) or true-positive rate (TPR) against the false-positive rate (FPR) or 1-specificity ($1 - S_P$) for each possible threshold, $x \in \mathbb{R}$.

ROC curve overview. Definition

Hence, the ROC curve is the geometric place of the points $\{1 - S_P(x); S_E(x)\}$ with $x \in \mathbb{R}$.

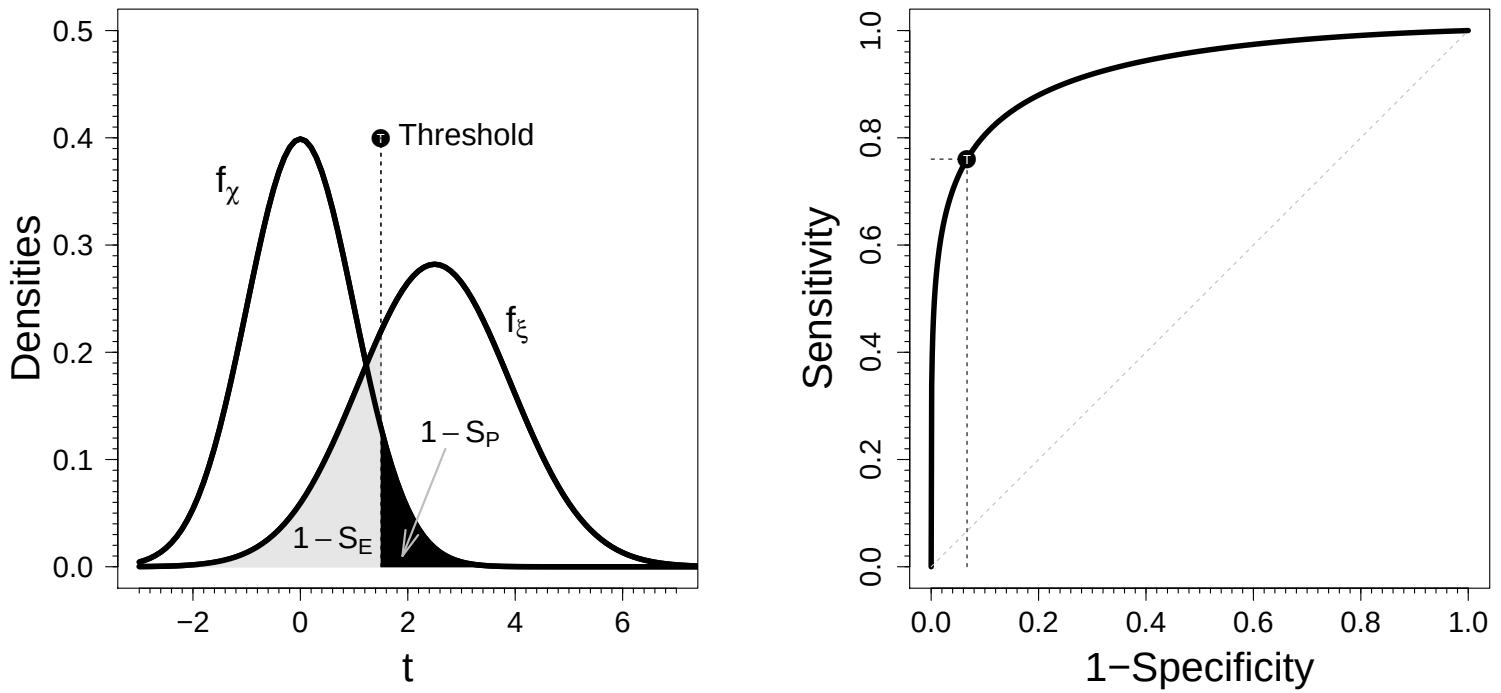


Figure: *Density functions for the negative and positive subjects (left) and corresponding ROC curve (right).*

ROC curve overview. Definition

Conventionally (wlg), it is assumed that the larger values of the marker indicate the larger confidence that a given subject is positive. Let χ and ξ be two random variables representing the (bio)marker values for negative and positive subjects, respectively, for a fixed point $t \in [0, 1]$, the ROC curve is

Definition

$$\begin{aligned}\mathcal{R}(t) =& 1 - F_\xi(F_\chi^{-1}(1-t)) \\ =& \mathcal{P}\{\xi > F_\chi^{-1}(1-t)\} \\ =& \mathcal{P}\{1 - F_\chi(\xi) \leq t\} = F_{1-F_\chi(\xi)}(t), \end{aligned} \tag{1}$$

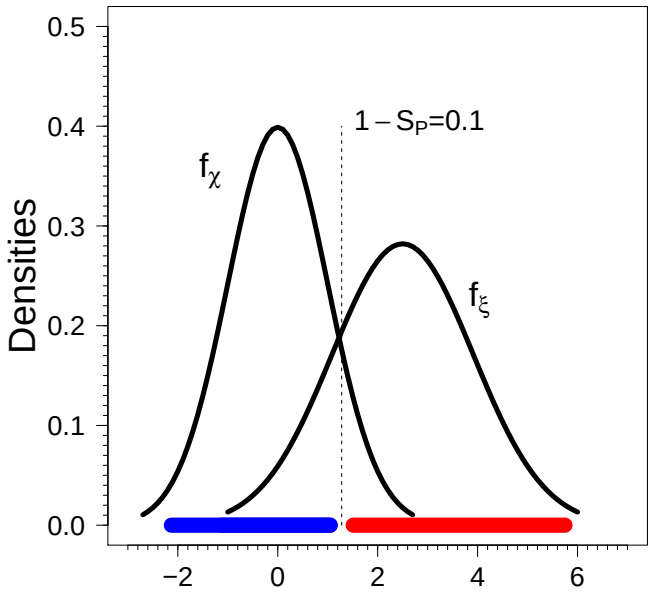
where F_χ and F_ξ denote the CDF for the variables χ and ξ.

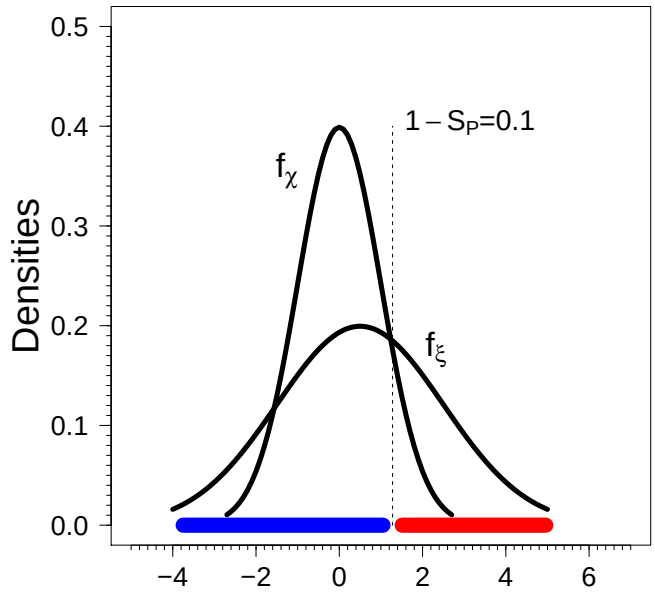
ROC curve overview. Definition

Note that, under the above assumption, the ROC curves can be read as

$$\mathcal{R}(t) = \sup_{u_t \in \mathcal{U}_t} \mathcal{P}\{\xi \in u_t\} \tag{2}$$

where $\mathcal{U}_t = \{u_t = [a, \infty),\ a \in \mathbb{R}$ such that $\mathcal{P}\{\chi \in u_t\} \leq t\}$.





ROC curve overview. Empirical non-parametric estimator

The direct empirical non-parametric ROC curve estimator is the resulting of replacing, in (1), the (unknown) CDF by the ECDF. Let X and Y be two random samples drawed from ξ and χ, for each $t \in [0, 1]$, the empirical ROC curve estimator is defined by

Definition

$$\hat{\mathcal{R}}(t) = 1 - \hat{F}_n(X, \hat{F}_m^{-1}(Y, (1-t)), \tag{3}$$

where $\hat{F}_n(X, \cdot)$ is the ECDF referred to the sample X (with size n) and $\hat{F}_m^{-1}(Y, \cdot) = \inf\{s \in \mathbb{R} / \hat{F}_m(Y, s) \geq \cdot\}$.

