Analysis of Data Acquired Using ROC Paradigm and Its Extensions

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Abstract

A common task in medical imaging is assessing whether a new imaging system or device is an improvement over an existing one. Observer performance methodology, such as receiver operating characteristic (ROC) analysis, is widely used for this purpose. ROC studies are often required for regulatory approval of new devices. The purpose of this work is to describe **RJafroc**, which implements software for analysis of data acquired using the ROC paradigm and its location specific extensions. It is an enhanced implementation of existing Windows software called JAFROC (jackknife alternative free-response ROC, V4.2.1, http://www.devchakraborty.com). In the ROC paradigm the radiologist rates each image for confidence in presence of disease. The images are typically split equally between actually non-diseased and diseased. A common figure of merit (FOM) is the area under the ROC curve, which has the physical interpretation as the probability that a diseased image is rated higher than a non-diseased one. In ROC studies a number of radiologists (readers) rate images in two or more treatments, and the object of the analysis is to determine the significances of the inter-treatment differences between reader-averaged FOMs. In the free-response (FROC) paradigm the reader marks the locations of suspicious regions and rates each region for confidence in presence of disease, and credit for detection is only given if a true lesion is correctly localized. In the region of interest (ROI) paradigm each image is divided into a number of ROIs and the reader rates each ROI. Each paradigm requires definition of a valid FOM that rewards correct decisions and penalizes incorrect ones and specialized significance testing procedure are applied. The package reads data in all currently used data formats including Excel. Significance testing uses two models in widespread use, a jackknife pseudovalue based model due to Dorfman-Berbaum-Metz (DBM) and an ANOVA model with correlated errors due to Obuchowski-Rockette (OR), both of which have been improved by Hillis. Included are tools for (1) calculating a variety of free-response FOMs; (2) ROC sample size estimation for planning a future study based on pilot data; (3) viewing empirical operating characteristics in ROC and free-response paradigms; (4) producing formatted report files; and (5) saving data files in appropriate formats for analysis with alternate software.

Keywords: medical imaging, observer performance, assessment methodology, ROC, FROC, JAFROC software, R.

1. Introduction

A common task in medical imaging is assessing whether a new imaging system is an improvement over an existing one. Observer performance measurements, widely used for this purpose, require data collection and analyses methods that fall under the rubric of what is loosely termed "ROC analysis", where ROC is an abbreviation for Receiver Operating Characteristic (Metz 1986). ROC analysis is a specialized branch of statistics that is of great importance in medicine, where new imaging technology and the accuracy of interpretations often need to be assessed. The Food and Drug Administration (FDA), which regulates medical imaging devices, requires ROC studies as part of the device approval process (see document "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests" available at `http://www.fda.gov/RegulatoryInformation/Guidances`). There are, conservatively, at least 1000 publications describing ROC studies and a seminal paper (Metz 1986) by the late Prof. C.E. Metz has been cited over 1800 times. Since they involve numbers of radiologists interpreting large number of images in different modalities, ROC studies can be very expensive to conduct. For example (Pisano, Gatsonis, Hendrick, Yaffe, Baum, Acharyya, Conant, Fajardo, Bassett, D'Orsi, Jong, and Rebner 2005), the Digital Mammography for Imaging Screening Trial (DMIST) cost about $30 million (this study involved about 50,000 asymptomatic women at 33 mammography centers, and each mammogram was interpreted by two radiologists per mammography center). More typical ROC studies proposed in National Institutes of Health (NIH) grant applications are budgeted in the hundreds of thousands of dollars and often take years to complete. Consequently, there is much interest in optimizing methodology for analyzing ROC studies and its extensions, and four websites disseminate software for analyzing such studies: the University of Chicago has a site for ROC analysis software (`http://metz-roc.uchicago.edu/`) as does the University of Iowa (`http://perception.radiology.uiowa.edu/`) and the FDA (`https://code.google.com/p/imrmc/`); Windows software called JAFROC (jackknife alternative free-response ROC, V4.2.1), which can analyze ROC studies and its extensions (Chakraborty and Berbaum 2004; Chakraborty 2013), is available at `http://www.devchakraborty.com`. Software from the University of Iowa and University of Chicago websites have been used in several hundred publications (Professor Kevin Berbaum, University of Iowa, personal communication, ca 2014). JAFROC has been used in 77 publications: the list is viewable at `http://www.devchakraborty.com/JafrocApplications.pdf`. The purpose of this work is to describe a package called **RJafroc**, which is an enhanced implementation of JAFROC. In this section we introduce terminology used in the `RJafroc-package` page of the documentation that accompanies this paper. Several reviews of this field may be consulted for details (Metz 1978, 1986, 1989; Wagner, Beiden, Campbell, Metz, and Sacks 2002; Wagner, Metz, and Campbell 2007; Kundel, Berbaum, Dorfman, Gur, Metz, and Swensson 2008; Metz 2008) regarding basics of ROC methodology. [An existing package **ROCR** (Sing, Sander, Beerenwinkel, and Lengauer 2005) for classifier performance evaluation and visualization, while useful in the machine learning, pattern recognition and artificial intelligence fields, is not suitable for the medical imaging applications addressed in the various software modules mentioned above.]

In an ROC study the radiologist is shown images of *patients* (*images* and *cases* are used interchangeably as synonyms for patients), the radiologist is "blinded," of course, to the true disease states, and the radiologist's task is to *rate* each patient for confidence in presence or absence of disease. The rating r is typically on a numeric scale, with higher values representing increasing confidence in presence of disease and lower values representing increasing confidence in absence of disease. Typically 5 or 6 integer ratings are used but the ratings could have higher precision. With a 6 rating scale a 1-rating would correspond to high confidence that patient is non-diseased and a 6-rating would correspond to high confidence that patient is diseased. The normalized counts in the different ratings bins, cumulated separately for actually non-diseased and actually diseased patients, can be used to construct an *operating point*. For example, the cumulated counts in diseased ratings bins 3, 4 and 5, divided by the number of actually diseased images, yields *true positive fraction* TPF_{3+}, where TPF is the ordinate of the ROC plot, and the corresponding cumulated counts for non-diseased images, divided by the number of non-diseased images, yields *false positive fraction* FPF_{3+}, where FPF is the abscissa. It can be seen that as long as no bin has zero counts for both non-diseased and diseased images, an R rating ROC study will yield $R-1$ non-trivial operating points $\{FPF_{r+}, TPF_{r+}; r = 2, 3, ..., R\}$. The origin $(0, 0)$ and the upper right corner $(1, 1)$ are trivial operating points, belonging to any dataset, obtained by counting none and all of the binned ratings, respectively. The empirical ROC curve is defined by connecting neighboring operating points (including the trivial ones) with straight lines. While several curve-fitting methods are available (Dorfman and Alf 1968, 1969; Dorfman and Berbaum 1986; Dorfman, Berbaum, Metz, Lenth, Hanley, and Abu Dagga 1997; Pan and Metz 1997; Metz and Pan 1999; Dorfman and Berbaum 2000; Pesce and Metz 2007) and have their merits, the trapezoidal area under the empirical ROC is frequently used as a non-parametric *figure of merit* (FOM) for quantifying observer performance (Hanley and McNeil 1982). It can be shown to be equivalent to the Mann-Whitney-Wilcoxon 2-sample U-statistic (Wilcoxon 1945; Mann and Whitney 1947). True positive fraction is synonymous with *sensitivity* and the complement of false positive fraction is synonymous with *specificity*, so the ROC curve is a plot of *sensitivity* vs. $1 - specificity$. ROC studies are typically conducted with about 50/50 or more non-diseased/diseased patients. The patients are imaged in two or more imaging systems (termed *modalities* or *treatments*) and the images are rated by a number of radiologists (typically about 5 to 10). This type of fully crossed study design is termed multiple reader multiple case (MRMC) and, although methods are available for partially paired interpretations (Metz, Herman, and Roe 1998; Obuchowski 2009), MRMC studies are the focus of this work.

A limitation of the ROC paradigm is that it acquires a single rating per image, where the rating applies to the image as a whole, not to any specific region(s) in the image. Typically, disease is manifested by the presence of localized diseased regions or *lesions*. For example, lung cancer often presents as localized malignant nodules found on chest x-rays or computed tomography (CT) scans. Ignoring localization can result in an overestimate of true performance (Obuchowski, Mazzone, and Dachman 2010); for example, suppose a true lesion on a diseased case is missed and a disease-free region is perceived as abnormal by the radiologist - the two mistakes would effectively cancel each other and the event would be credited as a true positive at the level of confidence associated with the disease-free region. There are two data collection paradigms that allow for localization information to be collected to different extents (a third important paradigm (Starr, Metz, Lusted, and Goodenough 1975; Starr, Metz, and Lusted 1977; Swensson and Judy 1981; Swensson 1996), termed *location ROC* (LROC) is not included in this description, as it is not currently implemented in any of the websites mentioned so far). In the *free-response* paradigm (Egan, Greenburg, and Schulman 1961; Miller 1969; Bunch, Hamilton, Sanderson, and Simmons 1978) the radiologist marks and rates regions that are suspicious for disease. A mark is classified as *lesion localization* (LL) if it successfully locates an actual lesion to within clinically acceptable spatial accuracy, or *non-lesion localization* (NL) otherwise (usage of ROC-specific terms like true positive and false positive in the FROC, LROC or ROI contexts can lead to confusion). Unmarked lesions are assigned the –infinity rating. By treating the rating of the highest rated mark on a *non-diseased* image (or –infinity if the image has no marks) as its *inferred* FP rating, it is possible to define an inferred FPF quantity that is analogous to true FPF obtained in an actual ROC study. By cumulating LL events and dividing by the total number of lesions it is possible to define a *lesion localization fraction* (LLF) quantity that is analogous to TPF, but because it requires correct localization, may not reach unity, even when all ratings are cumulated. A plot of LLF along the ordinate vs. FPF is defined as the *alternative* FROC, or AFROC (Chakraborty 1989; Chakraborty and Winter 1990), where it is understood that the uppermost operating point, obtained by cumulating all the marks, is to be connected to (1,1) by a dotted line (while inaccessible to the observer, it needs to be taken into account in defining the area under the AFROC as a valid figure of merit (Chakraborty 2006b,a); essentially it gives credit for unmarked non-diseased cases and penalizes for unmarked lesions). Non-lesion localization fraction (NLF) is defined as the cumulated number of NLs divided by the total number of cases. The FROC plot is defined as that of LLF along the ordinate vs. NLF (Bunch, Hamilton, Sanderson, and Simmons 1978; Chakraborty, Breatnach, Yester, Soto, Barnes, and Fraser 1986; Niklason, Hickey, Chakraborty, Sabbagh, Yester, Fraser, and Barnes 1986; Barnes, Sabbagth, Chakraborty, Nath, Luna, Sanders, and Fraser 1989). By treating the rating of the highest rated mark on a diseased image (or negative infinity if the image has no marks) as its inferred TP rating, it is possible to define an inferred TPF. The plot of inferred TPF vs. inferred FPF is the inferred ROC curve. Regarding the highest rated NL mark on *any* image as an inferred FP1 rating (the 1 denotes that NL marks on diseased cases could be contributing to this FP-like rating) and the corresponding AFROC1 plot is that of LLF vs. FPF1. By assigning clinically relevant weights to different lesions on the same diseased image, it is possible to define weighted LLF, weighted AFROC and weighted AFROC1 plots (the weights, which add up to unity on any diseased image, are the relative importances of finding the lesions: from the clinical perspective all lesions are not alike; some are more aggressive than others and therefore more important to find). With the exception of the FROC, the trapezoidal areas under all of these curves qualify as valid figures of merit (a valid figure of merit is one that rewards good decisions and penalizes bad decisions, where good and bad are defined with respect to patient outcome). That the area under the FROC is a particularly bad figure of merit can be appreciated from the fact that a perfect observer's FROC curve would be a vertical line extending from (0,0) to (0,1), for which the area measure would be zero.

