pROC: an open-source package for R and S+ to analyze and compare ROC curves

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Abstract

Background: Receiver operating characteristic (ROC) curves are useful tools to evaluate classifiers in biomedical and bioinformatics applications. However, conclusions are often reached through inconsistent use or insufficient statistical analysis. To support researchers in their ROC curves analysis we developed pROC, a package for R and S+ that contains a set of tools displaying, analyzing, smoothing and comparing ROC curves in a user-friendly, object-oriented and flexible interface.
Results: With data previously imported into the R or S+ environment, the pROC package builds ROC curves and includes functions for computing confidence intervals, statistical tests for comparing total or partial area under the curve or the operating points of different classifiers, and methods for smoothing ROC curves. Intermediary and final results are visualised in user-friendly interfaces. A case study based on published clinical and biomarker data shows how to perform a typical ROC analysis with pROC.
Conclusions: pROC is a package for R and S+ specifically dedicated to ROC analysis. It proposes multiple statistical tests to compare ROC curves, and in particular partial areas under the curve, allowing proper ROC interpretation. pROC is available in two versions: in the R programming language or with a graphical user interface in the S+ statistical software. It is accessible at expasy.org/tools/pROC/ under the GNU General Public License. It is also distributed through the CRAN and CSAN public repositories, facilitating its installation.

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Abbreviations: aSAH: aneurysmal subarachnoid haemorrhage; AUC: area under the curve; CI: confidence interval; CRAN: comprehensive R archive network; CSAN: comprehensive S-PLUS archive network; pAUC: partial area under the curve; ROC: receiver operating characteristic.

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Background

A ROC plot displays the performance of a binary classification method with continuous or discrete ordinal output. It shows the sensitivity (the proportion of correctly classified positive observations) and specificity (the proportion of correctly classified negative observations) as the output threshold is moved over the range of all possible values. ROC curves do not depend on class probabilities, facilitating their interpretation and comparison across different data sets. Originally invented for the detection of radar signals, they were soon applied to psychology (Swets 1973) and medical fields such as radiology (Pepe 2003). They are now commonly used in medical decision making, bioinformatics (Sonego et al. 2008), data mining and machine learning, evaluating biomarker performances or comparing scoring methods (Fawcett 2006; Pepe 2003).

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In the ROC context, the area under the curve (AUC) measures the performance of a classifier and is frequently applied for method comparison. A higher AUC means a better classification. However, comparison between AUCs is often performed without a proper statistical analysis partially due to the lack of relevant, accessible and easy-to-use tools providing such tests. Small differences in AUCs can be significant if ROC curves are strongly correlated, and without statistical testing two AUCs can be incorrectly labelled as similar. In contrast a larger difference can be non significant in small samples, as shown by Hanczar *et al.* (Hanczar *et al*.), who also provide an analytical expression for the variance of AUC's as a function of the sample size. We recently identified this lack of proper statistical comparison as a potential cause for the poor acceptance of biomarkers as diagnostic tools in medical applications (Robin *et al*. 2009). Evaluating a classifier by means of total AUC is not suitable when the performance assessment only takes place in high specificity or high sensitivity regions (Robin *et al*. 2009). To account for these cases, the partial AUC (pAUC) was introduced as a local comparative approach that focuses only on a portion of the ROC curve (Jiang *et al*. 1996; McClish 1989; Streiner & Cairney 2007).

Software for ROC analysis already exists. A previous review (Stephan *et al*. 2003) compared eight ROC programs and found that there is a need for a tool performing valid and standardized statistical tests with good data import and plot functions.

The R (R Development Core Team 2010) and S+ (TIBCO Spotfire S+ 8.2, 2010, Palo Alto, CA) statistical environments provide an extensible framework upon which software can be built. No ROC tool is implemented in S+ yet while four R packages computing ROC curves are available:

1. *ROCR* (Sing *et al*. 2005) provides tools computing the performance of predictions by means of precision/recall plots, lift charts, cost curves as well as ROC plots and AUCs. Confidence intervals (CI) are supported for ROC analysis but the user must supply the bootstrapped curves.
2. The *verification* package (NCAR 2010) is not specifically aimed at ROC analysis; nonetheless it can plot ROC curves, compute the AUC and smooth a ROC curve with the binomial model. A Wilcoxon test for a single ROC curve is also implemented, but no test comparing two ROC curves is included.
3. Bioconductor includes the *ROC* package (Carey & Redestig 2008) which can only compute the AUC and plot the ROC curve.
4. Pcvsuite (Pepe *et al*. 2009) is an advanced package for ROC curves which features advanced functions such as covariate adjustment and ROC regression. It was originally designed for Stata and ported to R. It is not available on the CRAN (comprehensive R archive network), but can be downloaded for Windows and MacOS from labs.fhcrc.org/pepe/dabs/rocbasic.html.

Package name	ROCR	Verification	ROC (Bioconductor)	pcvsuite	pROC
Smoothing	No	Yes	No	Yes	Yes
Partial AUC	Only SP[1]	No	Only SP[1]	Only SP	SP and SE
Confidence intervals	Partial[2]	Partial[3]	No	Partial[4]	Yes
Plotting Confidence Intervals	Yes	Yes	No	Yes	Yes
Statistical tests	No	AUC (one sample)	No	AUC, pAUC, SP	AUC, pAUC, SP, SE, ROC
Available on CRAN	Yes	Yes	No, bioconductor.org	No, labs.fhcrc.org/pepe/dabs/	Yes

Table 1: Features of the R packages for ROC anaylsis.
[1]Partial AUC only between 100% and a specified cutoff of specificity
[2]Bootstrapped ROC curves must be computed by the user
[3]Only threshold averaging
[4]Only at a given specificity or inverse ROC

Table 1 summarizes the differences between these packages. Only pcvsuite enables the statistical comparison between two ROC curves. Pcvsuite, ROCR and ROC can compute AUC or pAUC, but the pAUC can only be defined as a portion of specificity.

The *pROC* package was designed in order to facilitate ROC curve analysis and apply proper statistical tests for their comparison. It provides a consistent and user-friendly set of functions building and plotting a ROC curve, several methods smoothing the curve, computing the full or partial AUC over any range of specificity or sensitivity, as well as computing and visualizing various CIs. It includes tests for the statistical comparison of two ROC curves as well as their AUCs and pAUCs. The software comes with an extensive documentation and relies on the underlying R and S+ systems for data input and plots. Finally, a graphical user interface (GUI) was developed for S+ for users unfamiliar with programming.