ROC curve overview. Asymptotic properties

Of course, asymptotic properties have been deeply studied. Hsieh and Turnbull (1995) enunciated the results:

Theorem (consistency)

Under usual (and mild) conditions,

$$\|\hat{\mathcal{R}} - \mathcal{R}\|_\infty \to_n 0 \ \ a.s.$$

and,

Theorem (weak convergence)

Under usual (and mild) conditions,

$$\sqrt{n} \cdot [\hat{\mathcal{R}}(t) - \mathcal{R}(t)] = \lambda^{1/2} \cdot r(t) \cdot B_1^{(m)}(1-t) + B_2^{(n)}(1-\mathcal{R}(t)) + o(1) \ a.s.$$

where $r = \mathcal{R}'$, $\lambda = \lim(m/n)$ *and* $B_1^{(m)}$, $B_2^{(n)}$ *Brownian Bridges.*

ROC curve overview. Area under the curve

The area under the ROC curve (AUC), defined as

Definition

$$\mathcal{A} = \int \mathcal{R}(t)dt, \tag{4}$$

is frequently used for summarizing the diagnostic capacity. In (this) *right-side* context, it has a direct probabilistic interpretarion,

$$\begin{aligned}\mathcal{A} =& 1 - \int F_\xi(F_\chi^{-1}(1-t))dt \\ =& 1 - \int F_\xi(u)dF_\chi(u) = \mathcal{P}\{\chi \leq \xi\}.\end{aligned}$$

ROC curve overview. Area under the curve

The direct non-parametric estimator (again, replacing unknown CDF by the respective ECDF) is the well-known Mann-Whitney statistics,

Definition

$$\hat{\mathcal{A}} = \frac{1}{n \cdot m} \sum_{i=1}^{n} \sum_{j=1}^{m} I\{y_j < x_i\}. \tag{5}$$

From the previous weak convergence is derived (Hsieh and Turnbull; 1995),

Theorem (weak convergence)

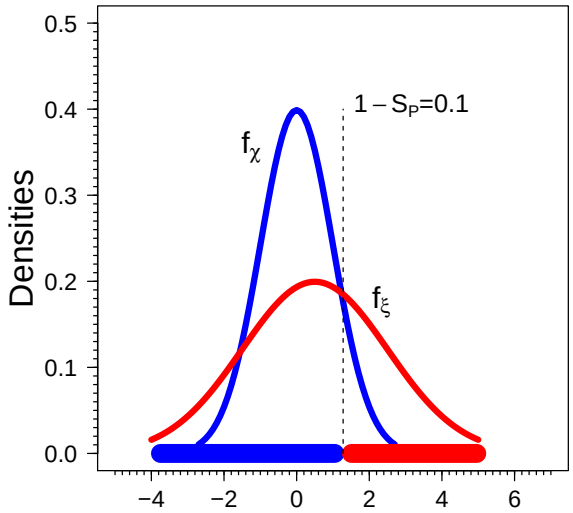
Under usual (and mild) conditions,

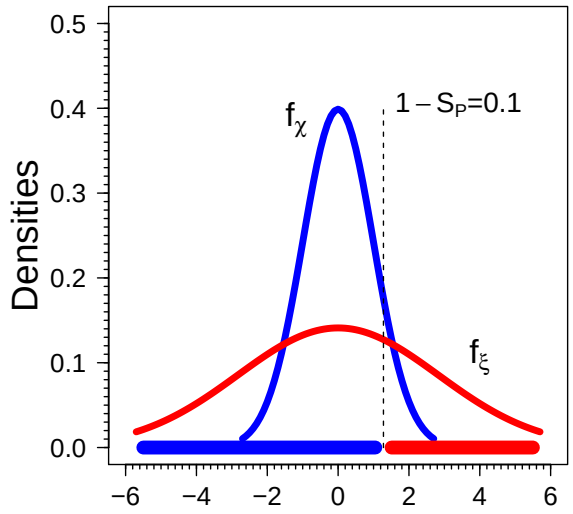
$$\sqrt{n} \cdot [\hat{\mathcal{A}} - \mathcal{A}] \longrightarrow_n N(0, \sigma_\lambda).$$

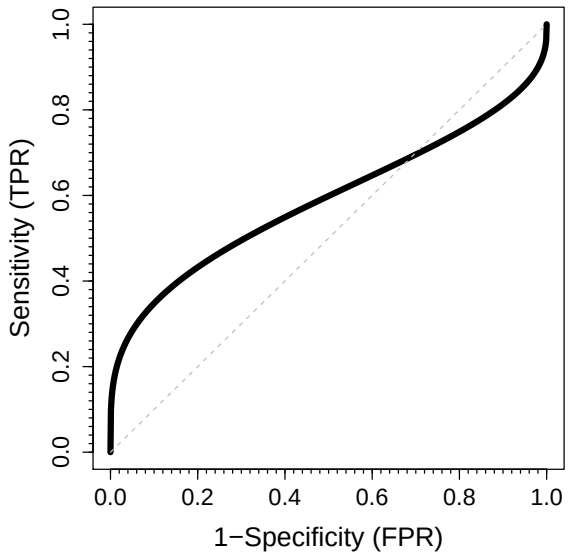
ROC curve generalization. Motivation and definition

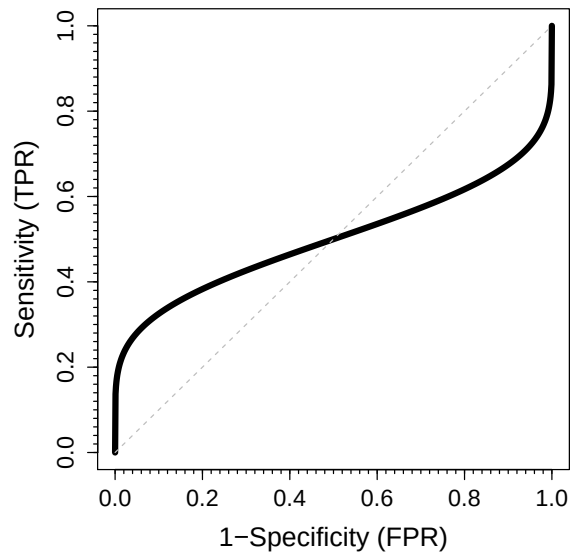
However, sometimes not only the larger (lower) marker values are associated with disease, but both the lower and larger values are related to the presence of the studied feature. For instance, in haemodialysis population, both the high and low levels of serum iPTH, calcium and phosphate are associated with higher risk of mortality. Also, in the intensive care units, leukocyte counts greater than 20,000 (leukocytosis) or below 5,000 (leukopenia) are associated with bad prognosis in critically ill patients.

ROC curve generalization. Motivation and definition









ROC curve generalization. Motivation and definition

From the ROC definition given in (2),

Remember!

$$\mathcal{R}(t) = \sup_{u_t \in \mathcal{U}_t} \mathcal{P}\{\xi \in u_t\},$$

where $\mathcal{U}_t = \{u_t = [a, \infty),\ a \in \mathbb{R} \text{ such that } \mathcal{P}\{\chi \in u_t\} \leq t\}$.

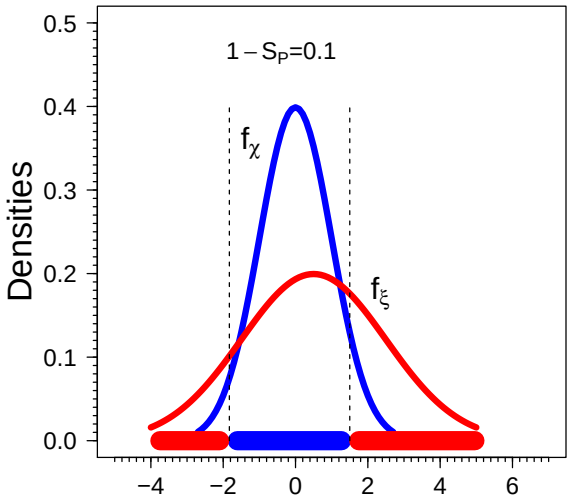
it can be extended to the *two-side* situations just considering the following definition