In the *region of interest* (ROI) paradigm (Obuchowski, Lieber, and Powell 2000) each image is divided into Q regions of interest (typically Q is 4 or 5) where each region is either non-diseased or diseased, and the reader gives a ROC-like rating to each region. Regarding each of the regions as a mini-image, it is possible to define ROC-like quantities TPF' and FPF', where the primes distinguish them from true FPF and TPF. For example, FPF' and TPF' can be defined for a dataset containing only diseased images, for which it would be impossible to define FPF. The data collection paradigms are summarized in Table 1.

Analysis of the data starts with estimation, for each treatment - reader combination, of the figure of merit. One object of the analysis is to determine the significance of the reader-averaged differences in FOMs between pairs of modalities. While several significance-testing methods have been proposed, see Table 2, we focus on two that are easily accessible and consequently in widespread use: the *Dorfman-Berbaum-Metz* (DBM) method (Dorfman, Berbaum, and Metz 1992) and the *Obuchowski-Rockette* (OR) method (Obuchowski and Rockette 1995), both of which have been significantly improved by contributions by Hillis, and are henceforth referred to as DBMH and ORH, respectively. A third method (Gallas 2006; Gallas, Bandos, Samuelson, and Wagner 2009) often termed a mechanistic or first-principles approach to MRMC analysis, is also available online, that yields independent estimates of variability parameters used in DBMH and ORH analyses, in addition to its own estimates. *All significance-testing methods are applicable to any scalar figure of merit.* In fact current JAFROC software uses the DBMH significance testing method and applies it to different figures of merit, e.g., the trapezoidal area under the AFROC curve.

Table 1: Data collection paradigms, associated operating characteristics, figures of merit and common terminology

Data collection paradigm	Operating characteristic(s)	FOM	Terminology
Receiver operating characteristic	ROC = TPF vs. FPF	Trapezoidal area under ROC	AUC
Free-response	AFROC = LLF vs. FPF	Trapezoidal area under AFROC	JAFROC, weighted JAFROC
	AFROC1 = LLF vs. FPF1	Trapezoidal area under AFROC1	JAFROC1, weighted JAFROC1
	FROC = LLF vs. NLF	Not recommended	
	Inferred ROC	Trapezoidal area under inferred ROC	AUC
Region of interest	ROC’=TPF’ vs. FPF’	Trapezoidal area under ROC’	AUC’

If a non-significant result is obtained (i.e., $p > \alpha$) in a *pilot* study then the investigator may wish to plan a new *pivotal* study that is sufficiently powered to detect a clinically relevant difference between two modalities of interest. The pilot study is used to get estimates of variability components entering a figure of merit model, as these determine the sample size. Sample-size estimation methods for ROC studies are available on all referenced websites. A preliminary sample-size method for free-response studies is available on the JAFROC website. We are unaware of any sample size estimation method for ROI studies.

2. Statistical Models and Methods

The figure of merit is a critical determinant of statistical power (Chakraborty 2008) and clinical relevance (Chakraborty 2012) of the measurement. Even for the relatively simple ROC paradigm, several FOMs have been proposed, e.g., partial area measures (Jiang, Metz, and Nishikawa 1996; Yousef, Wagner, and Loew 2005), the Youden index (Youden 1950) and others (Pepe 2003). In the following sections we define the implemented ROC data

Table 2: Software availability of MRMC observer performance methods.

Significance testing methods	Online software name and website	Supported data collection paradigms	Supported FOMs
DBMH, ORH	OR-DBM MRMC / http://perception.radiology.uiowa.edu	ROC	Wilcoxon and parametric fits
DBMH	Metz ROC Software / http://metz-roc.uchicago.edu/MetzROC/software		Wilcoxon and parametric fits
Mechanistic MRMC	iMRMC / https://code.google.com/p/imrmc		Wilcoxon
DBMH	JAFROC / http://devchakraborty.com	ROC, FROC, ROI	Trapezoidal areas under ROC, AFROC, AFROC1, weighted versions and ROC', and other FOMs
Ordinal regression(Toledano and Gatsonis 1996; Toledano 2003)	NA	ROC	AUC and other ROC figures of merit
Wald test on U-statistics(Song 1997)			
Hierarchical ordinal regression(Ishwaran and Gatsonis 2000; Obuchowski, Beiden, Berbaum, Hillis, Ishwaran, Song, and Wagner 2004)			
Multiple bootstraps(Beiden, Wagner, and Campbell 2000)			

FOM, two FOMs commonly used in analyzing free-response data (several other implemented free-response figures of merit are defined in Appendix A.1), followed by the ROI figure of merit. Two implemented significance-testing methods are described followed by sample-size estimation for ROC studies. No derivations are given: we simply refer the journal reader to the appropriate literature.

2.1. Figure of merit for ROC data

Images are indexed by $k_t t$, where t is the truth state (1 for disease-free cases and 2 for diseased cases) and k_t indexes the cases for truth state t, specifically, $k_1 = 1, 2 \ldots, K_1$ and $k_2 = 1, 2 \ldots, K_2$ where K_1 is the number of disease-free cases and K_2 is the number of diseased cases. Let $z_{ijk_t t}$ denote the rating given to case $k_t t$ by the reader j using modality i with $i = 1, 2 \ldots, I$ and $j = 1, 2 \ldots, J$, where I is the number of modalities and J is the number of readers. The trapezoidal area under the ROC curve, θ, estimated for reader j in modality i by the Wilcoxon statistic (Wilcoxon 1945; Mann and Whitney 1947):

$$\widehat{\theta}_{ij} = \frac{1}{K_1 K_2} \sum_{k_1}^{K_1} \sum_{k_2}^{K_2} \psi\left(z_{ijk_1 1}, z_{ijk_2 2}\right) \tag{1}$$

The kernel function ψ is defined by:

$$\left.\begin{array}{ll} \psi\left(z_{ijk_1 1}, z_{ijk_2 2}\right) = 1 & z_{ijk_1 1} < z_{ijk_2 2} \\ \psi\left(z_{ijk_1 1}, z_{ijk_2 2}\right) = 0.5 & z_{ijk_1 1} = z_{ijk_2 2} \\ \psi\left(z_{ijk_1 1}, z_{ijk_2 2}\right) = 0 & z_{ijk_1 1} > z_{ijk_2 2} \end{array}\right\} \tag{2}$$

This figure of merit can be shown to be identical to the area under the empirical (trapezoidal) ROC curve (Bamber 1975). It has the physical interpretation as the probability that a randomly picked diseased image will be rated higher than a randomly picked non-diseased image (Hanley and McNeil 1982).

2.2. Figures of merit for free-response data

Since free-response data allows for varying number of lesions and mark/rating pairs per case, the notation is necessarily more complex. The *case-truth* index t refers to the case (or patient) as a whole (non-diseased, $t = 1$, or diseased, $t = 2$), not to specific locations in the case. Let $N_{k_2 2}$ denote the number of lesions in diseased case $k_2 2$, where $N_{k_2 2} \geq 1$. The total number of lesions in the data set is N_2:

$$N_2 = \sum_{k_2=1}^{K_2} N_{k_2 2} \tag{3}$$

The notation is driven by the Chakraborty *search-model* for the free-response paradigm (Chakraborty 2006a,b) that involves two phases, a *search phase* during which suspicious regions (*decision sites*) are identified (based on eye-tracking measurements this phase is quite rapid (Kundel, Nodine, Conant, and Weinstein 2007), typically 100 ms for experts) and a *decision phase* during which each decision-site is examined (typically 1 sec per site) and a decision is made on whether to mark it. Decision sites can be either *noise sites* (not corresponding to real lesions) or *signal sites* (corresponding to real lesions). Marked noise sites are non-lesion localizations while marked signal sites are lesion localizations. Marks are labeled by a *location index* l_s $(l_s = 1, 2, \ldots)$ *and* a *site-truth* index s which determines the *type* of the site, i.e., $s = 1$ for a non-lesion localization and $s = 2$ for a lesion localization. The rating for modality i, reader j, case $k_t t$ and site $l_s s$ is denoted $r_{ijk_t t l_s s}$.

Several methods have been proposed to infer ROC-like data (i.e., single rating per image) from free-response data. The highest rating inferred ROC (IR) figure of merit θ_{ij}^{IR} is estimated by (this is identical to the A0 figure of merit defined by Song, Bandos, Rockette, and Gur (2008)):

$$\widehat{\theta}_{ij}^{IR} = \frac{1}{K_2 K_1} \sum_{k_2=1}^{K_2} \sum_{k_1=1}^{K_1} \psi \left(max(r_{ijk_1 1*1}), max(r_{ijk_2 2**}) \right) \tag{4}$$

The *max* function is the maximum over the indices indicated by the asterisks. For the second max function, the maximum over diseased cases, the maximum is over all marks (NLs and LLs), so on a diseased case there is a possibility that a non-lesion localization is rated higher than any lesion localization on that case. If all lesions are marked and no noise sites are marked, signifying perfect performance, the ψ function is unity, and $\widehat{\theta}_{ij}^{IR}$ is unity. If no lesions are marked and the distribution of the numbers and ratings of NL marks is the same for non-diseased and diseased images, signifying the observer is unable to discriminate between them, the ψ function comparisons yield 0.5, on the average, implying $\widehat{\theta}_{ij}^{IR} = 0.5$, which is the worst possible ROC performance. Therefore, $\widehat{\theta}_{ij}^{IR}$ ranges between 0.5 and unity. The Song et al (Song *et al.* 2008) A1 figure of merit takes the average rating of all marked regions on an image to infer an ROC-like single rating for the image. The Song A2 figure of merit involves a stochastic dominance idea.