Implementation

AUC and pAUC

In *pROC*, the ROC curves are empirical curves in the sensitivity and specificity space. AUCs are computed with trapezoids (Fawcett 2006). The method is extended for pAUCs by ignoring trapezoids outside the partial range and adding partial trapezoids with linear interpolation when necessary. The pAUC region can be defined either as a portion of specificity, as originally described by McClish (McClish 1989), or as a portion of sensitivity, as proposed later by Jiang *et al.* (Jiang *et al*. 1996). Any section of the curve pAUC(t_0, t_1) can be analyzed, and not only portions anchored at 100% specificity or 100% sensitivity. Optionally, pAUC can be standardized with the formula by McClish (McClish 1989):

$$\frac{1}{2}\left(1+\frac{\mathrm{pAUC}-\min}{\max-\min}\right) \qquad \text{Equation 1}$$

where *min* is the pAUC over the same region of the diagonal ROC curve, and *max* is the pAUC over the same region of the perfect ROC curve. The result is a standardized pAUC which is always 1 for a perfect ROC curve and 0.5 for a non-discriminant ROC curve, whatever the partial region defined.

Comparison

Two ROC curves are "paired" (or sometimes termed "correlated" in the literature) if they derive from multiple measurements on the same sample. Several tests exist to compare paired (Bandos *et al*. 2005; Bandos *et al*. 2006; Braun & Alonzo 2008; DeLong *et al*. 1988; Hanley & McNeil 1983; Moise *et al*. 1988; Venkatraman & Begg 1996) or unpaired (Venkatraman 2000) ROC curves. The comparison can be based on AUC (Bandos *et al*. 2005; Bandos *et al*. 2006; Braun & Alonzo 2008; DeLong *et al*. 1988; Hanley & McNeil 1983), ROC shape (Moise *et al*. 1988; Venkatraman 2000; Venkatraman & Begg 1996), a given specificity (Pepe *et al*. 2009) or confidence bands (Campbell 1994; Sonego *et al*. 2008). Several tests are implemented in *pROC*. Three of them are implemented without modification from the literature (DeLong *et al*. 1988; Venkatraman 2000; Venkatraman & Begg 1996), and the others are based on the bootstrap percentile method.

The bootstrap test to compare AUC or pAUC in *pROC* implements the method originally described by Hanley and McNeil (Hanley & McNeil 1983). They define Z as

$$Z=\frac{\theta_1-\theta_2}{\mathrm{sd}\,(\theta_1-\theta_2)} \qquad \text{Equation 2}$$

where θ_1 and θ_2 are the two (partial) AUCs. Unlike Hanley and McNeil, we compute sd(θ_1 - θ_2) with N (defaults to 2000) bootstrap replicates. In each replicate *r*, the original measurements are resampled with replacement; both new ROC curves corresponding to this new sample are built, the resampled AUCs $\theta_{1,r}$ and $\theta_{2,r}$ and their difference $D_r = \theta_{1,r} - \theta_{2,r}$ are computed. Finally, we compute sd(θ_1 - θ_2) = sd(D). As Z approximately follows a normal distribution, one or two-tailed p-values are calculated accordingly. This bootstrap test is very flexible and can be applied to AUC, pAUC and smoothed ROC curves.

Bootstrap is stratified by default; in this case the same number of case and control observations than in the original sample will be selected in each bootstrap replicate. Stratification can be disabled and

observations will be resampled regardless of their class labels. Repeats for the bootstrap and progress bars are handled by the *plyr* package (Wickham 2010).

The second method to compare AUCs implemented in *pROC* was developed by DeLong et al. (DeLong *et al*. 1988) based on U-statistics theory and asymptotic normality. As this test does not require bootstrapping, it runs significantly faster, but it cannot handle pAUC or smoothed ROC curves. For both tests, since the variance depends on the covariance of the ROC curves (Equation 3), strongly correlated ROC curves can have similar AUC values and still be significantly different.

$$\mathrm{var}(\theta_1 - \theta_2) = \mathrm{var}(\theta_1) - 2\,\mathrm{cov}(\theta_1, \theta_2) \qquad \text{Equation 3}$$

Venkatraman and Begg (Venkatraman & Begg 1996) and Venkatraman (Venkatraman 2000) introduced tests to compare two actual ROC curves as opposed to their respective AUCs. Their method evaluates the integrated absolute difference between the two ROC curves, and a permutation distribution is generated to compute the statistical significance of this difference. As the measurements leading to the two ROC curves may be performed on different scales, they are not generally exchangeable between two samples. Therefore, the permutations are based on ranks, and ranks are recomputed as described in (Venkatraman & Begg 1996) to break the ties generated by the permutation.

Finally a test based on bootstrap is implemented to compare the ROC curve at a given level of specificity or sensitivity as proposed by Pepe *et al.* (Pepe *et al*. 2009). It works similar to the (p)AUC test, but instead of computing the (p)AUC at each iteration, the sensitivity (or specificity) corresponding to the given specificity (or respectively sensitivity) is computed. This test is equivalent to a pAUC test with a very small pAUC range.

Confidence intervals

CIs are computed with Delong's method (DeLong *et al*. 1988) for AUCs and with bootstrap for pAUCs (Carpenter & Bithell 2000). The CIs of the thresholds or the sensitivity and specificity values are computed with bootstrap resampling and the averaging methods described by Fawcett (Fawcett 2006). In all bootstrap CIs, patients are resampled and the modified curve is built before the statistics of interest is computed. As in the bootstrap comparison test, the resampling is done in a stratified manner by default.