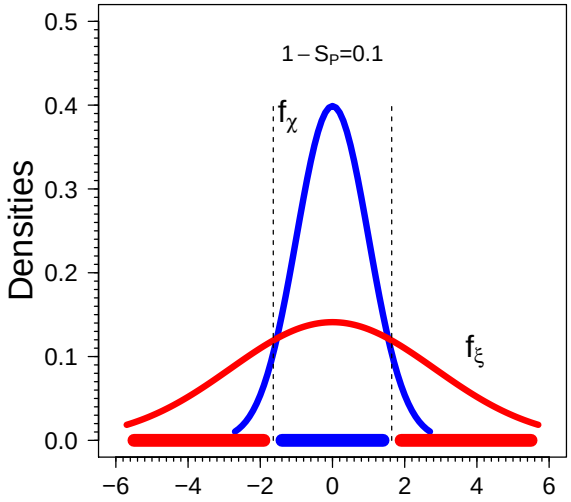
Definition

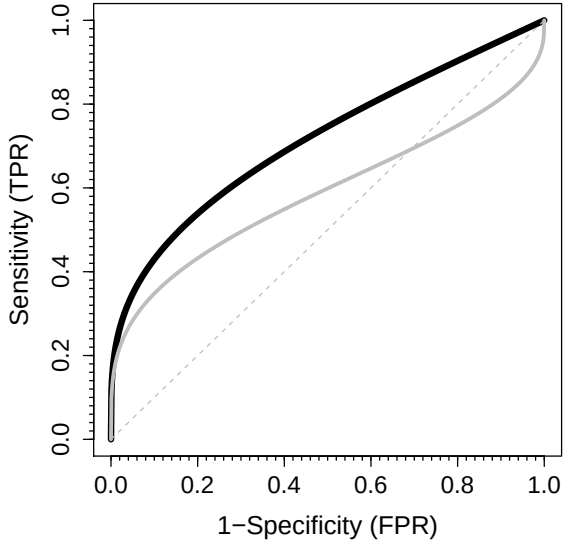
$$\mathcal{R}_g(t) = \sup_{v_t \in \mathcal{V}_t} \mathcal{P}\{\xi \in v_t\}, \tag{6}$$

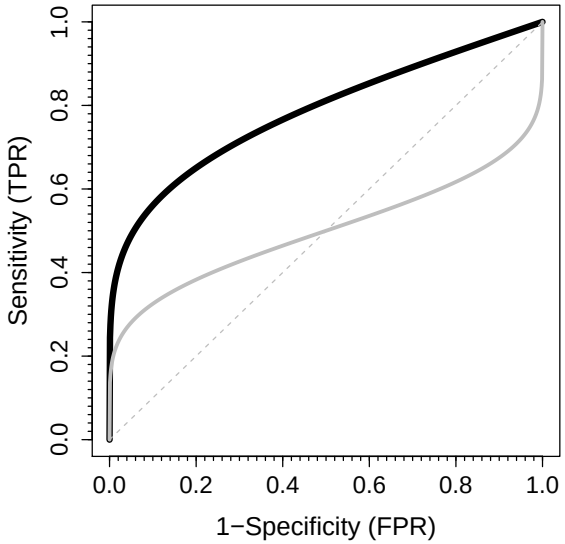
where $\mathcal{V}_t = \{v_t = (-\infty, x_l] \cup [x_u, \infty),\ x_l < x_u \in \mathbb{R} \text{ such that } \mathcal{P}\{\chi \in v_t\} \leq t\}$.

ROC curve generalization. Motivation and definition









ROC curve generalization. Motivation and definition

If for each $t \in [0,1]$ is defined

$$\mathcal{F}_t = \{(x_l, x_u) \in \mathbb{R}^2 \text{ such that } (-\infty, x_l] \cup [x_u, \infty) = v_t \in \mathcal{V}_t\},$$

from (6),

Remember!

$$\mathcal{R}_g(t) = \sup_{v_t \in \mathcal{V}_t} \mathcal{P}\{\xi \in v_t\},$$

where $\mathcal{V}_t = \{v_t \text{ such that } \mathcal{P}\{\chi \in v_t\} \leq t\}$.

$$\mathcal{R}_g(t) = \sup_{(x_l, x_u) \in \mathcal{F}_t} \{F_\xi(x_l) + 1 - F_\xi(x_u)\},$$

ROC curve generalization. Motivation and definition

Besides, given $t \in [0,1]$, for $(x_l, x_u) \in \mathcal{F}_t$ (which implies $F_\chi(x_l) + 1 - F_\chi(x_u) \leq t$), there exists $\gamma \in [0,1]$ ($\gamma = F_\chi(x_l)/t$) such that

$$F\chi(x_l) = \gamma \cdot t \Longrightarrow x_l = F_\chi^{-1}(\gamma \cdot t),$$

and then

$$F\chi(x_u) \geq 1 - [1-\gamma] \cdot t \Longrightarrow x_u \geq F_\chi^{-1}(1 - [1-\gamma] \cdot t).$$

Hence,

$$\mathcal{R}_g(t) = \sup_{\gamma \in (0,1)} \left\{ F_\xi(F_\chi^{-1}(\gamma \cdot t)) + 1 - F_\xi(F_\chi^{-1}(1 - [1-\gamma] \cdot t)) \right\}.$$

ROC curve generalization. Motivation and definition

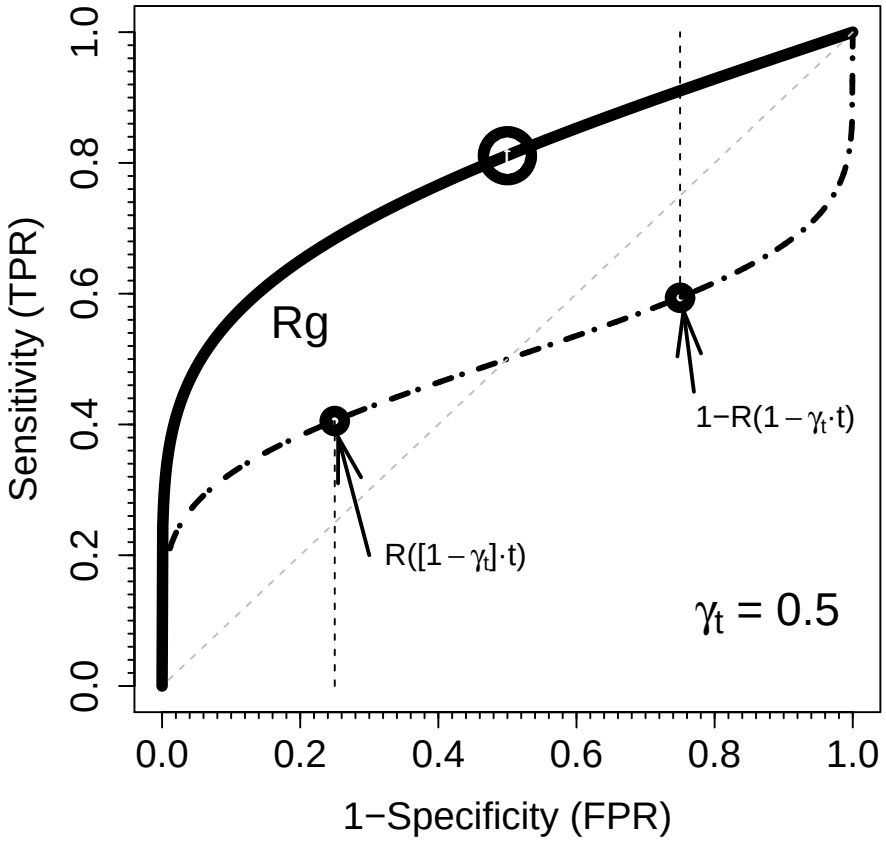
or, equivalently

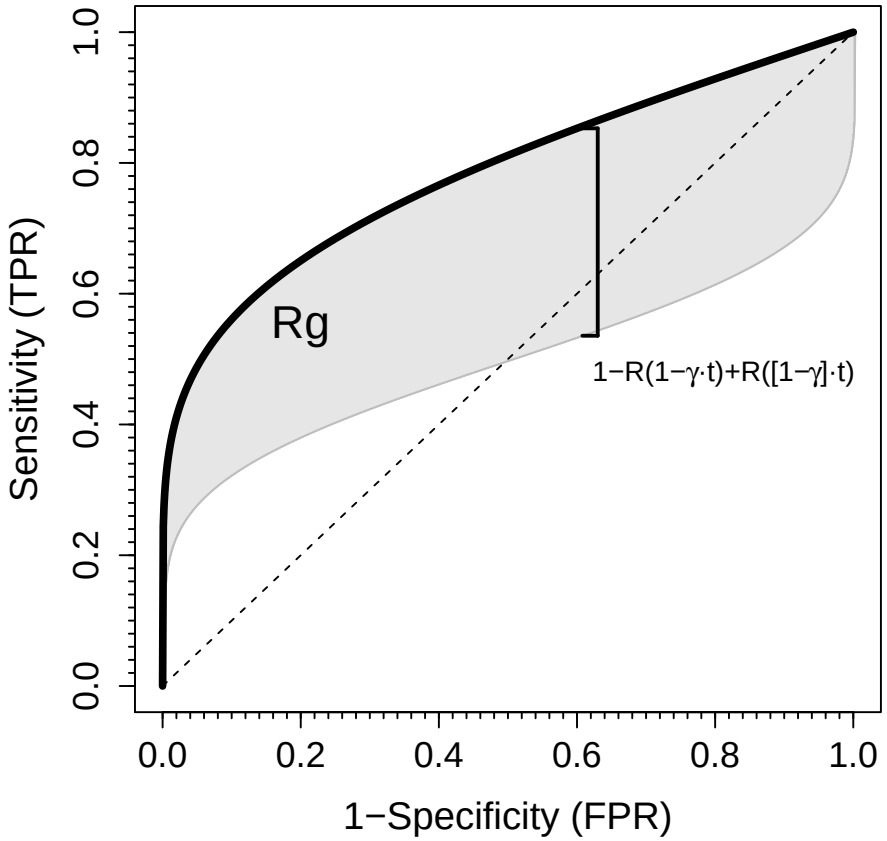
$$\begin{aligned}\mathcal{R}_g(t) &= \sup_{\gamma\in(0,1)} \{1-\mathcal{R}(1-\gamma\cdot t)+\mathcal{R}([1-\gamma]\cdot t)\} \\ &= \{1-\mathcal{R}(1-\gamma_t\cdot t)+\mathcal{R}([1-\gamma_t]\cdot t)\},\end{aligned}$$