Let $W_{k_2 l_2}$ denote the weight of lesion $l_2 2$ in abnormal case $k_2 2$ such the weights on any given diseased case add up to unity:

$$\sum_{l_2=1}^{N_{k_2 2}} W_{k_2 l_2} = 1 \tag{5}$$

The weighted (according to clinical importance) JAFROC figure of merit $\theta_{ij}^{wJAFROC}$ is estimated by:

$$\widehat{\theta}_{ij}^{wJAFROC} = \frac{1}{K_2 K_1} \sum_{k_2=1}^{K_2} \sum_{k_1=1}^{K_1} \sum_{l_2=1}^{N_{k_2 2}} W_{k_2 l_2} \psi \left(max(r_{ijk_1 1*1}), r_{ijk_2 2 l_2 2} \right) \tag{6}$$

If all lesions are marked and no non-diseased image is marked the ψ function is unity and $\widehat{\theta}_{ij}^{wJAFROC}$ is unity, the best possible performance. If no lesions are marked and every non-diseased image has at least one mark the ψ function is zero and $\widehat{\theta}_{ij}^{wJAFROC}$ is zero, the worst possible performance. This figure or merit, like the one to be described next, ranges between 0 and unity, unlike the ROC area figure of merit that ranges between 0.5 and 1. The above figure of merit does not count NLs on diseased cases. The extension to include the highest rated NL on diseased cases, called the weighted JAFROC1 figure of merit, $\widehat{\theta}_{ij}^{wJAFROC1}$, is:

$$\widehat{\theta}_{ij}^{wJAFROC1} = \frac{1}{K_2\left(K_1+K_2\right)}\sum_{k_2=1}^{K_2}\left[\sum_{k_1=1}^{K_1}\sum_{l_2=1}^{N_{k_2 2}} W_{k_2 l_2}\psi\left(max(r_{ijk_1 1*1}), r_{ijk_2 2 l_2 2}\right)\right.$$
$$\left.+\sum_{k_2'=1}^{K_2}\sum_{l_2=1}^{N_{k_2 2}} W_{k_2 l_2}\psi\left(max(r_{ijk_2' 2*1}), r_{ijk_2 2 l_2 2}\right)\right] \tag{7}$$

The first term in the numerator compares LL ratings to the maximum NL ratings on non-diseased images, similar to Eqn. 6. The second term compares LL ratings to the maximum NL ratings on diseased images. Since the maximum of NL ratings in $k_2'2$ is being compared with each LL rating in $k_2 2$, we should use the lesion weights corresponding to $k_2 2$ and the l_2 index ranges from 1 to $N_{k_2 2}$. The above two figures of merit have covered the needs of most users of JAFROC. Other implemented free-response figures of merit, sometimes needed for specific clinical reasons, are described in Appendix A.1.

2.3. Figure of merit for ROI data

In this paradigm each image is divided into $Q_{k_t t}$ regions of interest (ROIs). Obuchowski's analytic significance testing procedure (Obuchowski 1997) can handle varying number of ROIs per image, but is currently unimplemented in **RJafroc**, which instead uses resampling methods for signficance testing. Let $z_{ijk_2 2 l_2 2}$ denote the rating in modality i, reader j, for the lesion-present ROI indexed by $l_2 2$ in diseased case $k_2 2$ and let $q_{k_2 22}$ denote the total number of lesion-containing ROIs in the case. Similarly, let $z_{ijk_t t l_1 1}$ denote the rating in modality i, reader j, for the lesion-absent ROI indexed by $l_1 1$ in case $k_t t$ (which could be non-diseased or diseased) and let $q_{k_t t1}$ be the total number of non-lesion containing ROIs in the case. The trapezoidal area under the ROI-level ROC curve is estimated by Obuchowski *et al.* (2000)

$$\widehat{\theta}_{ij}^{ROI} = \frac{\sum\limits_{k_1=1}^{K_1}\sum\limits_{k_2=1}^{K_2}\sum\limits_{t=1}^{2}\sum\limits_{l_1=1}^{q_{k_t t1}}\sum\limits_{l_2=1}^{q_{k_2 22}}\psi\left(z_{ijk_t t l_1 1}, z_{ijk_2 2 l_2 2}\right)}{\sum\limits_{k_1=1}^{K_1}\sum\limits_{k_2=1}^{K_2}\sum\limits_{t=1}^{2}\sum\limits_{l_1=1}^{q_{k_t t1}}\sum\limits_{l_2=1}^{q_{k_2 22}}(1)} \tag{8}$$

For $t = 1$ the comparisons are between ratings of lesion-containing ROIs and ratings of ROIs on non-diseased cases and for t = 2 comparisons are between ratings of lesion-containing ROIs and ratings of lesion-absent ROIs on diseased cases. Unlike the ROC figure of merit and the weighted JAFROC figure of merit, the ROI figure of merit, like the weighted JAFROC1 figure of merit, can be defined over a dataset with no non-diseased cases. Table 3 summarizes the figures of merit described so far.

2.4. DBMH significance testing method

The DBM method (Dorfman *et al.* 1992) models the jackknife derived pseudovalues (Efron and Tibshirani 1993) of $\widehat{\theta}_{ij}$, denoted Y_{ijk}' for modality i, reader j and case k ($k = 1, 2, \ldots K$; where $K = K_1 + K_2$ is the total number of cases). The pseudovalues are defined by:

$$Y_{ijk}' = K\widehat{\theta}_{ij} - (K-1)\,\widehat{\theta}_{ij(k)} \tag{9}$$

Table 3: Summary of the figures of merit for the different observer performance measurement data collection methods. [IR = inferred ROC using the highest rating; A1, A2 are inferred ROC figures of merit]

Paradigm	Description of FOM	Symbol	Comments
ROC	Trapezoidal area under ROC	$\widehat{\theta}_{ij}$	Equivalent to Wilcoxon statistic
FROC	Highest rating inferred ROC	$\widehat{\theta}_{ij}^{IR}$	
	Average rating inferred ROC	A1	
	Stochastic dominance inferred ROC	A2	
	Weighted JAFROC	$\widehat{\theta}_{ij}^{wJAFROC}$	Recommended FOM for FROC data
	Weighted JAFROC1	$\widehat{\theta}_{ij}^{wJAFROC1}$	To be used only in absence of non-diseased cases
ROI	Trapezoidal area under ROI-level ROC'	$\widehat{\theta}_{ij}^{ROI}$	

Here $\widehat{\theta}_{ij(k)}$ is the estimate of θ_{ij} for modality i, reader j and case k removed (jackknifed) from the analysis. Hillis, Berbaum, and Metz (2008) have defined a centering transformation

$$Y_{ijk} = Y'_{ijk} + \left(\widehat{\theta}_{ij} - Y'_{ij\bullet}\right) \tag{10}$$

The effect of this transformation is that the average of the centered pseudovalues over the case index is identical to the estimate of the figure of merit:

$$Y_{ij\bullet} = Y'_{ij\bullet} + \left(\widehat{\theta}_{ij} - Y'_{ij\bullet}\right) = \widehat{\theta}_{ij} \tag{11}$$

This has the practical advantage that all confidence intervals are correctly centered. While this transformation is unnecessary if one uses the Wilcoxon as the figure-of-merit, for generality with other possible figures of merit, *it is understood that all calculations from now on will use centered pseudovalues*. The DBM pseudovalue model (Dorfman *et al.* 1992) is:

$$\begin{aligned} &Y_{ijk} = \mu + \tau_i + R_j + C_k + (\tau R)_{ij} + (\tau C)_{ik} + (RC)_{jk} + \varepsilon_{ijk} \\ &\sum_{i=1}^{I} \tau_i = 0 \end{aligned} \tag{12}$$

The right hand side consists of 2 fixed effects, μ, τ_i, and 6 random effects modeled as mutually independent samples from zero-mean normal distributions with variances (in the same order of appearance in the above equation) σ_R^2, σ_C^2, $\sigma_{\tau R}^2$, $\sigma_{\tau C}^2$, σ_{RC}^2 and σ_ε^2. Using the dot symbol to denote an average over the corresponding index, the first term can be μ estimated by averaging the observed left hand side over all three indices:

$$\mu = Y_{\bullet\bullet\bullet} \tag{13}$$

The modality effect can be estimated by:

$$\tau_i = Y_{i\bullet\bullet} - \mu \tag{14}$$

The reader and case averaged difference between two different modalities i and i' (often termed the *observed effect size*) is given by

$$\tau_i - \tau_{i'} = Y_{i\bullet\bullet} - Y_{i'\bullet\bullet} = \widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet} \tag{15}$$

Estimating the strengths of the random terms involves analysis of variance (ANOVA) methods specially adapted to this problem by Dorfman, Berbaum, Metz, Hillis and others. Only the final results are summarized here. The starting point is calculation of the mean squares. In the following definitions the Y subscript emphasizes that the relevant mean-square quantities are calculated using pseudovalues, not figure-of-merit values.

$$\begin{aligned}
MS_Y\left(T\right) &= \frac{JK\sum\limits_{i=1}^{I}\left(Y_{i\bullet\bullet}-Y_{\bullet\bullet\bullet}\right)^2}{I-1}\\
MS_Y\left(R\right) &= \frac{IK\sum\limits_{j=1}^{J}\left(Y_{\bullet j\bullet}-Y_{\bullet\bullet\bullet}\right)^2}{J-1}\\
MS_Y\left(TR\right) &= \frac{K\sum\limits_{i=1}^{I}\sum\limits_{j=1}^{J}\left(Y_{ij\bullet}-Y_{ij\bullet}-Y_{\bullet j\bullet}+Y_{\bullet\bullet\bullet}\right)^2}{(I-1)(J-1)}\\
MS_Y\left(TC\right) &= \frac{J\sum\limits_{i=1}^{I}\sum\limits_{k=1}^{K}\left(Y_{i\bullet k}-Y_{i\bullet\bullet}-Y_{\bullet\bullet k}+Y_{\bullet\bullet\bullet}\right)^2}{(I-1)(K-1)}\\
MS_Y\left(\varepsilon\right) &= \frac{\sum\limits_{i=1}^{I}\sum\limits_{j=1}^{J}\sum\limits_{k=1}^{K}\left(Y_{ijk}-Y_{ij\bullet}-Y_{i\bullet k}-Y_{\bullet jk}+Y_{i\bullet\bullet}+Y_{\bullet j\bullet}+Y_{\bullet\bullet k}-Y_{\bullet\bullet\bullet}\right)^2}{(I-1)(J-1)(K-1)}
\end{aligned} \tag{16}$$

Hillis proposes the following statistic for testing the null hypothesis of no modality effect (Hillis 2007):

$$F_{DBMH} = \frac{MS_Y\left(T\right)}{MS_Y\left(TR\right) + H\left(MS_Y\left(TC\right) - MS_Y\left(\varepsilon\right)\right)} \tag{17}$$

Here $H\left(x\right)$ is the unit step function, defined as unity for positive x and zero otherwise. Hillis has shown that F_{DBMH} is distributed as an F-statistic with numerator degrees of freedom $ndf = I - 1$ (i.e., one less than the number of treatments) and ddf_H denominator degrees of freedom, i.e.,

$$F_{DBMH} \sim F_{ndf,ddf_H} \tag{18}$$

The denominator degrees of freedom ddf_H is defined by (this is different from the original definitions by DBM):

$$ddf_H = \frac{\left[MS_Y\left(TR\right) + H\left[MS_Y\left(TC\right) - MS_Y\left(\varepsilon\right)\right]\right]^2}{\frac{MS_Y\left(TR\right)^2}{(I-1)(J-1)}} \tag{19}$$

The critical value of the F-statistic for rejection of the null hypothesis is given by $F_{1-\alpha,ndf,ddf_H}$. The p-value of the test is given by:

$$p = P\left(F > F_{DBMH} | F \sim F_{ndf,ddf_H}\right) \tag{20}$$

The $(1-\alpha)\,100$ percent confidence interval for $(\theta_i - \theta_{i'})$is given by

$$CI_{1-\alpha} = \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet}\right) \pm t_{\alpha/2;ddf_H}\sqrt{\frac{2}{JK}\left(MS_Y\left(TR\right) + \max\left(MS_Y\left(TC\right) - MS_Y\left(\varepsilon\right),0\right)\right)} \tag{21}$$

The analysis described so far treats both readers and cases as random factors, so it is termed *random-reader random-case* (RRRC). Special cases of the analysis, which regards either readers or cases as fixed factors, is possible, and the results are given in Appendix A.2. These are sometimes necessary if the number of readers or the number of cases is not large enough to support treating them as random factors (for example, one could have a single reader interpret a set of cases in two modalities).