Smoothing

Several methods to smooth a ROC curve are also implemented. Binormal smoothing relies on the assumption that there exists a monotone transformation to make both case and control values normally distributed (Pepe 2003). Under this condition a simple linear relationship (Equation 4) holds between the normal quantile function (ϕ) values of sensitivities and specificities. In our implementation, a linear regression between all quantile values defines *a* and *b*, which then define the smoothed curve.

$$\phi^{-1}(\mathrm{SE}) = \mathrm{a} + \mathrm{b}\,\phi^{-1}(\mathrm{SP}) \qquad \text{Equation 4}$$

This is different from the method described by Metz et al. (Metz *et al*. 1998) who use maximum likelihood estimation of *a* and *b*. Binormal smoothing was previously shown to be robust and to provide good fits in many situations even when the deviation from basic assumptions is quite strong (Hanley 1988). For continuous data we also include methods for kernel (density) smoothing (Zou *et al*. 1997), or to fit various known distributions to the class densities with *fitdistr* in the MASS package (Venables & Ripley 2002). If a user would like to run a custom smoothing algorithm that is optimized for the analysed data, then *pROC* also accepts class densities or the customized smoothing function as input. CI and statistical tests of smoothed AUCs are done with bootstrap.

Results and Discussion

We first evaluate the accuracy of the ROC comparison tests. Results in Appendices show that all unpaired tests give uniform p-values under a null hypothesis (Appendix figure 1) and that there is a very good correlation between DeLong's and bootstrap tests (Appendix figure 2). The relation between Venkatraman's and the other tests is also investigated (Appendix figure 3).

We now present how to perform a typical ROC analysis with *pROC*. In a recent study (Turck *et al*. 2010), we analyzed the level of several biomarkers in the blood of patients at hospital admission after aneurysmal subarachnoid haemorrhage (aSAH) to predict the 6-month outcome. The 141 patients collected were classified according to their outcome with a standard neurological scale, the Glasgow outcome scale (GOS). The biomarker performances were compared with the well established neurological scale of the World Federation of Neurological Surgeons (WFNS), also obtained at admission.

Case study on clinical aSAH data

The purpose of the case presented here is to identify patients at risk of poor post-aSAH outcome, as they require specific healthcare management; therefore the clinical test must be highly specific. Detailed results of the study are reported in (Turck *et al*. 2010). We only outline the features relevant to the ROC analysis.

ROC curves were generated in *pROC* for five biomarkers (H-FABP, S100β, Troponin I, NKDA and UFD-1) and three clinical factors (WFNS, Modified Fisher score and age).

AUC and pAUC

Since we are interested in a clinical test with a high specificity, we focused on partial AUC between 90% and 100% specificity.

The best pAUC is obtained by WFNS, with 3.1%, closely followed by S100β with 3.0% (Figure 1). A perfect clinical test within the same region corresponds to a pAUC of 10%, while a ROC curve without any discrimination power would yield only 0.5%. In the case of WFNS, we computed a standardized pAUC of 63.7% with McClish's formula (Equation 1). Of these 63.9%, 50% are due to the small portion (0.5% non-standardized) of the ROC curve below the identity line, and the remaining 13.9% are made of the larger part (2.6% non-standardized) above the curve. In the R version of *pROC*, the standardized pAUC of WFNS can be computed with:

```
roc(response = aSAH$outcome, predictor = aSAH$wfns, partial.auc = c(100, 90),
partial.auc.correct = TRUE, percent = TRUE)
```

In the rest of this paper, we report only not standardized pAUCs.

CI

Given the pAUC of WFNS, it makes sense to compute a 95% CI of the pAUC to assess the variability of the measure. In this case, we performed 10000 bootstrap replicates and obtained the 1.6-5.0% interval. In our experience, 10000 replicates give a fair estimate of the second significant digit. A lower number of replicates (for example 2000, the default) gives a good estimate of the first significant digit only. Other confidence intervals can be computed. The threshold with the point farthest to the diagonal line in the specified region was determined with pROC to be 4.5 with the *coords* function. A rectangular confidence interval can be computed and the bounds are 89.0-98.9 in specificity and 26.0-54.0 in sensitivity (Figure 1). If the variability of sensitivity at 90% specificity is considered more relevant than at a specific threshold, the interval of sensitivity is computed as 32.8-68.8. As shown in Figure 1 for S100β, a CI shape can be obtained by simply computing the CI's of the sensitivities over several constantly spaced levels of specificity, and these CI bounds are then joined to generate the shape. The following R code calculates the confidence shape:

```
plot(x = roc(response = aSAH$outcome, predictor = aSAH$s100, percent=TRUE,
ci=TRUE, of="se", sp=seq(0, 100, 5)), ci.type="shape")
```

The confidence intervals of a threshold or of a predefined level of sensitivity or specificity answer different questions. For instance, it would be wrong to compute the CI of the threshold 4.5 and report only the CI bound of sensitivity without reporting the CI bound of specificity as well. Similarly, determining the sensitivity and specificity of the cut-off 4.5 and then computing both CIs separately would also be inaccurate.