where $\gamma_t = \arg\sup_{\gamma\in(0,1)} \{1-\mathcal{R}(1-\gamma\cdot t)+\mathcal{R}([1-\gamma]\cdot t)\}$.

The value of γ_t determines the optimum proportion of false-positives, $\boldsymbol{\gamma_t\cdot t}$, due to the negative subjects with a marker below x_l (left tail), and those due to the negative subjects with a marker larger than x_u (right tail), $\boldsymbol{[1-\gamma_t]\cdot t}$.

ROC curve generalization. Motivation and definition





ROC curve generalization. Non-parametric estimator

Replacing the unknown (right- and left-side) ROC curves from their empirical estimators (previous and directly defined in (3)) it is obtained the empirical estimator for $\mathcal{R}_g$,

Definition

$$\hat{\mathcal{R}}_g(t) = \sup_{\gamma\in[0,1]} \left\{1 - \hat{\mathcal{R}}(1-\gamma\cdot t) + \hat{\mathcal{R}}([1-\gamma]\cdot t)\right\} \tag{7}$$

$$= \left\{1 - \hat{\mathcal{R}}(1-\hat{\gamma}_t\cdot t) + \hat{\mathcal{R}}([1-\hat{\gamma}_t]\cdot t)\right\}. \tag{8}$$

where $\hat{\gamma}_t = \arg\sup_{\gamma\in[0,1]} \left\{1 - \hat{\mathcal{R}}(1-\gamma\cdot t) + \hat{\mathcal{R}}([1-\gamma]\cdot t)\right\}$.

The supremum can be (must be) computed by numerical methods.

ROC curve generalization. Asymptotic properties

Generalized ROC curve inherits most of the usual ROC curve properties. Particularly, can be *easily* derived the uniform consistency:

Theorem (consistency)

Under usual (and mild) conditions,

$$\|\hat{\mathcal{R}}_g - \mathcal{R}_g\|_\infty \to_n 0 \ \ a.s.$$

Proof

For each $t, \gamma \in [0,1]$, let be

$$\hat{\mathcal{H}}(t,\gamma) = \{1 - \hat{\mathcal{R}}(1 - \gamma \cdot t) + \hat{\mathcal{R}}([1-\gamma] \cdot t)\} \text{ and}$$
$$\mathcal{H}(t,\gamma) = \{1 - \mathcal{R}(1 - \gamma \cdot t) + \mathcal{R}([1-\gamma] \cdot t)\}.$$

Cont.

From the ROC curve properties, for each $\gamma \in [0,1]$,

$$\sup_{0 \leq t \leq 1} |\hat{\mathcal{H}}(t,\gamma) - \mathcal{H}(t,\gamma)| \longrightarrow_n 0 \quad a.s.$$

and the result is derived from the obvious inequalities,

$$\hat{\mathcal{R}}_g(t) - \mathcal{R}_g(t) \geq \hat{\mathcal{H}}(t,\hat{\gamma}_t) - \mathcal{H}(t,\hat{\gamma}_t),$$
$$\hat{\mathcal{R}}_g(t) - \mathcal{R}_g(t) \leq \hat{\mathcal{H}}(t,\gamma_t) - \mathcal{H}(t,\gamma_t).$$

□

ROC curve generalization. Asymptotic properties

When the function γ_t satisfies that γ_t' is bounded for each $t \in [0,1]$, then it holds

Theorem (weak convergence)

Under usual (and mild) conditions,

$$\begin{aligned}\sqrt{n}\cdot[\hat{\mathcal{R}}_g(t)-\mathcal{R}_g(t)] = \\ &\lambda^{1/2}\cdot[1-\gamma_t-\gamma_t'\cdot t]\cdot r([1-\gamma_t]\cdot t)\cdot B_1^{(m)}(1-[1-\gamma_t]\cdot t)\\ &+B_2^{(n)}(1-\mathcal{R}([1-\gamma_t]\cdot t))\\ &-\lambda^{1/2}\cdot[-\gamma_t-\gamma_t'\cdot t]\cdot r(1-\gamma_t\cdot t)\cdot B_1^{(m)}(\gamma_t\cdot t)\\ &-B_2^{(n)}(1-\mathcal{R}(1-\gamma_t\cdot t))+o(1) \qquad a.s.\end{aligned}$$

where $r=\mathcal{R}'$, $\lambda=\lim(m/n)$ *and* $B_1^{(m)}$, $B_2^{(n)}$ *Brownian Bridges.*

Proof

The proof is not difficult but it is really tedious. The standard ROC curve properties are applied on

$$\sqrt{n} \cdot [\hat{\mathcal{H}}(t, \gamma_t) - \mathcal{H}(t, \gamma_t)]$$

and the two-term Taylor expansion

$$\begin{aligned}\sqrt{n} \cdot \mathcal{H}(t, \hat{\gamma}_t) =& \sqrt{n} \cdot \mathcal{H}(t, \gamma_t) - \sqrt{n} \cdot h_{(2)}(t, \gamma_t) \cdot (\hat{\gamma}_t - \gamma_t) \\ &+ \frac{1}{2!} \cdot \sqrt{n} \cdot h'_{(2)}(t, \tau_t) \cdot (\hat{\gamma}_t - \gamma_t)^2\end{aligned}$$

with $\tau_t \in (\min\{\hat{\gamma}_t, \gamma_t\}, \max\{\hat{\gamma}_t, \gamma_t\})$. The γ_t definition and the M-statistics properties lead to the equality

$$\sqrt{n} \cdot \mathcal{H}(t, \hat{\gamma}_t) = \sqrt{n} \cdot \mathcal{H}(t, \gamma_t) + o(1) \quad a.s.$$

□

ROC curve generalization. Area under the gROC curve

Directly, the area under the generalizated ROC curve is

Definition

$$\mathcal{A}_g = \int \mathcal{R}_g(t)dt.$$

Its direct empirical estimator,

Definition

$$\hat{\mathcal{A}}_g = \int \hat{\mathcal{R}}_g(t)dt.$$

ROC curve generalization. Area under the gROC curve

Asymptotic distribution of $\hat{\mathcal{A}}_g$ can be derived, particularly, it can be obtain a result in the way,

Theorem (Weak convergence)

Under usual (and mild) conditions, and under regularity on γ_t.

$$\sqrt{n} \cdot [\hat{\mathcal{A}}_g - \mathcal{A}_g] \longrightarrow_n N(0, \delta_\lambda).$$

Unfortunately, the value of δ_λ^2 is not easy to compute, even assuming $\gamma_t' = 0$ (unrealistic). It must approximated via resampling.

Real data applications.
Leukocyte count and mortality risk in critically ill children

Background

- Having available tools to determine the risk of mortality at admission to the Paediatric Intensive Care Unit (PICU), or during the first 24 hours after admission, is a clinical necessity.
- Leukocyte count measurement constitutes a routinely determination when a patient is admitted to the PICU.
- Classically, low leukocyte or high leukocyte counts are described as one of the criteria for the diagnosis of sepsis.

Design

- Prospective observational study set in two PICUs of University Hospitals. The study was conducted in a number of consecutive patients, age below 18 years, who were admitted to one of these PICUs.

Real data applications. Leukocyte count...