2.5. ORH significance testing method

The statistical model underlying the OR method is (Obuchowski and Rockette 1995):

$$\begin{aligned} &\widehat{\theta}_{ij\{c\}} = \theta_0 + \Delta\theta_i + R_j + (\tau R)_{ij} + \varepsilon_{ij\{c\}} \\ &\sum_{i=1}^{I}\Delta\theta_i = 0 \end{aligned} \tag{22}$$

The left hand side is the estimated figure-of-merit $\widehat{\theta}_{ij\{c\}}$ for modality i and *case-set* index $\{c\}$, where $c = 1, 2, \ldots, C$ denote different case sets (i.e., different *collections* of cases, not individual cases, emphasized by the curly bracket notation) sampled from the patient population). In practice the dataset is limited to $c = 1$, but resampling and other methods, are available to estimate the case-sample variability from a single case set realization. The first two terms on the right hand side of Eqn. 22 have their usual meanings. The remaining terms are mutually independent random samples: R_j denotes a random contribution to the figure-of-merit of reader j, modeled as a sample from a zero-mean normal distribution with variance σ_R^2; $(\tau R)_{ij}$ denotes a treatment-dependent random contribution of reader j in modality i, modeled as a sample from a zero-mean normal distribution with variance $\sigma_{\tau R}^2$. [We are abusing the notation but it is implicit that the variances in the OR model refer to the FOM, while those in the DBM model apply to pseudovalues.] The error term is modeled by a zero mean vector multivariate normal distribution with covariance matrix Σ described by 4 parameters, Var, Cov_1, Cov_2, Cov_3, defined as follows:

$$Cov\left(\varepsilon_{ij\{c\}}, \varepsilon_{i'j'\{c\}}\right) = \begin{cases} Var & i = i', j = j' \\ Cov_1 & i \neq i', j = j' \\ Cov_2 & i = i', j \neq j' \\ Cov_3 & i \neq i', j \neq j' \end{cases} \tag{23}$$

OR have suggested that the 4 elements of the covariance matrix should be ordered as follows:

$$Var \geq Cov_1 \geq Cov_2 \geq Cov_3 \tag{24}$$

Resampling methods are used to estimate the parameters of the covariance matrix. Using the bootstrap method (Efron and Tibshirani 1993), where $\{b\}$ is the b^{th} bootstrap replicate, $b = 1, 2, \ldots, B$,

$$\widehat{Cov}\left(\varepsilon_{ij\{c\}}, \varepsilon_{i'j'\{c\}}\right) = \left\langle \frac{1}{B-1} \sum_{b=1}^{B} \left(\theta_{ij\{b\}} - \theta_{ij\{\bullet\}}\right) \left(\theta_{i'j'\{b\}} - \theta_{i'j'\{\bullet\}}\right) \right\rangle_{ij} \tag{25}$$

As with the case-set index $\{c\}$, the bootstrap index $\{b\}$ denotes a set of cases. The averages, indicated by the bracket symbols, over modalities and readers are necessary since the covariances in the OR model are assumed to be independent of modality and reader. The jackknife estimate is:

$$\widehat{Cov}\left(\varepsilon_{ij\{c\}}, \varepsilon_{i'j'\{c\}}\right) = \left\langle \frac{K-1}{K} \sum_{k=1}^{K} \left(\theta_{ij(k)} - \theta_{ij(\bullet)}\right) \left(\theta_{i'j'(k)} - \theta_{i'j'(\bullet)}\right) \right\rangle_{ij} \tag{26}$$

DeLong, DeLong, and Clarke-Pearson (1988) have described an analytical covariance estimation method that is applicable as long as one restricts to the ROC paradigm and the Wilcoxon FOM (the bootstrap and the jackknife are more generally applicable to any figure of merit).

Because of the correlated structure of the error term a customized ANOVA is needed. The null hypothesis is that the true figure-of-merit of all modalities are identical, i.e.,

$$NH : \Delta\theta_i = 0 \, (i = 1, 2, ..., I) \tag{27}$$

A modified F-statistic is needed, denoted F_{ORH}^{*} and defined by (this is different from that originally suggested by OR):

$$F_{ORH}^{*} = \frac{MS\left(T\right)}{MS\left(TR\right) + H\left(J\left(\widehat{Cov}_2 - \widehat{Cov}_3\right)\right)} \tag{28}$$

Eqn. 28 incorporates Hillis' modification, which ensures that the constraint $Cov_2 \geq Cov_3$ is always obeyed. The mean square (MS) terms are defined by (note the lack of the Y subscript, as these are calculated directly using FOM values):

$$\begin{aligned} MS\left(T\right) &= \tfrac{J}{I-1} \sum_{i=1}^{I} \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{\bullet\bullet}\right)^2 \\ MS\left(TR\right) &= \tfrac{1}{(I-1)(J-1)} \sum_{i=1}^{I} \sum_{j=1}^{J} \left(\widehat{\theta}_{ij} - \widehat{\theta}_{i\bullet} - \widehat{\theta}_{\bullet j} + \widehat{\theta}_{\bullet\bullet}\right)^2 \end{aligned} \tag{29}$$

According to Hillis, the observed statistic F_{ORH}^{*} is distributed as an F-statistic with $ndf = I - 1$ and ddf_{ORH} degrees of freedom:

$$F_{ORH}^{*} \sim F_{ndf, ddf_{ORH}} \tag{30}$$

where

$$ddf_{ORH} = \frac{\left[MS\left(TR\right) + \left(J\left(\widehat{Cov_2} - \widehat{Cov_3}\right)\right)\right]^2}{\frac{\left[MS(TR)\right]^2}{(I-1)(J-1)}} \tag{31}$$

For the Wilcoxon statistic, the two definitions of ddf_H (Eqn. 19 and Eqn. 31) are equivalent. The critical value of the F-statistic for rejection of the null hypothesis is given by $F_{1-\alpha,ndf,ddf_H}$. The p-value of the test is given by:

$$p = P\left(F > F^*_{ORH} | F \sim F_{ndf,ddf_{ORH}}\right) \tag{32}$$

The percent $(1-\alpha)\,100$confidence interval for $\left(\widehat{\theta}_i - \widehat{\theta}_{i'}\right)$ is given by

$$CI_{1-\alpha} = \left(\widehat{\theta_{i\bullet}} - \widehat{\theta_{i'\bullet}}\right) \pm t_{\alpha/2;ddf_{ORH}} \sqrt{\frac{2}{J}\left(MS\left(TR\right) + J\max\left(Cov_2 - Cov_3, 0\right)\right)} \tag{33}$$

The analysis described so far treats both readers and cases as random factors (RRRC). Special cases of the analysis, which regards either readers or cases as fixed factors, are given in Appendix A.3.

2.6. Sample size estimation for ROC studies

We will illustrate the procedure for the ORH method. Two modalities are assumed. The *observed effect size* (absolute value of the difference in figures of merit between the two modalities) is $2\left|\widehat{\tau}_1\right|$. Under the alternative hypothesis $AH : \tau_i \neq 0$ the test statistic is distributed as a *non-central* F-distribution with $ndf = 1$ and to-be-determined ddf and non-centrality parameter Δ. The sample size procedure (Hillis, Obuchowski, and Berbaum 2011) assumes random-readers and random cases; different formulae apply when either readers or cases is treated as a fixed effect, see below.

1. Specify the effect size d: typically, when dealing with area under the ROC curve as the figure of merit, one might choose the value observed in the pilot study.

2. Estimate the OR modality-reader interaction variance component: this is given by (see Table 1 in Hillis (2007)):

$$\hat{\sigma}^2_{\tau R} = MS\left(TR\right) - \widehat{Var} + \widehat{Cov_1} + H\left(\widehat{Cov_2} - \widehat{Cov_3}\right)$$

   If this yields a negative variance, Hillis suggests setting it to zero.

3. Estimate the non-centrality parameter and the ddf of the F-distribution. Let K^* denote the number of cases in the pilot dataset, and let J, K be the numbers of readers, cases in the pivotal study. The non-centrality parameter Δ and the ddf are estimated by:

$$\widehat{\Delta} = \frac{J\frac{d^2}{2}}{\hat{\sigma}^2_{\tau R} + \frac{K^*}{K}\left(\widehat{Var} - \widehat{Cov_1} + \left(J-1\right)H\left(\widehat{Cov_2} - \widehat{Cov_3}\right)\right)}$$

$$\widehat{ddf} = (J-1)\,\frac{\left[\hat{\sigma}^2_{\tau R} + \frac{K^*}{K}\left(\widehat{Var} - \widehat{Cov}_1 + (J-1)\,H\left(\widehat{Cov}_2 - \widehat{Cov}_3\right)\right)\right]^2}{\left[\widehat{\sigma^2_{\tau R}} + \frac{K^*}{K}\left(\widehat{Var} - \widehat{Cov}_1 + (J-1)\,H\left(\widehat{Cov}_2 - \widehat{Cov}_3\right)\right)\right]^2}$$

4. The statistical power $1-\beta$ at significance level α can be calculated using:

$$1-\beta = P\left(F > F_{1-\alpha;1,\widehat{ddf}} | F \sim F_{1,\widehat{ddf};\widehat{\Delta}}\right)$$

   $F_{1,ddf;\Delta}$ denotes the non-central F-distribution with degrees of freedom 1, ddf, and non-centrality parameter Δ and $F_{1-\alpha;1,ddf}$ is the critical value of F such that fraction of the $1-\alpha$ central F distribution with degrees of freedom 1, ddf is below the critical value.

5. If the power is below the desired or target power, typically chosen to be 0.8, one tries successively larger value of K until the target power is reached. The procedure could be repeated with different values of J (depending on cost and other practicality issues, it might be better to have more reader each reading fewer cases to achieve the same target power).

Hillis has also described a procedure, currently unimplemented in **RJafroc**, for correcting the estimate if the numbers of non-diseased to diseased case ratio is substantially different between pilot and pivotal studies (Hillis *et al.* 2011).

Formulae for fixed reader random case (FRRC) sample size estimation

The only change needed is to define:

$$ddf = K - 1 \tag{34}$$

Formulae for random reader fixed case (RRFC) sample size estimation

The only change needed is to define:

$$ddf = J - 1 \tag{35}$$

3. Examples

It is assumed that the package has been installed from the CRAN website and that the package has been loaded using the `library()` function.