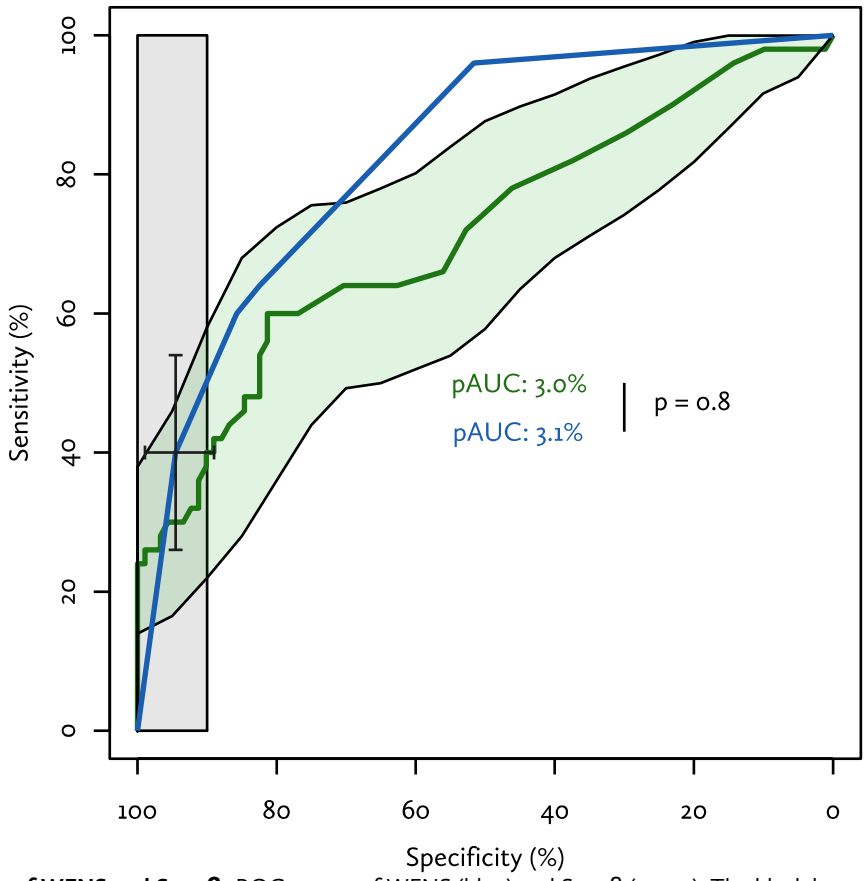

Figure 1: ROC curves of WFNS and S100β. ROC curves of WFNS (blue) and S100β (green). The black bars are the confidence intervals of WFNS for the threshold 4.5 and the light green area is the confidence interval shape of S100β. The vertical light grey shape corresponds to the pAUC region. The pAUC of both empirical curves is printed in the middle of the plot, with the p-value of the difference computed by a bootstrap test on the right.

Statistical comparison

The second best pAUC is that of S100β with 3.0%. The difference to WFNS is very small and the bootstrap test of *pROC* indicates that it is not significant (p=0.8, Figure 1). Surprisingly, a Venkatraman's test (over the total ROC curve) indicates a difference in the shape of the ROC curves (p=0.004), and indeed a test evaluating pAUCs in the high sensitivity region (90-100% sensitivity) would highlight a significant difference (p=0.005, pAUC=4.3 and 1.4 for WFNS and S100β respectively). However, since we are not interested in the high sensitivity region of the AUC there is no significant difference between WFNS and S100β.

In *pROC* pairwise comparison of ROC curves is implemented. Multiple testing is not accounted for and in the event of running several tests, the user is reminded that as with any statistical test, multiple tests should be performed with care, and if necessary appropriate corrections should be applied (Ewens & Grant 2005).

The bootstrap test can be performed with the following code in R:

```
roc.test(response = aSAH$outcome, predictor1 = aSAH$wfns, predictor2 = aSAH$s100,
partial.auc = c(100, 90), percent = TRUE)
```

Smoothing

Whether or not to smooth a ROC curve is a difficult choice. It can be useful in ROC curves with only few points, in which the trapezoidal rule consistently underestimates the true AUC (DeLong *et al.* 1988). This is the case with most clinical scores, such as the WFNS shown in Figure 2 where three smoothing methods available in *pROC* are plotted: (i) normal distribution fitting, (ii) density and (iii) binormal. In our case study:

(i) The normal fitting (red) gives a significantly lower AUC estimate (Δ = -5.1, p = 0.0006, Bootstrap test). This difference is due to the non-normality of WFNS. Distribution fitting can be very

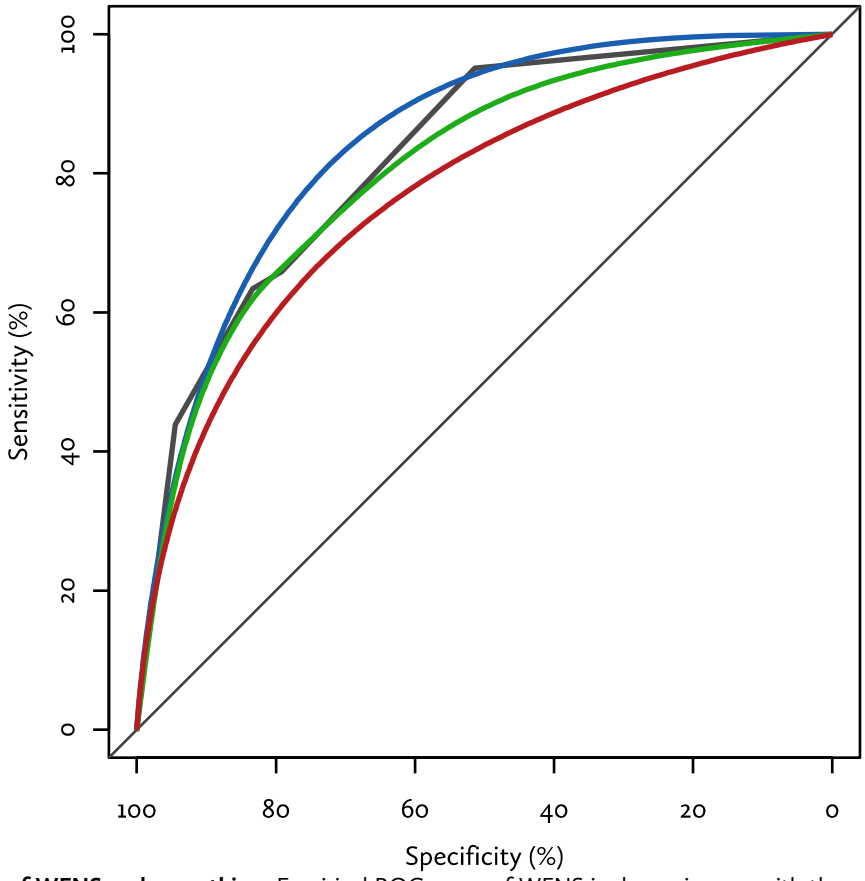

Figure 2: ROC curve of WFNS and smoothing. Empirical ROC curve of WFNS is shown in grey with three smoothing methods: binormal (blue), density (green) and normal distribution fit (red).

powerful when there is a clear knowledge of the underlying distributions, but should be avoided in other contexts.

(ii) The density (green) smoothing also produces a lower (Δ = -1.5, p=6*10^{-7}) AUC. It is interesting to note that even with a smaller difference in AUCs, the p-value can be more significant due to a higher covariance.

(iii) The binormal smoothing (blue) gives a slightly but not significantly higher AUC than the empirical ROC curve (Δ = +2.4, p=0.3). It is probably the best of the 3 smoothing estimates in this case (as mentioned earlier we were expecting a higher AUC as the empirical AUC of WFNS was underestimated). For comparison, Appendix figure 4 displays both our implementation of binormal smoothing with the one implemented in pcvsuite (Pepe *et al*. 2009).