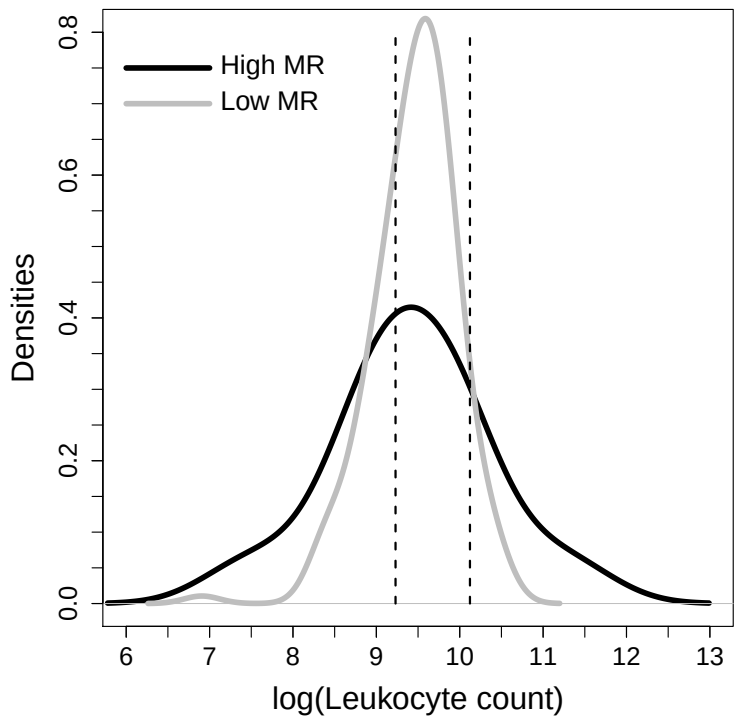
Sample

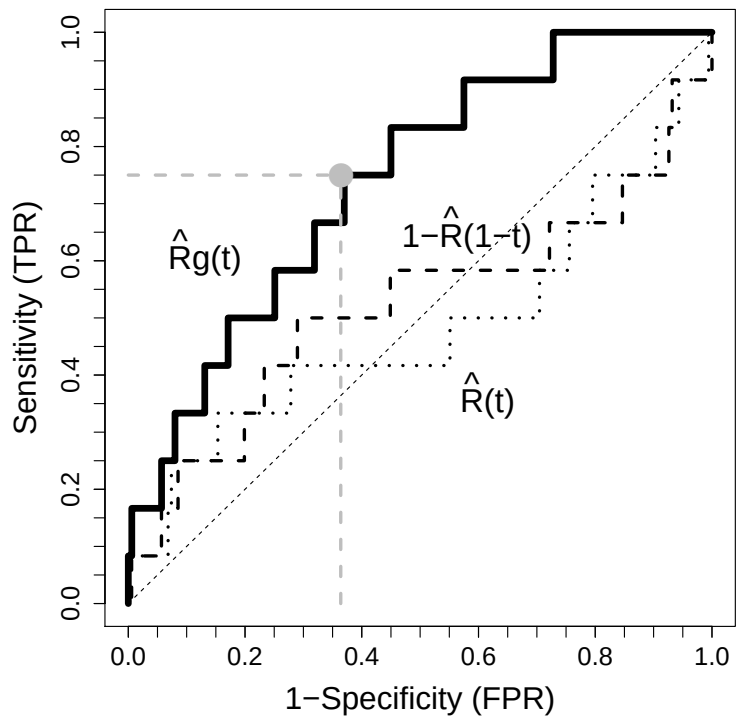
- A total of 188 patients were finally included.
- Leukocyte count routine determinations were performed during the first 12 hours after admission.
- Patients were divided in two groups: higher score risk mortality group (high MR) included patients with PIM 2 and PRISM III score greater than the percentile 75 ($N = 12$); lower score risk mortality group (low MR) included patients with a PIM 2 and/or PRISM score below the percentile 75 ($N = 176$).
- Rey, García-Hernández, Concha et al. (2013), for more information about this cohort.

Real data applications. Leukocyte count...

Table: Descriptive statistics for the leukocyte count.

	N	Mean ± sd	P_{25}	P_{50}	P_{75}
Low MR	176	14,290.7 ± 6,588	9,725	13,400	17,875
High MR	12	18,325.8 ± 20,343	7,250	11,400	22,850





Real data applications. Leukocyte count...

Results

- Left-side AUC=0.520 (0.275-0.693)
- $\hat{\mathcal{A}}_g = 0.74$ (0.596-0.884).
- If the children with leukocyte count lower than 24,900 (10.12 in logarithmic scale) and greater than 10,200 (9.23 in logarithmic scale) were classified within the low MR group (optimal thresholds in the Youden index sense) the observed TPR and the TNR were 0.750 and 0.636, respectively.

Real data applications. Response to the *OnabotulinumtoxinA* treatment for the chronic migraine headaches and the CGRP levels in women

Background

- The OnabotulinumtoxinA (*BoToX*) is the first and only FDA-approved (United State food and drug administration), preventive treatment for chronic migraine in adults
- On the other hand, serum CGRP levels are increased in chronic migraineurs indicating a chronic activation of the trigemino-vascular system, and it is proposed as the first biomarker for this entity (Cernuda-Morollón et al. (2015)).
- We explored the relationship between basal levels of CGRP and the response to the BoToX.

Real data applications. CGRP levels...