3.1. Structure of the dataset

The package comes pre-loaded with three datasets: (1) an ROC dataset named `rocData`, which has been repeatedly used by Berbaum, Hillis and colleagues to illustrate advances in ROC methodology (Hillis 2007) (and referred to in their papers as Van Dyke data (Van Dyke, White, Obuchowski, Geisinger, Lorig, and Meziane 1993)), (2) an FROC dataset named `frocData`, contributed by Dr. Zanca (Zanca, Jacobs, Van Ongeval, Claus, Celis, Geniets, Provost, Pauwels, Marchal, and Bosmans 2009), and a simulated ROI dataset named `roiData` (see Appendix A.4 for details regarding the ROI simulator). Their structures are shown below:

```
str(rocData)

## List of 8
##  $ NL          : num [1:2, 1:5, 1:114, 1] 1 3 2 3 2 2 1 2 3 2 ...
##  $ LL          : num [1:2, 1:5, 1:45, 1] 5 5 5 5 5 5 5 5 5 5 ...
##  $ lesionNum   : int [1:45] 1 1 1 1 1 1 1 1 1 1 ...
##  $ lesionID    : num [1:45, 1] 1 1 1 1 1 1 1 1 1 1 ...
##  $ lesionWeight: num [1:45, 1] 1 1 1 1 1 1 1 1 1 1 ...
##  $ dataType    : chr "ROC"
##  $ modalityID  : chr [1:2] "0" "1"
##  $ readerID    : chr [1:5] "0" "1" "2" "3" ...
```

```
str(frocData)

## List of 8
##  $ NL          : num [1:2, 1:4, 1:200, 1:7] -Inf -Inf -Inf -Inf -Inf ...
##  $ LL          : num [1:2, 1:4, 1:100, 1:3] 5 4 4 3 5 5 4 2 4 5 ...
##  $ lesionNum   : int [1:100] 1 1 1 1 1 1 1 1 1 1 ...
##  $ lesionID    : num [1:100, 1:3] 1 1 1 1 1 1 1 1 1 1 ...
##  $ lesionWeight: num [1:100, 1:3] 1 1 1 1 1 1 1 1 1 1 ...
##  $ dataType    : chr "FROC"
##  $ modalityID  : chr [1:2] "4" "5"
##  $ readerID    : chr [1:4] "1" "3" "4" "5"
```

```
str(roiData)

## List of 8
##  $ NL          : num [1:2, 1:5, 1:90, 1:4] 0.957 0.907 0.57 0.824 1.473 ...
##  $ LL          : num [1:2, 1:5, 1:40, 1:4] 1.51 2.32 2.37 2.19 2.34 ...
##  $ lesionNum   : int [1:40] 2 3 2 2 3 3 1 2 3 3 ...
##  $ lesionID    : num [1:40, 1:4] 2 1 1 1 1 2 4 1 1 1 ...
##  $ lesionWeight: num [1:40, 1:4] 0.5 0.333 0.5 0.5 0.333 ...
##  $ dataType    : chr "ROI"
##  $ modalityID  : chr [1:2] "1" "2"
##  $ readerID    : chr [1:5] "1" "2" "3" "4" ...
```

The ROC dataset has two modalities, five readers, 69 (= 114 - 45) non-diseased and 45 diseased cases. The FROC data set has two modalities, 4 readers, 100 non-diseased and 100 diseased cases. Since ROC and ROI data are special cases of free-response data, the same data structure is used to accommodate all of them. The `dataType` field can be `ROC`, `FROC` or `ROI`. For a given modality and reader, for ROC data the FP ratings are addressed by the first K_1 values of the third dimension of the NL array and the corresponding TP ratings are addressed by the K_2 values of the third dimension of the LL array. The fourth dimension on the NL and LL arrays, only the first value of which is used to address ROC ratings, corresponds to the location index $l_s s$, i.e., the multiple marks of a given type, NL ($s = 1$) or LL ($s = 2$), that are possible for FROC data. In the above example, the dimensioning of the NL array shows that there is least one image in the dataset with 7 NL marks, while the dimensioning of the LL array shows that there is at least one diseased image with 3 lesions. The `lesionNum` field is an array of length K_2 whose elements contain the number of lesions in the diseased cases, i.e., $N_{k_2 2}$. The `lesionID` field is an integer label (not necessarily consecutive or even positive) used to distinguish between different lesions on the same case. This is necessary when weighted FOMs are used, as it is necessary to keep track of which lesion is getting which rating in order to assign it the correct weight. For example, `LL[1,1,1,2]` is the rating assigned to the 2^{nd} lesion for the first diseased case, first reader in the first modality and the corresponding label is `lesionID[1, 2]`. The `lesionWeight` field, corresponding to $W_{k_2 l_2}$, has the same dimensions as `lesionID`. The variables `ModalityID` and `readerID` are string arrays of length I, J, respectively, that are used to identify the modalities and readers, respectively. The ROI dataset has two modalities, 5 readers, 50 non-diseased and 40 diseased images, each with 4 ROIs. On the diseased images, the number of actually diseased ROIs varies from 1 to 4. The simulator is available from http://www.devchakraborty.com/RoiData/RoiSimulator.zip.

3.2. Creating dataset objects

The user can manually (or using code) create dataset objects by adhering to the structure described above (this could be useful in running simulation studies). For single datasets it is more convenient to enter the data into an Excel sheet (both `.xlsx` and `.xls` files are supported) following the JAFROC data file format detailed in the help page for the package `RJafroc-package` and summarized below. The `ReadDataFile()` function reads the data in JAFROC format (the default). If `format = "MRMC"`, it will read `.csv`, `.txt` or `.lrc` files (http://perception.radiology.uiowa.edu/). If `format = "iMRMC"` it will read `.imrmc` files (https://code.google.com/p/imrmc/). In each case it returns a dataset object. The MRMC and iMRMC formats apply to ROC data only while the JAFROC format applies to all paradigms. The JAFROC Excel file contains three worksheets:

1. A Truth worksheet, which contains a list of all cases in the dataset and the number of lesions, if any, on each case, and the weight of each lesion.

2. A TP or LL worksheet (use TP for ROC data and LL for all other paradigms), which contains the ratings of TPs or LLs.

3. A FP or NL worksheet (use FP for ROC data and NL for all other paradigms), which contains the ratings of FPs or NLs.

For FROC data, except for the Truth worksheet, where each case must occur at least once, the number of rows in the other worksheets is variable. For ROC data each case appears once in the Truth worksheet and it appears once in either the FP or TP worksheet. Sample data files are available on the JAFROC website. The following example downloads each of them and reads them.

```
rocXlsx <- "http://www.devchakraborty.com/RocData/rocData.xlsx"
rocLrc <- "http://www.devchakraborty.com/RocData/rocData.lrc"
```

```
rocCsv <- "http://www.devchakraborty.com/RocData/rocData.csv"
rocImrmc <- "http://www.devchakraborty.com/RocData/rocData.imrmc"
frocXlsx <- "http://www.devchakraborty.com/FrocData/frocData.xlsx"
roiXlsx <- "http://www.devchakraborty.com/RoiData/roiData.xlsx"

fullName <- rocXlsx
download.file(url = fullName, basename(fullName), mode = "wb")
RocDataXlsx<- ReadDataFile(fileName = basename(fullName))

fullName <- rocLrc
download.file(url = fullName, basename(fullName))
RocDataLrc<- ReadDataFile(fileName = basename(fullName), format = "MRMC")

fullName <- rocCsv
download.file(url = fullName, basename(fullName))
RocDataCsv<- ReadDataFile(fileName = basename(fullName), format = "MRMC")

fullName <- rocImrmc
download.file(url = fullName, basename(fullName))
RocDataImrmc<- ReadDataFile(fileName = basename(fullName), format = "iMRMC")

fullName <- frocXlsx
download.file(url = fullName, basename(fullName), mode = "wb")
FrocDataXlsx<- ReadDataFile(fileName = basename(fullName))

fullName <- roiXlsx
download.file(url = fullName, basename(fullName), mode = "wb")
RoiDataXlsx<- ReadDataFile(fileName = basename(fullName))
```

3.3. Analyzing an ROC dataset

One has two choices, DBMH significance testing, implemented by the function `DBMHAnalysis()`, or ORH significance testing, implemented by the function `ORHAnalysis()`. Both of these take a dataset object as the first argument, and have options for changing the significance level α of the test (the default is 0.05), and which factors (readers and/or cases) to regard as random (the default is `ALL`). The return value of the `DBMHAnalysis()` is a list of 22 elements. Both functions use the weighted JAFROC figure of merit as the default, so to analyze ROC and ROI paradigm data one must explicitly specify the figure of merit options as shown below. To apply DBMH significance testing to a ROC dataset object:

```
# ROC example
retDbmRoc  <- DBMHAnalysis(rocData, fom = "Wilcoxon")
print(retDbmRoc)
```

The returned data object, which can be viewed using the `print()` function of R, has the structure shown in Table 4. The output can be understood if one uses the following abbreviations, often used in combination: `Trt` = treatment, `Rdr` = reader, `RRRC` = random reader random case, `FRRC` = fixed reader random case, `RRFC` = random reader fixed case, `ci` = $1-\alpha$ confidence interval, `fomArray` = $\widehat{\theta}_{ij}$, `f` = value of observed F-statistic, `p` = p-value for rejecting the null hypothesis, `DiffTrt` = reader-averaged FOM differences between pairs of modalities, `ddf` = denominator degrees of freedom for F-test (the numerator degrees of freedom is always $I-1$), `AvgRdrEachTrt` = the FOM is averaged over all readers, separately for each treatment, `varComp` = the DBM pseudovalue variance components defined in connection with Eqn. 12. For the dataset shown, the reader-averaged difference between the two modalities is not significant for `RRRC` ($p = 0.0517$), but is significant if either reader ($p = 0.021$) or case ($p = 0.042$) is regarded as a fixed factor.

To perform ORH significance testing one uses the function `ORHAnalysis()`, which takes the same arguments as `DBMHAnalysis()`, and additional optional arguments allowing choice of the covariance estimation method: `CovEstMethod` = `Jackknife`, `Bootstrap` or `DeLong` (`Jackknife` is the default) and if the bootstrap method is selected one can optionally specify the number of bootstraps (default = 200). The function will generate an error if the DeLong method is selected with a figure of merit that is not the Wilcoxon statistic. The return value of the `ORHAnalysis()`is a list of 21 elements, Table 5, similar to that of `DBMHAnalysis()`, but instead of 6 pseudovalue derived variance components, it returns the elements of the covariance matrix ($Var, Cov1, Cov2, Cov3$) and the mean-squares and variance components for the reader and treatment-reader effects.

```
retORRoc  <- ORHAnalysis(rocData, fom = "Wilcoxon")
print(retORRoc)
CovOR <- retORRoc$varComp
cov1 <- CovOR$varCov[3]
cov2 <- CovOR$varCov[4]
cov3 <- CovOR$varCov[5]
varEps <- CovOR$varCov[6]
msTR <- retORRoc$msTR
msT <- retORRoc$msT
```

```
CovOR

##                    varCov
## Var(R)      0.0015349993
## Var(T*R)    0.0002004025
## COV1        0.0003466137
## COV2        0.0003440748
## COV3        0.0002390284
## Var(Error) 0.0008022883
```

Table 6 summarizes the results of DBMH and ORH analysis, for the latter the results of using different covariance estimation methods are shown, and compared to results yielded by OR-DBM MRMC (the University of Iowa Windows software). Since ORH yields similar results as DBMH (they are identical for the Wilcoxon figure of merit) henceforth we will only show results for DBMH.