Figure 3 shows how to create a plot with multiple smoothed curves with *pROC* in S+. One loads the pROC library within S+, selects the new *ROC curve* item in the S*tatistics* menu, selects the data on which the analysis is to be performed, and then moves to the *Smoothing* tab to set parameters for smoothing.

Conclusion

In this case study we showed how *pROC* could be run for ROC analysis. The main conclusion drawn from this analysis is that none of the measured biomarkers can predict the patient outcome better than the neurological score (WFNS).

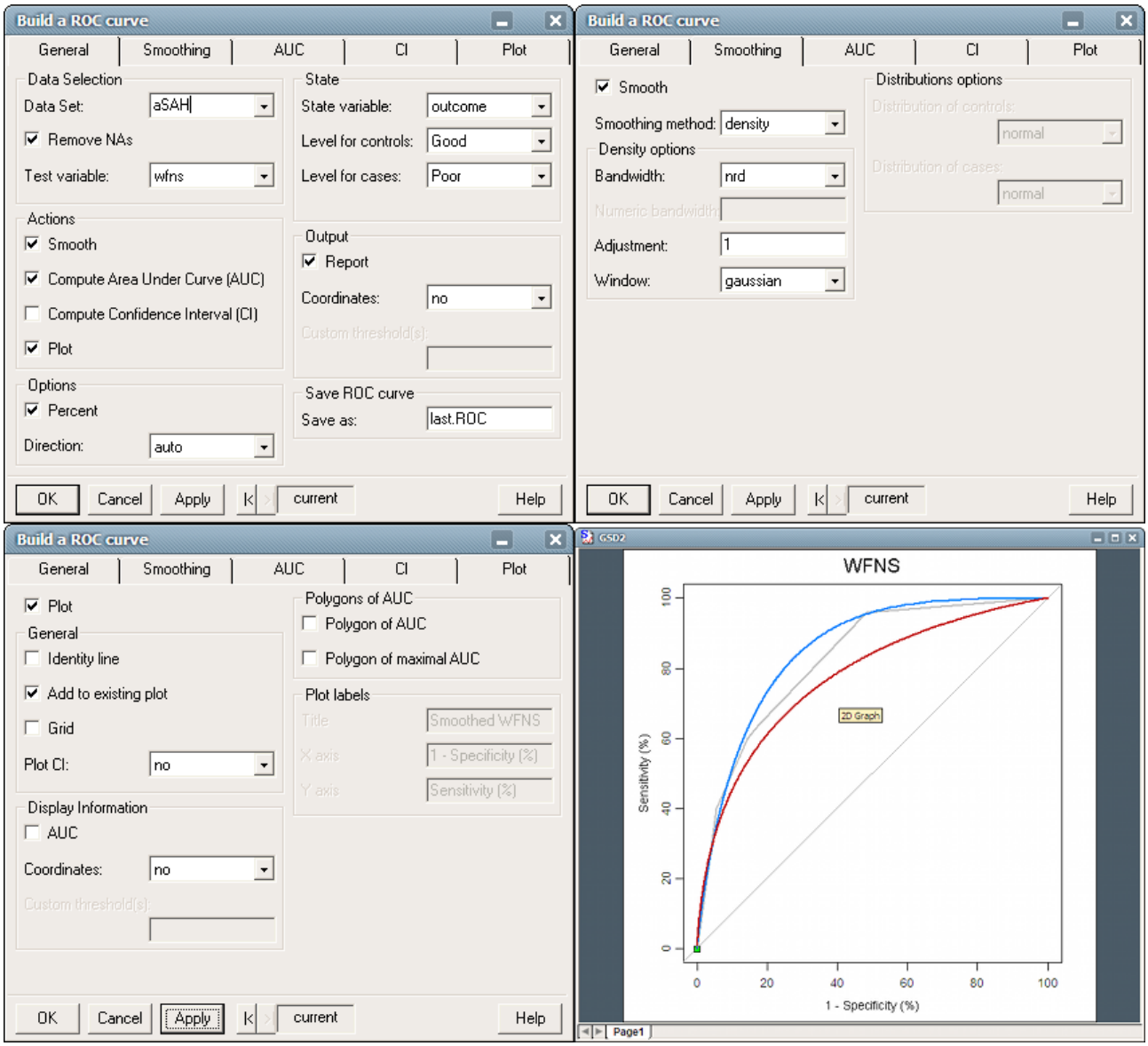

Figure 3: Screenshot of pROC in S+ for smoothing WFNS ROC curve. Top left: the General tab, where data is entered. Top right: the details about smoothing. Bottom left: the details for the plot. Checking the box "Add to existing plot" allows drawing several curves on a plot. Bottom right: the result in the standard S+ plot device.

Installation and usage

R

pROC can be installed in R by issuing the following command in the prompt:

```
install.packages("pROC")
```

Loading the package:

```
library(pROC)
```

Getting help:

```
?pROC
```

S+

pROC is available from the *File* menu, item *Find Packages...*. It can be loaded from the *File* menu, item *Load Library...*.

In addition to the command line functions, a GUI is then available in the *Statistics* menu. It features one window for univariate ROC curves (which contains options for smoothing, pAUC, CIs and plotting) and two windows for paired and unpaired tests of two ROC curves. In addition a specific help file for the GUI is available from the same menu.

Functions and methods

A summary of the functions available to the user in the command line version of pROC is shown in Table 2. Table 3 shows the list of the methods provided for plotting and printing.

Conclusions

The *pROC* package is a powerful set of tools analyzing and comparing ROC curves in R and S+. Unlike existing packages such as *ROCR* or *verification*, it is solely dedicated to ROC analysis, but provides in our knowledge the most complete set of statistical tests and plots for ROC curves. As shown in the case study reported here, *pROC* features the computation of AUC and pAUC, various kinds of confidence intervals, several smoothing methods, and the comparison of two paired or unpaired ROC curves. We believe that *pROC* should provide researchers, especially in the biomarker community, with the necessary tools to better interpret their results in biomarker classification studies.

pROC is available in two versions for R and S+. A thorough documentation with numerous examples is provided in the standard R format. For users unfamiliar with programming, a graphical user interface is provided for S+.