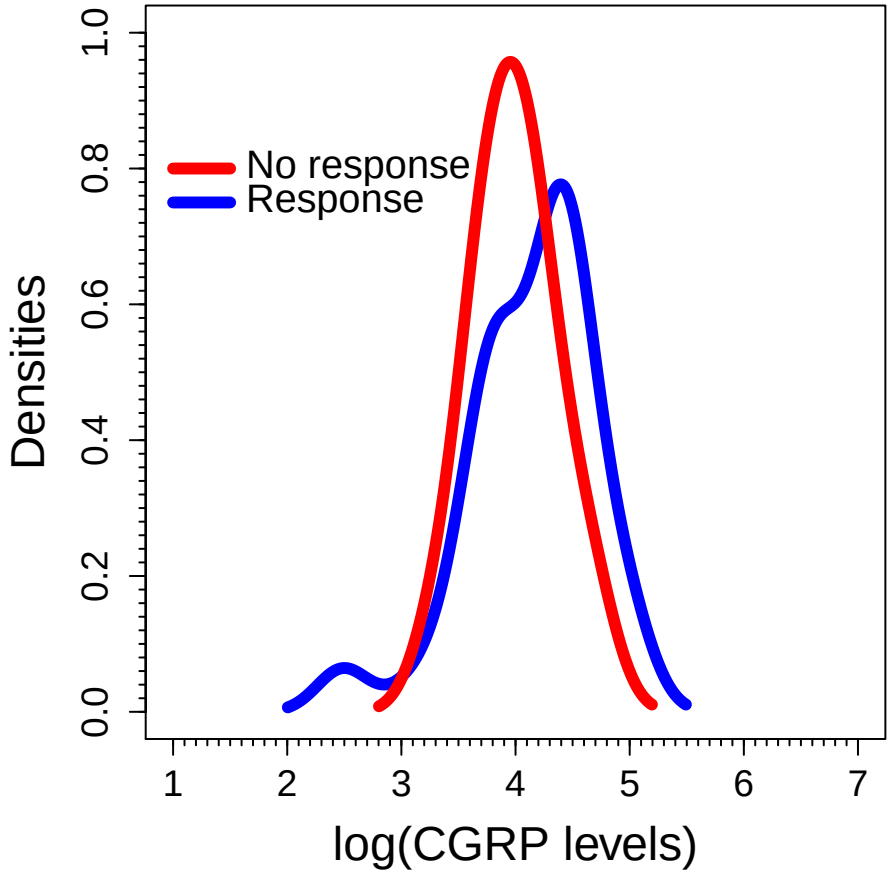
Sample

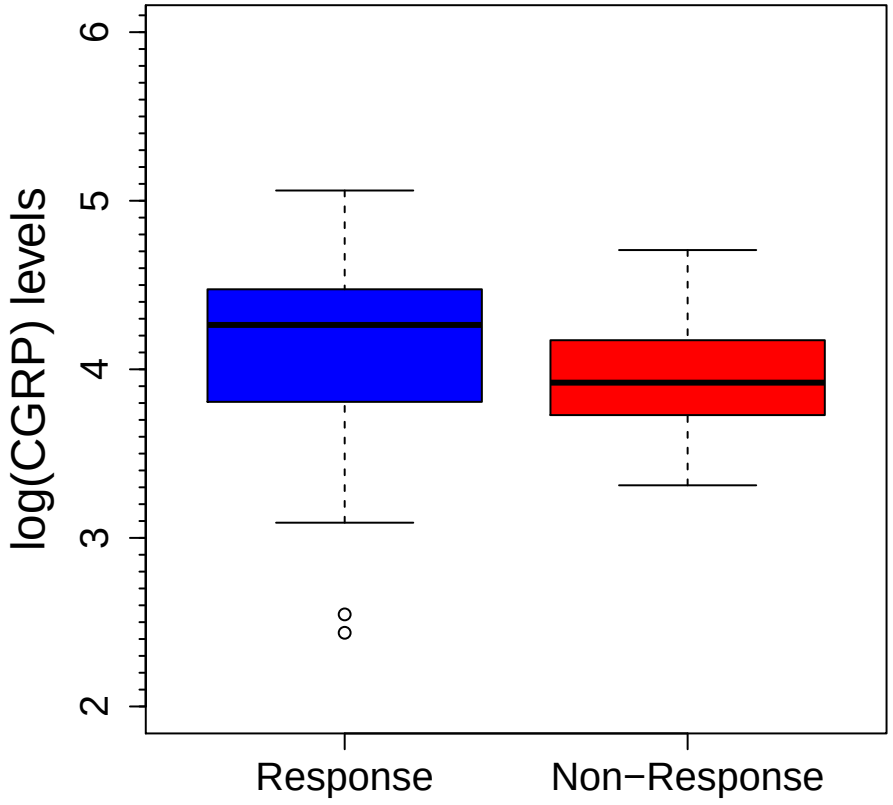
- Finally, a total of 70 women meeting chronic migraine criteria were included (all of then treated at the HUCA).
- Migraine patients are usually considered as responders when attack frequency is decreased by 50%, so we adopted this criterion and we checked it by the use of monthly headache calendars in all patients.

Table: Descriptive statistics for the CGRP levels in the response and non-response groups.

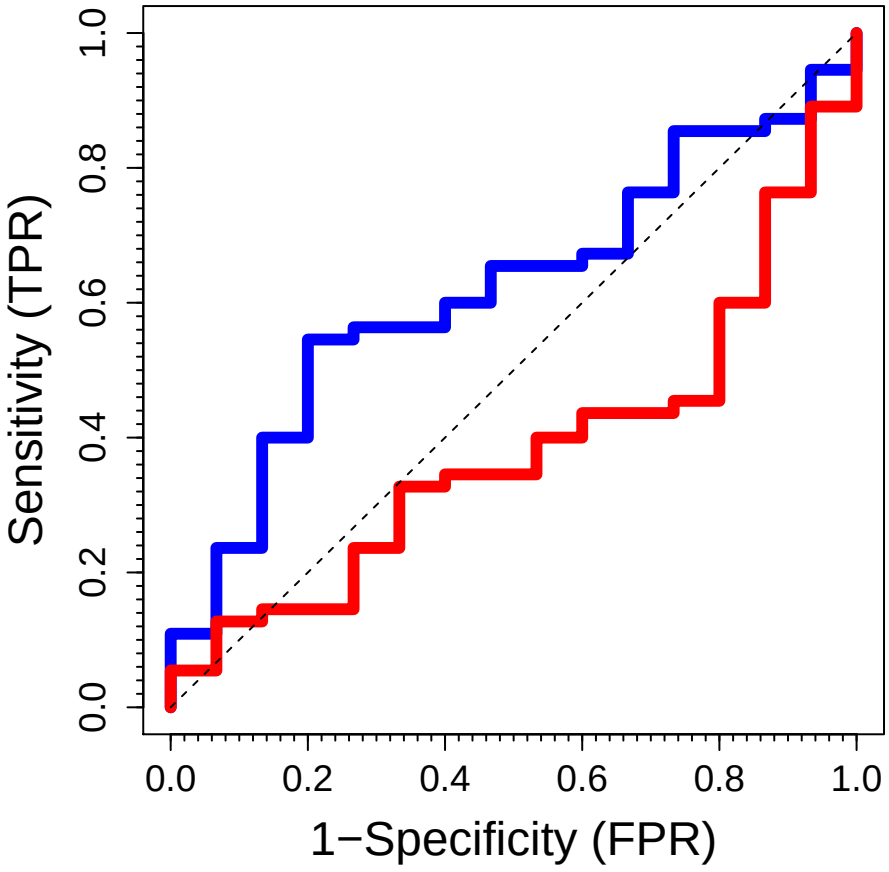
	N	**Mean ± sd**	P_{25}	P_{50}	P_{75}
No response	15	57.68 ± 22.01	38.71	50.45	66.91
Response	55	70.97 ± 33.01	45.01	71.04	88.34

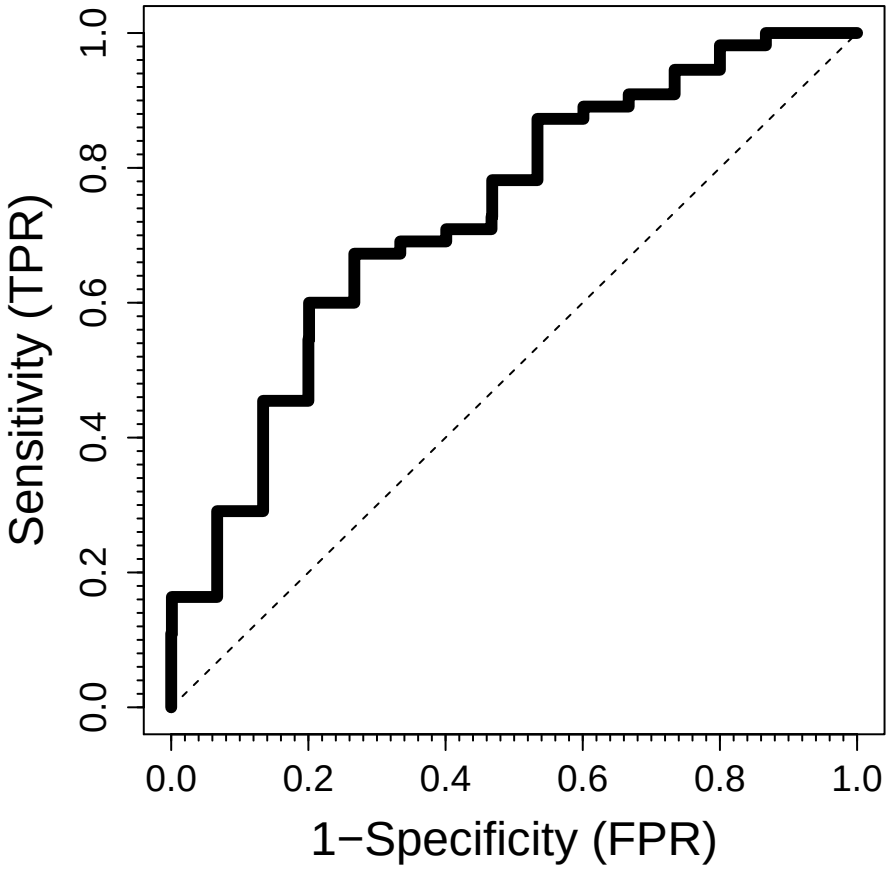
Real data applications. CGRP levels...





Real data applications. CGRP levels...





Real data applications. CGRP levels...

Results

- Right-side AUC=0.619 (0.473-0.765).
- $\hat{\mathcal{A}}_g = 0.73$ (0.579-0.881).
- Women with CGRP levels below 36.51 and larger than 66.97 are the optimal group. These cut-off points lead to FPR of 0.267 and TPR of 0.673.
- Different possibilities: placebo effect, other mechanism....
- Of course, sample size must be increased...

Future work. Multivariate biomarkers

The introduced definition

same definition, again!