Table 4: The structure of the object `retDbmRoc` returned by `DBMHAnalysis`. [`Trt` = treatment, `Rdr` = reader, `RRRC` = random reader random case, `FRRC` = fixed reader random case, `RRFC` = random reader fixed case, `ci` = $1 - \alpha$ confidence interval, `fomArray` = $\widehat{\theta}_{ij}$, `f` = observed F-statistic, `p` = p-value, `DiffTrt` = reader-averaged FOM differences between pairs of modalities, `ddf` = denominator degrees of freedom for F-test (the numerator degrees of freedom is always $I - 1$), `AvgRdrEachTrt` = FOM averaged over all readers, for each treatment, `varComp` = the DBM pseudovalue variance components.]

Variable Name	Description
`fomArray`	The figure of merit array of each reader and modality.
`anovaY`	The ANOVA table of the pseudovalues.
`anovaYi`	The ANOVA table of the pseudovalues for each modality.
`varComp`	The table of DBM variance components estimates.
`fRRRC`	The F statistic for testing the null hypothesis, for the RRRC condition.
`ddfRRRC`	The denominator degrees of freedom of the F statistic, for the RRRC condition.
`pRRRC`	The p-value of the significance test of the NH for the RRRC condition.
`ciDiffTrtRRRC`	The confidence intervals and related tests for the reader-averaged FOM differences between pairs of modalities, for the RRRC condition.
`ciAvgRdrEachTrtRRRC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the RRRC condition.
`fFRRC`	The F statistic for testing the null hypothesis, for the FRRC condition.
`ddfFRRC`	The denominator degrees of freedom of the FRRC F statistic.
`pFRRC`	The p-value of the significance test of the NH, for the FRRC condition.
`ciDiffTrtFRRC`	The confidence intervals and related tests for the reader-averaged FOM differences between pairs of modalities, for the FRRC condition.
`ciAvgRdrEachTrtFRRC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the FRRC condition.
`ssAnovaEachRdr`	The sum of squares table of the ANOVA of the pseudovalues for each reader (based on the data only for the specified reader).
`msAnovaEachRdr`	The mean squares table of the ANOVA of the pseudovalues for each reader (based on the data only for the specified reader).
`ciDiffTrtEachRdr`	The confidence intervals and related tests of the FOM differences between pairs of modalities for each reader.
`fRRFC`	The F statistic for testing the null hypothesis, for the RRFC condition.
`ddfRRFC`	The denominator degrees of freedom of the F statistic, for the RRFC condition.
`pRRFC`	The p-value of the significance test of the NH, for the RRFC condition.
`ciDiffTrtRRFC`	The confidence intervals and related tests for the FOM differences between pairs of modalities, for the RRFC condition.
`ciAvgRdrEachTrtRRFC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the RRFC condition.

Table 5: The structure of the object `retORHRoc`returned by `ORHAnalysis`.

Variable Name	Description
`fomArray`	The figure of merit array of each reader and modality.
`msT`	The treatment mean square.
`msTR`	The treatment-reader mean square.
`varComp`	The first two elements contain the reader and modality-reader variance components, the rest contain, in order, Cov1, Cov2, Cov3 and Var.
`fRRRC`	The F statistic for testing the null hypothesis, for the RRRC condition.
`ddfRRRC`	The denominator degrees of freedom of the F statistic, for the RRRC condition.
`pRRRC`	The p-value of the significance test of the NH for the RRRC condition.
`ciDiffTrtRRRC`	The confidence intervals and related tests for the reader-averaged FOM differences between pairs of modalities, for the RRRC condition.
`ciAvgRdrEachTrtRRRC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the RRRC condition.
`fFRRC`	The F statistic for testing the null hypothesis, for the FRRC condition.
`ddfFRRC`	The denominator degrees of freedom of the FRRC F statistic.
`pFRRC`	The p-value of the significance test of the NH, for the FRRC condition.
`ciDiffTrtFRRC`	The confidence intervals and related tests for the reader-averaged FOM differences between pairs of modalities, for the FRRC condition.
`ciAvgRdrEachTrtFRRC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the FRRC condition.
`varCovEachRdr`	Obuchowski-Rockette Variance and Cov1 estimates for each reader.
`ciDiffTrtEachRdr`	The confidence intervals and related tests of the FOM differences between pairs of modalities for each reader.
`fRRFC`	The F statistic for testing the null hypothesis, for the RRFC condition.
`ddfRRFC`	The denominator degrees of freedom of the F statistic, for the RRFC condition.
`pRRFC`	The p-value of the significance test of the NH, for the RRFC condition.
`ciDiffTrtRRFC`	The confidence intervals and related tests for the FOM differences between pairs of modalities, for the RRFC condition.
`ciAvgRdrEachTrtRRFC`	The confidence intervals and related tests for reader averaged FOM in each modality, for the RRFC condition.

Table 6: Results of DBMH and ORH analysis (with different methods for estimating the covariance matrix) for `rocData` compared to that yielded by OR-DBM MRMC (the University of Iowa Windows software). Only results for random readers and random cases are shown.

	Statistic	**RJafroc**	OR-DBM MRMC
	$\widehat{\theta}_{1\bullet}, \widehat{\theta}_{2\bullet}$	0.897, 0.941	0.897, 0.941
DBMH	$\widehat{\theta}_{1\bullet} - \widehat{\theta}_{2\bullet}$	-0.0438	-0.0438
	p-value	0.0517	0.0517
	F-statistic	4.46	4.46
	ddf	15.3	15.26
	Confidence interval	(-0.088, 0.000359)	(-0.088,0.00036)
ORH Jackknife	$\widehat{\theta}_{1\bullet} - \widehat{\theta}_{2\bullet}$	-0.0438	-0.0438
	p-value	0.0517	0.0517
	F-statistic	4.46	4.46
	ddf	15.3	15.26
	Confidence interval	(-0.088, 0.000359)	(-0.088,0.00036)
ORH Bootstrap boots = 200	$\widehat{\theta}_{1\bullet} - \widehat{\theta}_{2\bullet}$	-0.0438	-0.0438
	p-value	0.0501	0.0558
	F-statistic	4.56	4.21
	ddf	14.5	17.07
	Confidence interval	(-0.0876, 0.0000164)	(-0.0888, 0.00121)
ORH DeLong	$\widehat{\theta}_{1\bullet} - \widehat{\theta}_{2\bullet}$	-0.0438	-0.0438
	p-value	0.0512	0.0512
	F-statistic	4.48	4.48
	ddf	15.1	15.07
	Confidence interval	(-0.0879, 0.000267)	(-0.0879,0.00027)

3.4. Sample size estimation for ROC studies

For the ROC dataset analyzed above, since random reader random case analysis was unable to reject the null hypothesis, a sample size estimate may be of interest for the purpose of planning a future study. We equate the effect size to the magnitude of the observed effect size, 0.0438, which is our best information about the magnitude of the true effect size (if the modalities will be further optimized prior to the pivotal study, it may be reasonable to posit 0.05 as the true effect size). The following commands performs DBH analysis and extracts the relevant pseudovalue variance components and effect size for sample size estimation:

```
retDbm  <- DBMHAnalysis(rocData, fom = "Wilcoxon")
effectSize <- retDbm$ciDiffTrtRRRC$Estimate
varYTR <- retDbm$varComp$varComp[3]
varYTC <- retDbm$varComp$varComp[4]
varYEps <- retDbm$varComp$varComp[6]
```

The function `SampleSizeGivenJ()` can be used to determine the number of cases necessary to achieve a specified target power (default 0.8) for different specified values of J. Since the pilot study was conducted with 5 readers and barely reached significance, it is of interest to try different values 6:10 as in the code snippet below:

```
for (J in 6:10) {
  ret <- SampleSizeGivenJ(J, varYTR, varYTC, varYEps,
                          effectSize = effectSize)
  message("# of readers = ", J, ", estimated # of cases = ", ret$K, "\n",
      "predicted power = ", signif(ret$power, 4), "\n")
}

## # of readers = 6, estimated # of cases = 251
## predicted power = 0.8005
##
## # of readers = 7, estimated # of cases = 211
## predicted power = 0.8008
##
## # of readers = 8, estimated # of cases = 188
## predicted power = 0.8007
##
## # of readers = 9, estimated # of cases = 173
## predicted power = 0.8005
##
## # of readers = 10, estimated # of cases = 163
## predicted power = 0.8016
```

This type of information can be used to test the practicality of different study designs. The preceding analysis assumed `RRRC`; to get results assuming fixed readers, supply the option `randomOption = "CASES"`; to get results assuming fixed cases, supply the option `randomOption = "READERS"`.

Similar analysis can be conducted using the ORH method.

```
retOR  <- ORHAnalysis(rocData, fom = "Wilcoxon")
effectSize <- retDbm$ciDiffTrtRRRC$Estimate
CovOR <- retOR$varComp
cov1 <- CovOR$varCov[3]
cov2 <- CovOR$varCov[4]
cov3 <- CovOR$varCov[5]
varErrOR <- CovOR$varCov[6]
msTR <- retOR$msTR
KStar <- length(rocData$NL[1,1,,1])
for (J in 6:10) {
  ret <- SampleSizeGivenJ(J, cov1 = cov1, cov2 = cov2, cov3 = cov3,
                          varEps = varErrOR, msTR = msTR, KStar = KStar,
                          effectSize = effectSize)
  message("# of readers = ", J, ", estimated # of cases = ", ret$K, "\n",
      "predicted power = ", signif(ret$power, 4), "\n")
}

## # of readers = 6, estimated # of cases = 251
## predicted power = 0.8005
##
## # of readers = 7, estimated # of cases = 211
## predicted power = 0.8008
##
## # of readers = 8, estimated # of cases = 188
## predicted power = 0.8007
##
## # of readers = 9, estimated # of cases = 173
## predicted power = 0.8005
##
## # of readers = 10, estimated # of cases = 163
## predicted power = 0.8016
```

These are identical to those obtained with DBMH analysis. Hillis, Obuchowski, Schartz, and Berbaum (2005) have shown that when the Wilcoxon is used as the figure of merit, and jackknifing is used to estimate the covariance matrix, the two methods will yield identical results for multiple reader studies.