Availability and requirements

- Project name: pROC
- Project home page: expasy.org/tools/pROC
- Operating system(s): Platform independent
- Programming language: R and S+
- Other requirements: R ≥ 2.10.0 or S+ ≥ 8.1.1
- License: GNU GPL
- Any restrictions to use by non-academics: none

are.paired	Determines if two ROC curves are possibly paired
auc	Computes the area under the ROC curve
ci	Computes the confidence interval of a ROC curve
ci.auc	Computes the confidence interval of the AUC
ci.se	Computes the confidence interval of sensitivities at given specificities
ci.sp	Computes the confidence interval of specificities at given sensitivities
ci.thresholds	Computes the confidence interval of thresholds
coords	Returns the coordinates (sensitivities, specificities, thresholds) of a ROC curve
roc	Builds a ROC curve
roc.test	Compares the AUC of two correlated ROC curves
smooth	Smoothes a ROC curve

Table 2: Functions provided in pROC.

lines	ROC curves (roc) and smoothed ROC curves (smooth.roc)
plot	ROC curves (roc), smoothed ROC curves (smooth.roc) and confidence intervals (ci.se, ci.sp, ci.thresholds)
print	All pROC objects (auc, ci.auc, ci.se, ci.sp, ci.thresholds, roc, smooth.roc)

Table 3: Methods provided by pROC for standard functions.

Authors' contributions

XR carried out the programming and software design and drafted the manuscript. NTu, AH, NTi provided data and biological knowledge, tested and critically reviewed the software and the manuscript. FL helped to draft and to critically improve the manuscript. JCS conceived the biomarker study, participated in its design and coordination, and helped to draft the manuscript. MM participated in the design and coordination of the bioinformatics part of the study, participated in the programming and software design and helped to draft the manuscript. All authors read and approved the final manuscript.

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Errata

The R code given in the "Case study on clinical aSAH data section", "CI" sub-section on page 6 contained a typo and could not be executed. R complained that *argument "x" is missing, with no default*. The code read:

```
plot(roc = roc(response = aSAH$outcome, predictor = aSAH$s100, percent=TRUE,
ci=TRUE, of="se", sp=seq(0, 100, 5)), ci.type="shape")
```

The correct version is:

```
plot(x = roc(response = aSAH$outcome, predictor = aSAH$s100, percent=TRUE,
ci=TRUE, of="se", sp=seq(0, 100, 5)), ci.type="shape")
```

Thanks to Joanne Thandrayen for spotting the error.

Appendices

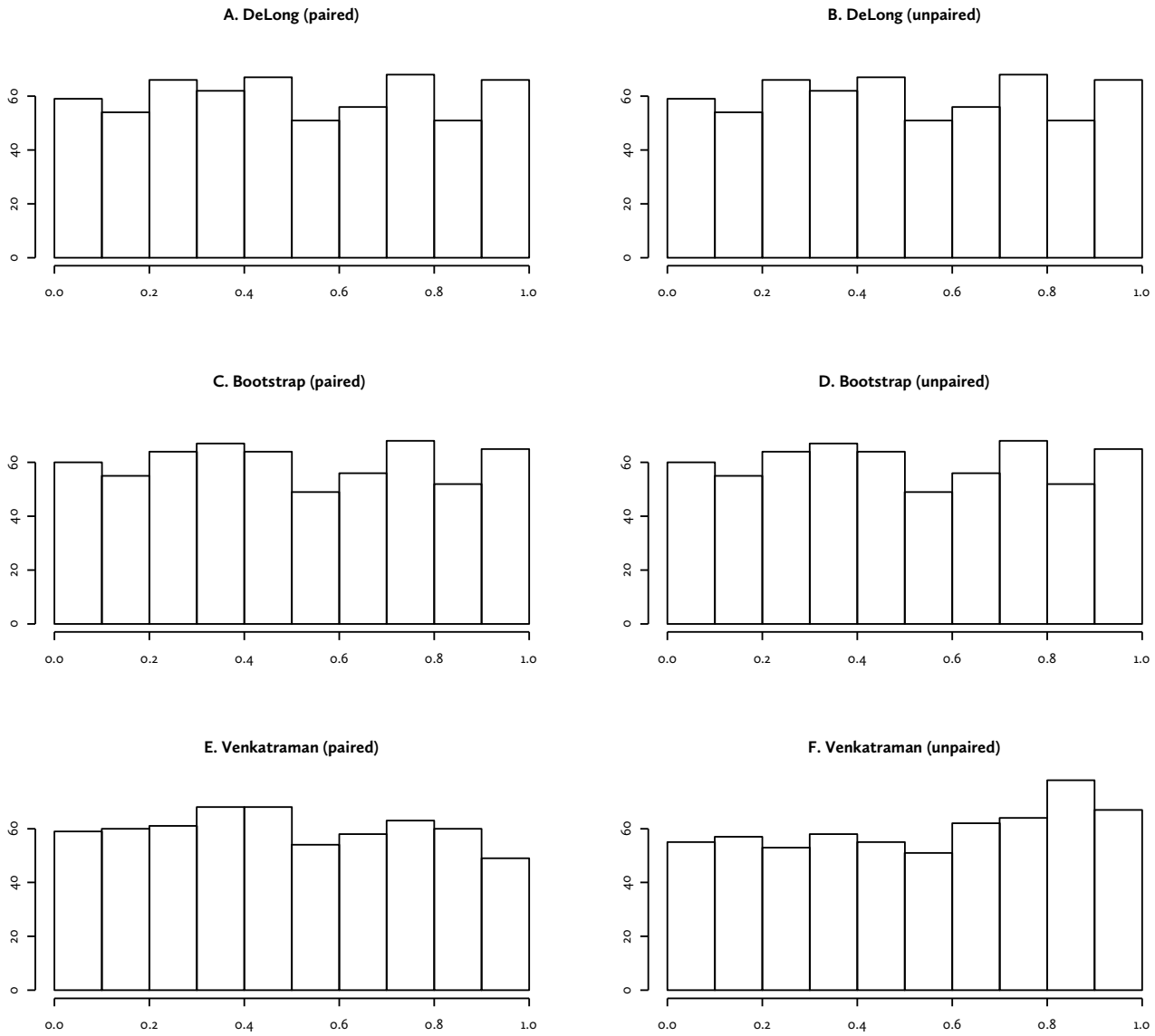
Assessment of the ROC comparison tests

To ensure that our implementations of the three statistical tests are correct, and to evaluate the correlation between them, we generated 600 p-values for each test under the null hypothesis (ROC curves are not different) by randomly switching the class labels of the 141 aSAH patients. For each null hypothesis, DeLong, Venkatraman (with 10000 permutations) and bootstrap (with 10, 100, 1000 and 10000 replicates) tests were performed with a paired and unpaired setup.