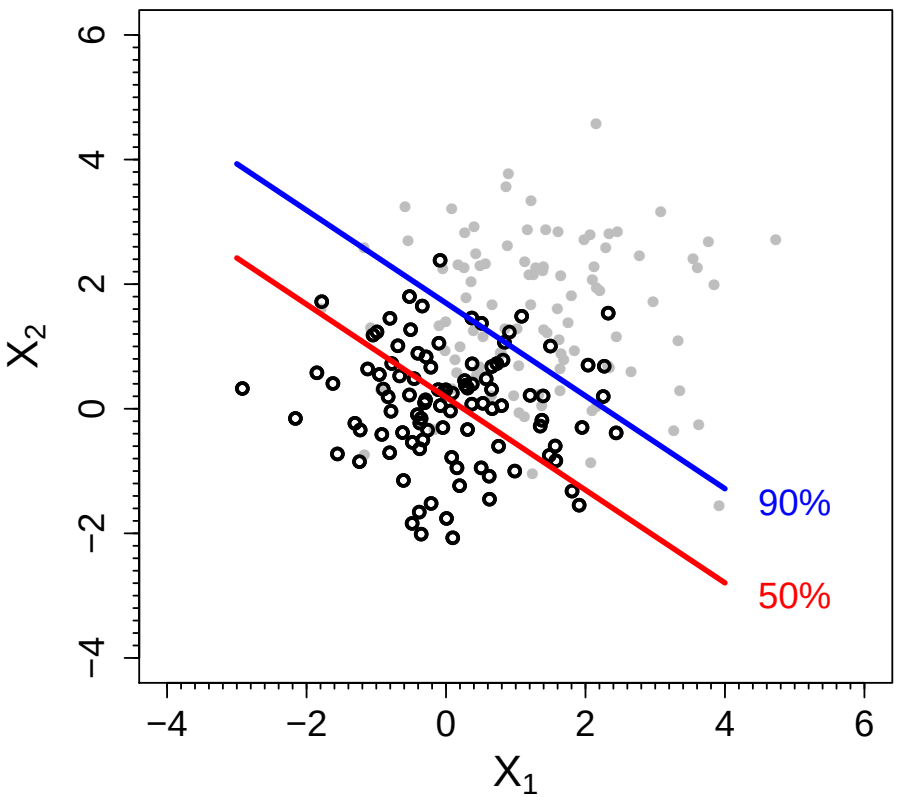
$$\mathcal{R}_g(t) = \sup_{u_t \in \mathcal{U}_t} \mathcal{P}\{\xi \in u_t\},$$

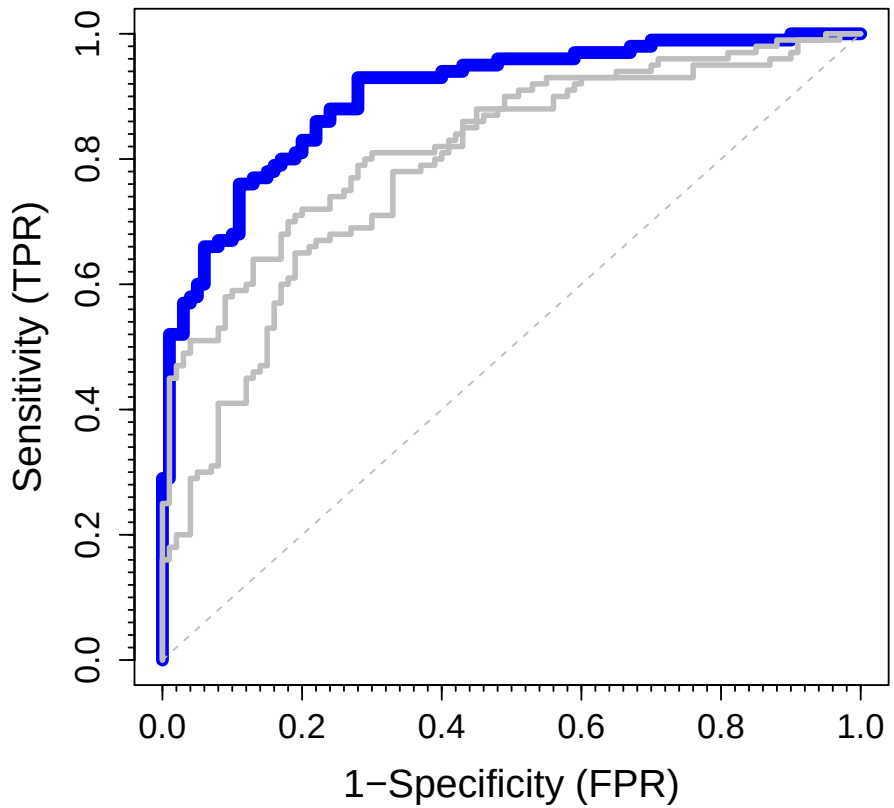
where $\mathcal{U}_t = \{u_t \in \mathcal{B}_{(t)} \text{ such that } \mathcal{P}\{\chi \in u_t\} \leq t\}$,

can be extended to different $\mathcal{U}_t$ subsets. We consider a multivariate problems; i.e., we have different variables which can be used in order to classified subjects.

Future work. Multivariate biomarkers

When we want to study the diagnostic capacity of several (bio)markers, a common procedure is to reduce the provided information into a one-dimensional marker (via logistic regression, linear discriminant analysis...).





Future work. Multivariate biomarkers

Of course, this is not a new problem and there exist a number of papers which deal with,

- Richard, Hammit and Tsevat (1996)
- Pepe and Thompson (2000)
- Pepe, Cai and Longton (2006)
- Gao et al. (2008)
- Pfeiffer and Bura (2008)
- Yu and Park (2015)
- Many others...

Most of them study/propose algorithms in order to maximize the AUC or the partial AUC but they are not looking for a real curve/parameter. They do not have a theoretical framework.

Future work. Multivariate biomarkers

$$\mathcal{R}_g(t) = \sup_{u_t \in \mathcal{U}_t} \mathcal{P}\{\xi \in u_t\},$$

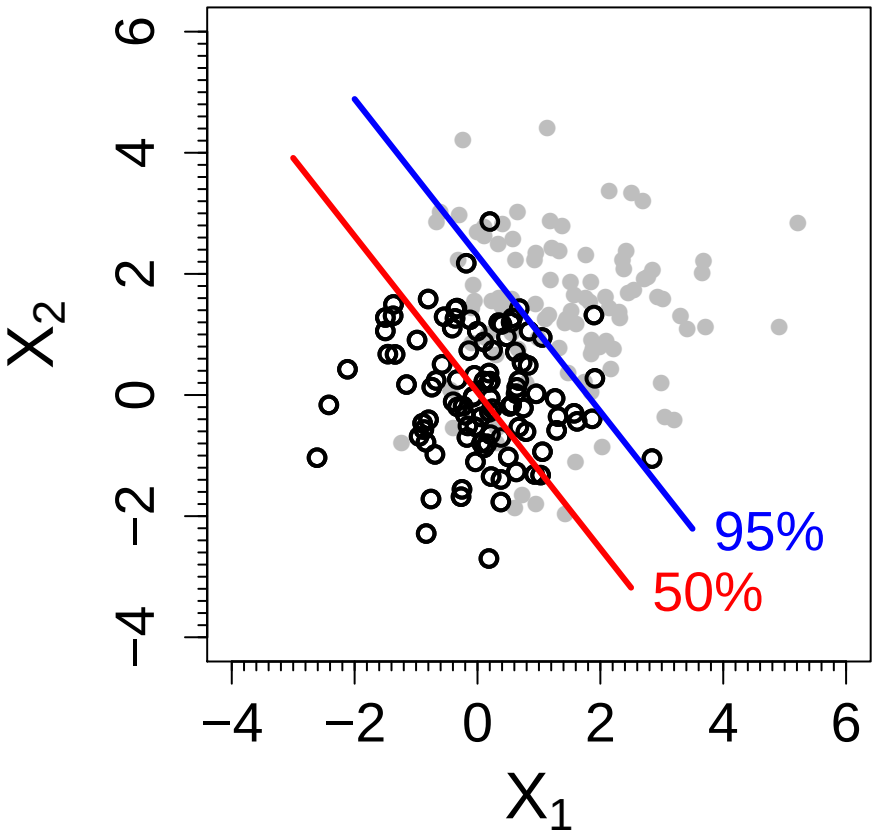
where $\mathcal{U}_t = \{u_t \in \mathcal{B}_{(t)} \text{ such that } \mathcal{P}\{\chi \in u_t\} \leq t\}$,