3.5. Analyzing an FROC dataset

Analysis of location specific data (free-response or ROI) is not fundamentally different from that of ROC paradigm data. As long as the figure of merit is a scalar, and well-behaved (rewards good decisions and penalizes bad decisions) significance testing methods developed for ROC apply to the selected figure of merit. We illustrate analysis of this dataset using the function `DBMHAnalysis()`, noting that `wJAFROC` is the default figure of merit. There are 100 non-diseased and 100 diseased images, with the number of lesions on the diseased images ranging from 1 to 3, in this free-response dataset. The two modalities are labeled 4 and 5 (the full dataset, containing data for 5 modalities, is available from author DPC).

```
## default JAFROC analysis, wJAFROC FOM is assumed
retDbmwJafroc  <- DBMHAnalysis(frocData)
print(retDbmwJafroc)
```

Other analyses options for free-response data are shown below.

```
## wJAFROC1 FOM (use only if there are no non-diseased cases)
retDbmwJafroc1  <- DBMHAnalysis(frocData, fom = "wJAFROC1")
print(retDbmwJafroc1)

retDbmJafroc  <- DBMHAnalysis(frocData, fom = "JAFROC")
print(retDbmJafroc)

## JAFROC1 FOM (use only if there are no non-diseased cases)
retDbmJafroc1  <- DBMHAnalysis(frocData, fom = "JAFROC1")
print(retDbmJafroc1)
```

Table 7 shows results of DBMH-analysis, using location specific figures of merit (`JAFROC`, `wJAFROC`, `JAFROC1` and `wJAFROC1`), applied to a free-response dataset and compared to results obtained using the Windows version V 4.2.1 of JAFROC software. Only results for random readers and random cases are shown. The reason for making `wJAFROC` the default figure of merit is that the software is primarily designed to analyze free-response data (none of the other mentioned websites have this capability) and by doing weighted analysis each diseased case gets the same importance in the analysis, regardless of the number of lesions in it. With un-weighted analysis, selected by setting the figure of merit option to `JAFROC` or `JAFROC1`, the results can be skewed by cases having a large number of lesions (we have encountered a nuclear medicine bone-scan dataset where the number of lesions per patient varied from a few to a hundred).

The `JAFROC1` figures of merit use all highest rated NL marks, even those on diseased cases. While `JAFROC1` may give higher statistical power, it mixes two types of discriminability, that between LLs and NLs on normal cases (clinically very important) and that between LLs and NLs on abnormal cases (clinically less important). For this reason we do not recommend `JAFROC1` or `wJAFROC1`, unless the dataset has no non-diseased cases, in which situation the mixing effect just referred to cannot occur. Another issue with the `JAFROC1` and `wJAFROC1` figures of merit is that they will depend on the case mix (i.e., the proportion of cases that are actually diseased). This means that two investigators sampling the same population but using different case mixes may get different results, even after sampling effects are accounted for. This issue also applies to the ROI paradigm, where one can use a dataset with no non-diseased cases. For these reasons we prefer `JAFROC` and particularly `wJAFROC` figures of merit for characterizing free-response performance.

Inferred ROC analysis can be performed on free-response data. Following are examples:

Table 7: Results of DBMH-analysis, using location specific figures of merit, applied to a free-response dataset and compared to results obtained using the Windows version of the software. Only results for random readers and random cases are shown.

FOM	Statistic	**RJafroc**	JAFROC V4.2.1
wJAFROC	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.768, 0.714	0.768, 0.714
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.0548	0.0548
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0328, 0.0769)	(0.0328, 0.0769)
	p-value	6.46E-06	<0.0001
	F-statistic	24.9	24.88
	ddf	54.96	54.96
JAFROC	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.758, 0.703	0.758, 0.703
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.0548	0.0548
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0315, 0.0780)	(0.0316, 0.0780)
	p-value	5.63E-06	<0.0001
	F-statistic	21.6	21.6
	ddf	236.4	236.4
wJAFROC1	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.783, 0.729	0.783, 0.729
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.054	0.054
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.036, 0.0715)	(0.036, 0.0715)
	p-value	1.91E-09	<0.0001
	F-statistic	36.5	36.51
	ddf	1491	1492
JAFROC1	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	(0.773, 0.720)	(0.773, 0.720)
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.0535	0.0535
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0291, 0.0779)	(0.0291, 0.078)
	p-value	5.55E-05	<0.0001
	F-statistic	19.3	19.4
	ddf	51.07	51.07

```
# following three examples are for ROC data inferred from FROC data using different methods
retDbmHrAuc  <- DBMHAnalysis(frocData, fom = "HrAuc")
# highest rating inferred ROC

retDbmSongA1  <- DBMHAnalysis(frocData, fom = "SongA1")
retDbmSongA2  <- DBMHAnalysis(frocData, fom = "SongA2")
```

Table 8 shows results of DBMH-analysis, using inferred ROC figures of merit (`HrAuc`, `SongA1` and `SongA2`), applied to a free-response dataset and compared to results obtained using the Windows version of the software. Only results for random readers and random cases are shown. The Song figures of merit, particularly A2, are computationally quite intensive (to put it in perspective, software run times in this field pale in comparison to the effort required to acquire the data, often 6 months or more).

Table 8: Results of DBMH-analysis, using inferred ROC figures of merit (`HrAuc`, `SongA1` and `SongA2`), applied to a free-response data

FOM	Statistic	**RJafroc**	JAFROC V4.2
`HrAuc`	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.851, 0.808	0.851, 0.808
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.04219	0.04219
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0098, 0.0746)	(0.0098, 0.0746)
	p-value	0.0240	0.0240
	F-statistic	14.96	14.96
	ddf	3.429	3.43
`SongA1`	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.853, 0.808	0.853, 0.808
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.04505	0.04505
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0186, 0.0715)	(0.0186, 0.0715)
	p-value	0.0095	0.0095
	F-statistic	23.1	23.1
	ddf	3.84	3.84
`SongA2`	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.847, 0.800	0.847, 0.800
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	0.0468	0.0468
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(0.0156, 0.0780)	(0.0156, 0.0780)
	p-value	0.0173	0.0173
	F-statistic	22.5	22.53
	ddf	3.03	3.03

Besides showing that the package gives identical results to JAFROC, the results illustrate some general principles. (1) While all methods reject the NH, the p-value is considerably smaller for weighted JAFROC (6.46e-06) as compared to the inferred ROC methods (range 0.0095 to 0.024). While one cannot infer statistical power from a comparison of p-values on a single dataset, the increased statistical power of JAFROC analysis has been confirmed with simulation studies (Chakraborty 2002; Chakraborty and Berbaum 2004; Chakraborty

2008) and is one reason this paradigm is gaining acceptance. (2) The JAFROC figure of merit for each modality is smaller than the corresponding inferred ROC figures of merit. This is because of the localization requirement, which implies that LLF is always less than the corresponding inferred TPF. In other words lesions are only counted towards LLF if they is correctly localized, while TPF is only concerned with the inferred single ratings per case. (3) The effect size is larger for JAFROC (0.0548) than for any of the inferred ROC methods (about 0.047 for Song A2). Since effect size appears as the square in sample size calculations, this contributes towards JAFROC's higher statistical power. The reason for the larger JAFROC effect size is that the figure of merit has a larger range over which it can vary, 0 to 1, while any ROC figure of merit is restricted to the range 0.5 to 1.

3.6. Analyzing an ROI dataset

The package comes pre-loaded with an ROI dataset, roiData. The NL[1:2, 1:5, 1:90, 1:4] array contains the ratings of all non-diseased ROIs while the LL[1:2, 1:5, 1:90, 1:4] array contains the ratings of all diseased ROIs. Since wJAFROC is the default figure of merit, one needs to explicitly specify the ROI figure of merit when using the function DBMHAnalysis().

```
# ROI example
retDbmRoi  <- DBMHAnalysis(roiData, fom = "ROI")
```

The results of RRRC analysis using **RJafroc** and C++ version of JAFROC are summarized in Table 9.

Table 9: DBMH applied to ROI data analysis. Only results for random readers and random cases are shown.

FOM	Statistic	**RJafroc**	JAFROC V4.2
ROI	$\widehat{\theta}_{4\bullet}, \widehat{\theta}_{5\bullet}$	0.884, 0.922	0.884, 0.922
	$\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}$	-0.038	-0.038
	$CI\left(\widehat{\theta}_{4\bullet} - \widehat{\theta}_{5\bullet}\right)$	(-0.064, -0.0116)	(-0.064, -0.0116)
	p-value	0.00823	0.00823
	F-statistic	9.687	9.69
	ddf	13.0	13.0

3.7. Generating an output report

The function OutputReport is used to generate a report closely patterned on that of OR-DBM MRMC and DBM-MRMC. The following commands illustrate the usage of this function.

```
OutputReport(dataset = rocData, method = "DBMH", fom = "Wilcoxon",
             dataDscrpt = "MyROCData",  showWarnings = FALSE)
OutputReport(dataset = rocData, method = "DBMH", fom = "Wilcoxon",
             reportFile = "MyROCDataAnalysis.txt",  showWarnings = FALSE)
```

```
OutputReport(dataset = rocData, method = "ORH", fom = "Wilcoxon",
             showWarnings = FALSE)
OutputReport(dataset = frocData, method = "DBMH", fom = "Wilcoxon",
             showWarnings = FALSE) # ERROR!
OutputReport(dataset = frocData, method = "ORH",
             showWarnings = FALSE) # default fom is wJAFROC
OutputReport(dataset = frocData, method = "DBMH", fom = "HrAuc",
             showWarnings = FALSE)
OutputReport(dataset = roiData, method = "ORH", fom = "ROI",
             showWarnings = FALSE)
```

The `dataDscrpt` option is only needed if a dataset object is specified. It is a string description of the dataset object, the default being the variable name of the dataset object. One can explicitly specify the output file name using the `reportFile` option, as in the second example. If this parameter is missing, the function will use the file name of the data file or the value of the `dataDscrpt` option followed by the underscore separated concatenation of the `method` and `fom` as the output file name. Since the Wilcoxon statistic only applies to ROC data, the fourth example generates an error.

Alternatively, one can read the data file directly and skip the dataset object creation step:

```
OutputReport("rocData.xlsx", format = "JAFROC", method = "DBMH",
             fom = "Wilcoxon", dataDscrpt = "MyROC2Data",
             showWarnings = FALSE)
```

3.8. Saving a data file in a specified format

The function `SaveDataFile` can be used to save an ROC dataset object in any compatible format, thereby allowing it to be analyzed with alternate software. The following examples illustrate its usage (the OR-DBM MRMC specified "*.csv" and "*.txt" files are identical except for the different file extensions).