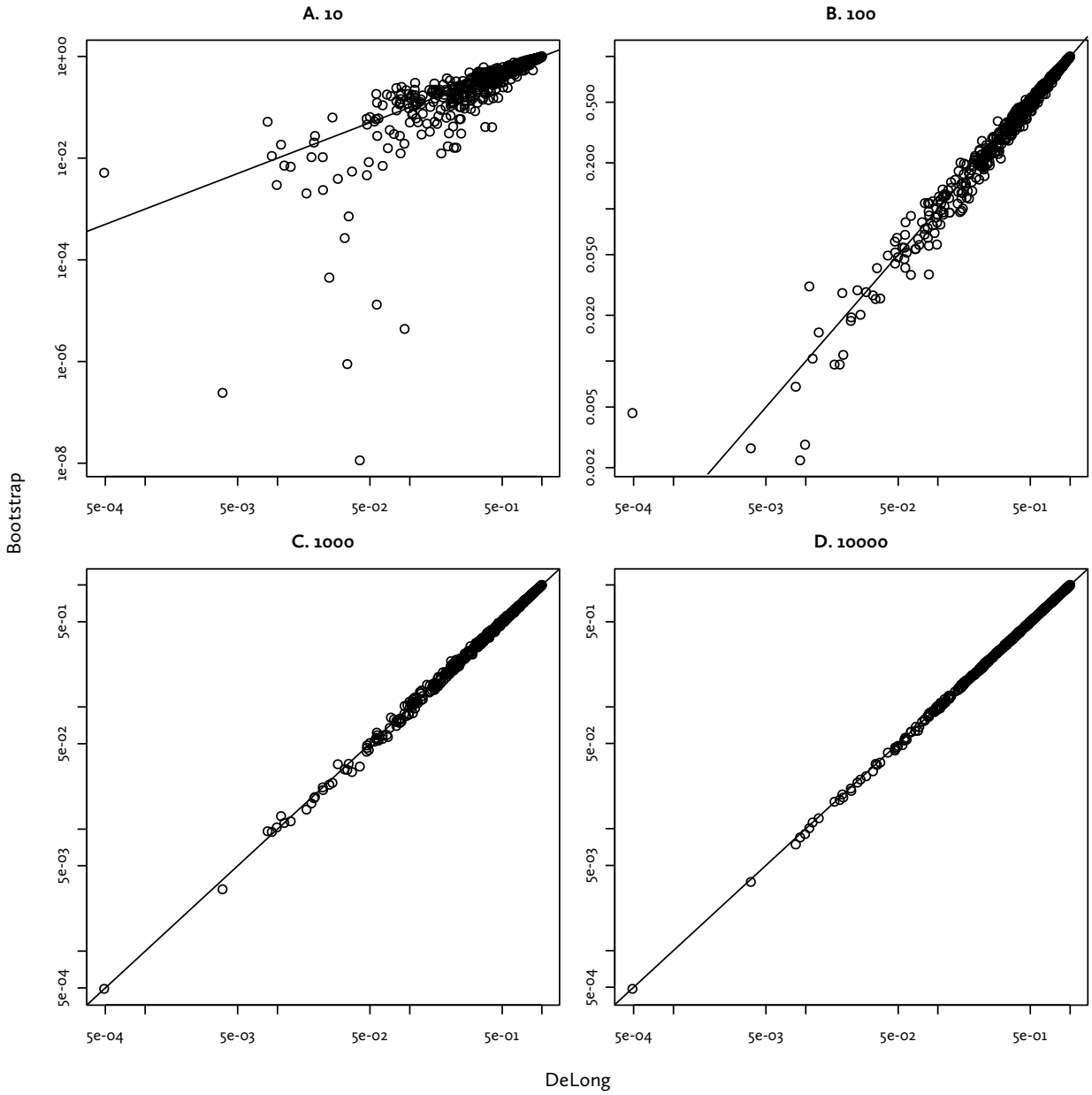
We first assessed the existence of a systematic bias towards high or low p-values. Appendix figure 1 shows that the paired tests do not deviate from uniformity under the null hypothesis (One-sample Kolmogorov-Smirnov test, $p = 0.99$ for DeLong's test, $p = 0.96$ for bootstrap test and $p = 0.32$ for Venkatraman's test). However paired test are slightly biased towards higher p-values (One-sample Kolmogorov-Smirnov test, $p = 0.02$ for DeLong's test, $p = 0.03$ for bootstrap, $p = 0.03$ for Venkatraman).

Next, we tested the relationship between DeLong and bootstrap tests. Both tests determine differences in AUCs and should produce similar results. Indeed, Appendix figure 2 shows that with enough bootstrap replicates, the bootstrap test converges to the values of DeLong's test. Note that DeLong's test is a deterministic test and thus is not subject to variations when repeated tests are performed on the same data. Spearman's rank correlation ρ is above 0.99 for all tests with 100 or more bootstrap replicates. For paired p-values lower than 0.1, the absolute difference between DeLong and bootstrap p-values obtained after 10000 replicates was lower than 0.005 in 95% of the tests. The 95% range of the differences increased to 0.011 and 0.03 for 1000 and 100 replicates respectively. For unpaired p-values, the same trend was observed with 95% of the differences within 0.007, 0.013 and 0.03 for 10000, 1000 and 100 replicates respectively. Therefore, the second decimal of the p-value is measured accurately with 10000 bootstrap replicates, but not with 1000 or less replicates.