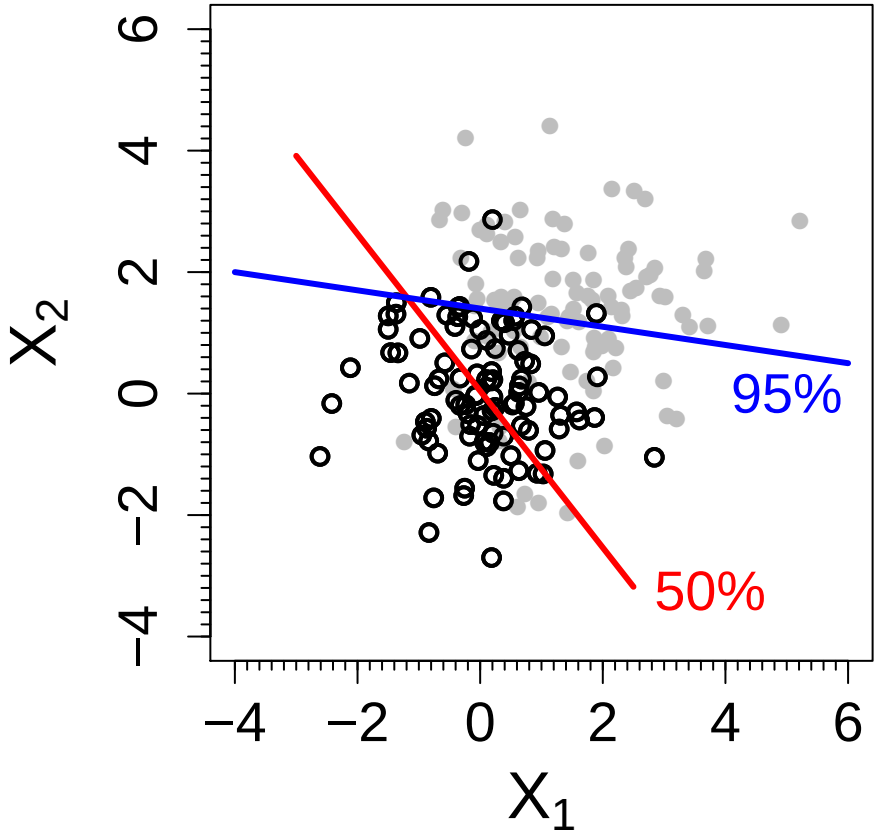
$$\mathcal{B} = \{x \in \mathbb{R}^p \text{ such that: } a \cdot \boldsymbol{X} < x\}, \text{ or}$$

$$\mathcal{B}_{(t)} = \{x \in \mathbb{R}^p \text{ such that: } a_t \cdot \boldsymbol{X} < x\},$$

where $\boldsymbol{X} = [X_1, \cdots, X_p, 1]$ contains the p-dimensional biomarker and the constant term.

Future work. Multivariate biomarkers





Future work. Multivariate biomarkers

Of course, we can consider non-linear regions. In this case, the problem is similar to this one (Lei, Robins and Wasserman (2013))

Prediction regions and density level sets

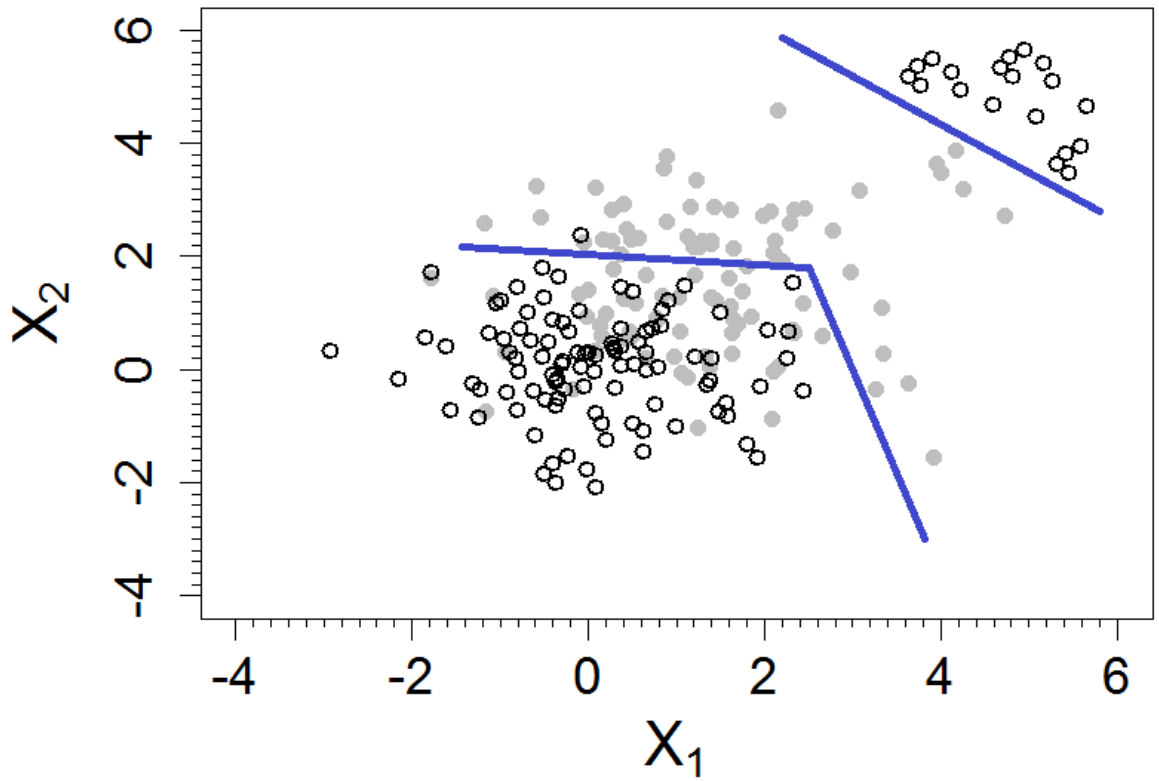
we observe *iid* data $Y_1, \ldots, Y_n \in \mathbb{R}^p$ from a distribution P and we want to construct a prediction region $C_n = C_n(Y_1, \cdots, Y_n) \subseteq \mathbb{R}^p$ such that

$$\mathbb{P}(Y_{n+1} \in C_n) \geq 1 - \alpha,$$

where $0 < \alpha < 1$ and $\mathbb{P} = P^{n+1}$ is the product probability measure over the $(n+1)$-tuple $(Y_1, \cdots, Y_{n+1})$.

Future work. Multivariate biomarkers

In the ROC curve context, two populations must be handled but, basically, is the same problem (conformal prediction regions). There is a number (big number) of papers.



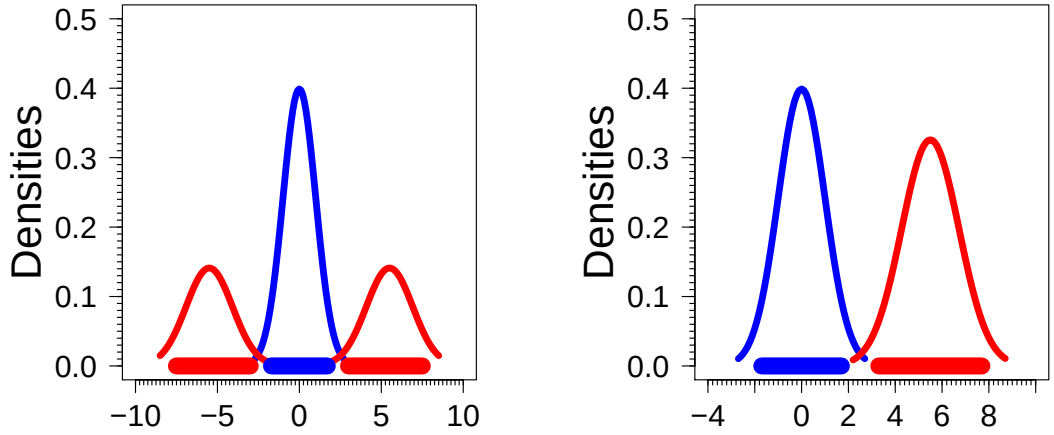
Future work. Multivariate biomarkers

The proposed generalizated ROC curve provides a theoretical framework. To take into account,

- Regions with biological sense, usefull in practice...
- Computational costs
- ....

Conclusions (Limitations)

- The introduced definition provides a useful theoretical framework.
- $\mathcal{R}_g(t) \geq \max\{\mathcal{R}(t), 1-\mathcal{R}(1-t)\}$, for each $t \in [0,1]$.
- $\hat{\mathcal{R}}(t) > \max\{\hat{\mathcal{R}}(t), 1-\hat{\mathcal{R}}(1-t)\} \Rightarrow \hat{\mathcal{A}}_g > 1/2$. Usual bootstrap does not work in order to check (the null) $H_0 : \mathcal{A}_g = 1/2$ neither to build confidence intervals when $\mathcal{A}_g$ is close to $1/2$. Equivalent to making it for $\max\{\hat{\mathcal{R}}(t), 1-\hat{\mathcal{R}}(1-t)\}$.
- In the consider case ($\mathcal{U}_t$ sets in the way $(-\infty, a_l] \cup [a_u, \infty)$) the AUC losses its probabilistic interpretation.
- In this situation, large AUCs must not be expected:



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Thanks for attention