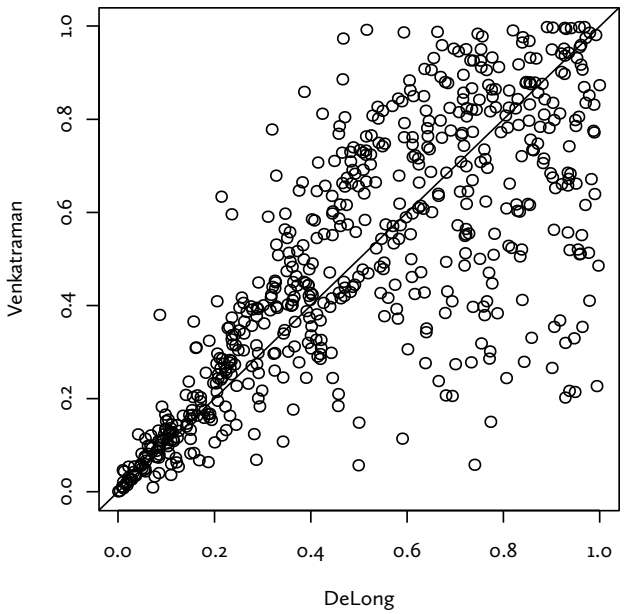
Finally, we looked at the association between Delong and Venkatraman's tests. In contrast with the bootstrap test, Venkatraman's test does not estimate the AUC but rather the shape of the ROC curve. Thus, we expect a lower correlation than with bootstrap, as two ROC curves with a different shape can have a similar or identical AUC value. Indeed, Appendix figure 3 shows a much lower correlation than that observed in Appendix figure 2 with bootstrap. Note that the figure is asymmetric: similar AUCs may have different shapes, but it is less likely that similar shapes would have different AUCs.



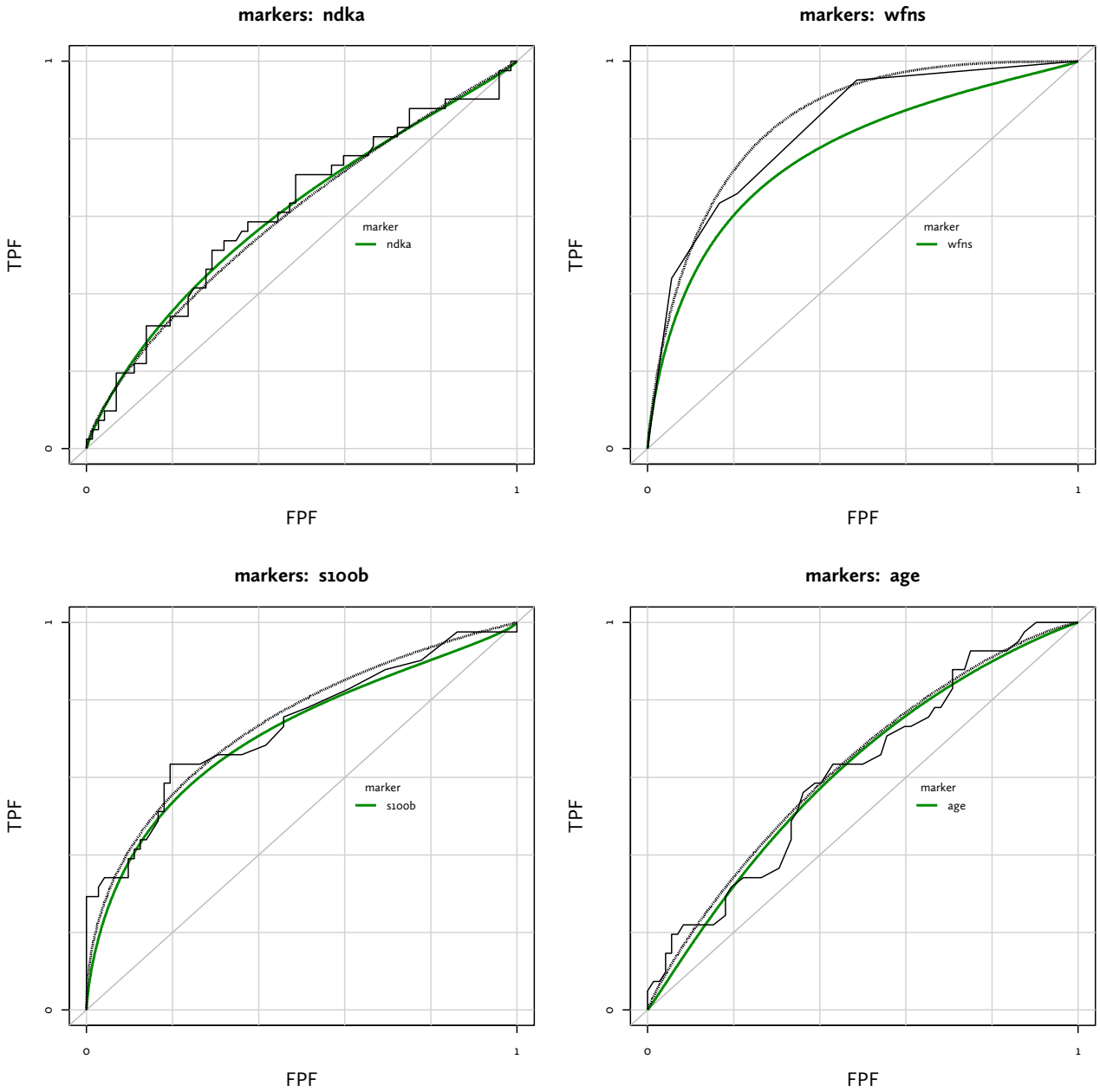
Appendix figure 1: Histograms of the frequency of 600 test p-values under the null hypothesis (ROC curves are not different). A: DeLong's paired test, B: DeLong's unpaired test, C: bootstrap paired test (with 10000 replicates), D: bootstrap unpaired test (with 10000 replicates) and E: Venkatraman's test (with 10000 permutations).



Appendix figure 2: Correlations between DeLong and bootstrap paired tests. X axis: DeLong's test; Y-axis: bootstrap test with number of bootstrap replicates. A: 10, B: 100, C: 1000 and D: 10000.



Appendix figure 3: Correlation between DeLong and Venkatraman's test. X axis: DeLong's test; Y-axis: Venkatraman's test with 10000 permutations.



Appendix figure 4: Binormal smoothing, Binormal smoothing with pcvsuite (green, solid) and pROC (black, dashed).