3.9. ROC data visualization

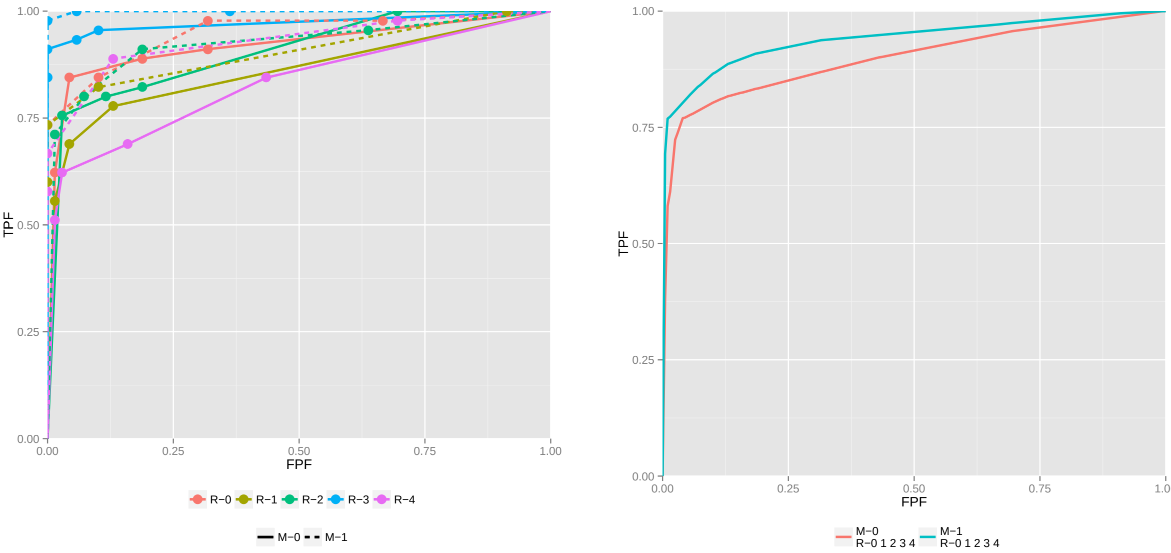
The package includes a function `EmpiricalOpCharac()` for plotting trapezoidal ROC curves. The following commands will create trapezoidal ROC curves for all combinations of modalities and readers in the `rocData` dataset:

```
plotM <- c(1:2)
plotR <- c(1:5)
plotROC <- EmpiricalOpCharac(data = rocData, trts = plotM,
                             rdrs = plotR, opChType = "ROC")
```

The `trts = plotM` argument tells the function to plot both modalities, and `rdrs = plotR` tells it to plot data for all five reader in each modality. The result of printing `plotROC`, a **ggplot2** object (Wickham 2009), is Fig. 1. Since ROC analysis is a subspecialty of statistics, and not all users may be familiar with it, we point out the obvious: an operating characteristic that approaches the top-left corner has greater area under the trapezoidal curve, which implies greater performance. The ROC curve for a guessing observer would be the diagonal line connecting $(0, 0)$ to $(1, 1)$.

Fig. 1(a) shows the large variability in performance between the readers, which is one reason one needs to adequately sample the reader population. The following construct can be used to plot operating characteristics for each modality, averaged over readers (Fig. 1(b)).

```r
plotMAvg <- list(1, 2)
plotRAvg <- list(c(1:5),c(1:5))
plotRocAvg <- EmpiricalOpCharac(dataset = rocData, trts = plotMAvg,
                                rdrs = plotRAvg, opChType = "ROC")
```



(a)

(b)

Figure 1: (a) shows empirical receiver operating characteristics for all 5 readers in both modalities. (b) shows reader-averaged receiver operating characteristics for the two modalities.

This tells the function to create two plots, one per modality, where each plot is averaged over all 5 readers.

3.10. Free-response data visualization

The function `EmpiricalOpCharac()` can be used to plot trapezoidal ROC/AFROC/FROC curves. The following commands will create trapezoidal ROC curves for all 8 combinations of 2 modalities and 4 readers in the `frocData` dataset, Fig. 2(a), and reader-averaged ROC, Fig. 2(b), reader-averaged AFROC, Fig. 2(c) and reader-averaged FROC curves, Fig. 2(d).

```
plotM <- c(1:2)
plotR <- c(1:4)
plotROC <- EmpiricalOpCharac(data = frocData, trts = plotM,
                             rdrs = plotR, opChType = "ROC")

plotMAvg <- list(1, 2)
plotRAvg <- list(c(1:4),c(1:4))
plotRocAvg <- EmpiricalOpCharac(data = frocData, trts = plotMAvg,
                                rdrs = plotRAvg, opChType = "ROC")

plotMAvg <- list(1, 2)
plotRAvg <- list(c(1:4),c(1:4))
plotAFROC <- EmpiricalOpCharac(data = frocData, trts = plotMAvg,
                               rdrs = plotRAvg, opChType = "AFROC")

plotMAvg <- list(1, 2)
plotRAvg <- list(c(1:4),c(1:4))
plotFROC <- EmpiricalOpCharac(data = frocData, trts = plotMAvg,
                              rdrs = plotRAvg, opChType = "FROC")
```

Panel (a) does show, for each reader, coded by color, that the dotted lines are above the corresponding solid lines. This is confirmed in the averaged ROC, AFROC and FROC curves (panels (b), (c) and (d)). Panel (c) shows the difference that was found to be significant by DBMH/ORH analysis using both `wJAFROC` and `HrAuc` figures of merit.

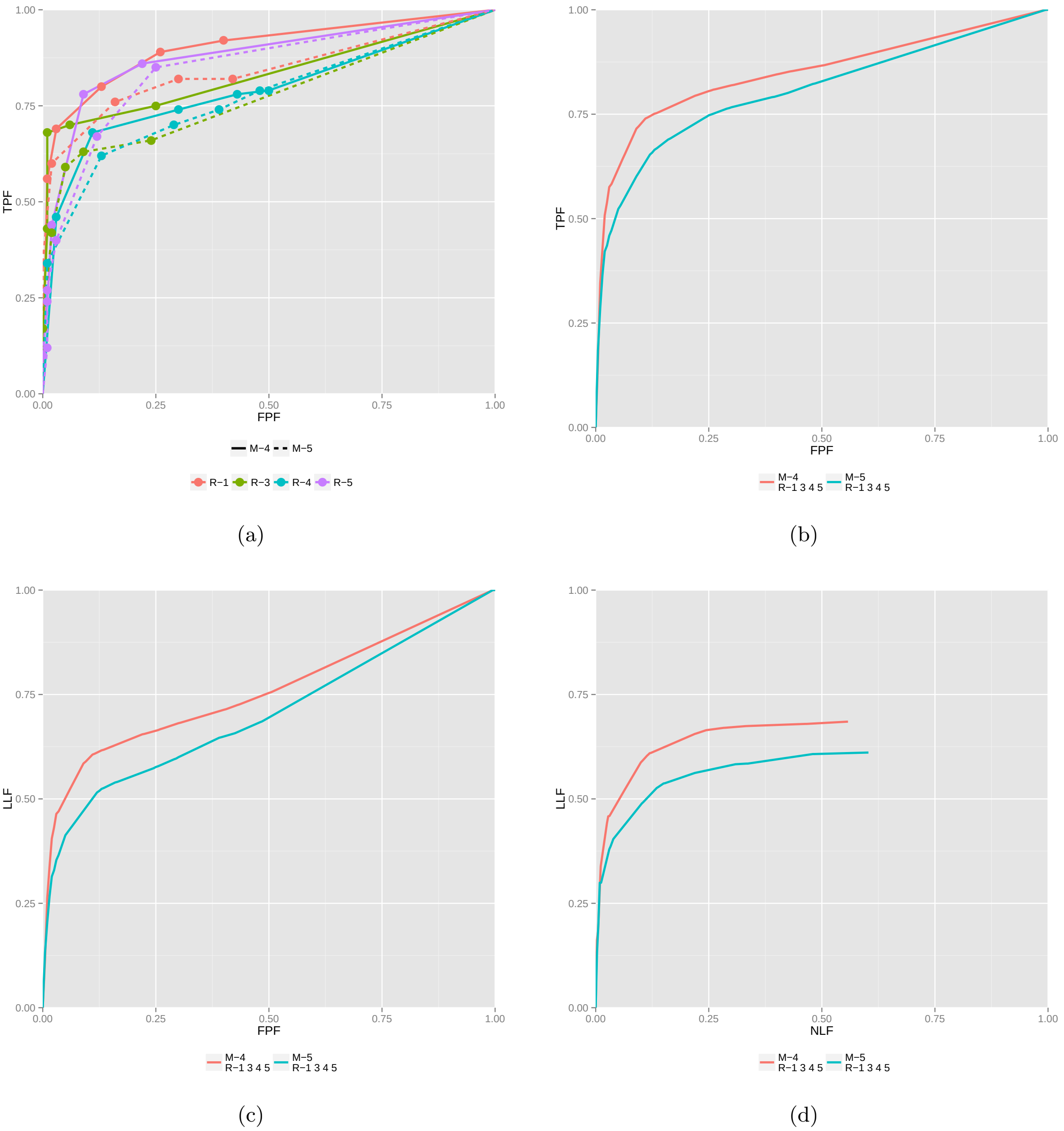
The numbering of the readers is not sequential; the reader IDs are actually string labels, and in this dataset for some reason the experimenter chose not to use the sequential labels 1 - 4. Comparing panels (b) and (c) one can appreciate that the AFROC curve is below the corresponding ROC curve, and that the difference is areas is larger for the AFROC than the ROC. Panel (d) shows the averaged FROC curves; although used by some investigators, this is a poor summary of performance. Even the partial area under the FROC to the left of some defined abscissa value is not a good figure of merit (Youden 1950; Hillis 2007), as it does not give credit for non-diseased images with no marks (these are actually high confidence correct decisions - i.e., perfect decisions).

3.11. Software comparison

Table 10 compares the features and capabilities of existing online software and **RJafroc**: data file format, whether they are open-source, and if so, the programming language expertise needed to understand them, whether they are cross platform applications, whether individual modules can be called from other languages, whether they include integrated visualization routines, and the degree to which they accommodate location paradigms.

4. Discussion

This paper has covered several topics that are relevant to assessment of medical imaging systems. These include the choice of data collection paradigm (ROC, FROC or LROC),



(a)

(b)

(c)

(d)

Figure 2: (a) shows the empirical highest rating inferred ROC curves for all combinations of modalities and readers. (b) shows the reader-averaged inferred ROC curves for both modalities. (c) shows the reader-averaged AFROC curves for both modalities. (d) shows the reader-averaged FROC curves for both modalities.

the choice of figure of merit, significance-testing methods (DBM and ORH), and sample-size estimation for ROC studies. Data visualization methods have been described that could benefit from better curve-fitting algorithms. In our experience statisticians tend to favor the empirical figures of merit, as these are least based on what would be considered restrictive assumptions. However, when the operating points do not span the ROC space adequately,

Table 10: Software capabilities comparison of available methods of analyzing observer performance data

Software	OR-DBM MRMC	iMRMC	JAFROC	**RJafroc**
Data entry	Plain text in specified format	Plain text in specified format	Excel file in JAFROC format	All text and Excel file formats
Open Source/Language	No/Fortran/C++	Yes/Java	No/C++	Yes/R
Cross platform	No	Yes	No	Yes
Call from other Languages	No	No	No	Yes
ROC curve fitting	Yes	No	No	No
Integrated data visualization capability	No	Yes	Yes	Yes
Localization paradigms (ROI and FROC)	No	No	Yes	Yes
Predicting search paradigm operating characteristics	No	No	Yes	Yes
Saving an ROC dataset in a different format	No	No	No	Yes

then empirical figures of merit become very dependent on the locations of the points, which can lead to misleading inferences.

A preliminary sample-size method for free-response studies is available on the JAFROC website. The problem is essentially one of determining the JAFROC effect size that would correspond to a particular inferred ROC effect size. Effect sizes are well understood in ROC methodology, since the paradigm is very familiar, dating to the early 1940s (it was originally introduced (Hilden 1991) to measure performance of radar in detecting enemy aircraft). The other figures of merit are less well understood. Until 2004 (Chakraborty and Berbaum 2004) there was no well-established way of analyzing FROC data, but attempts began in the late 70s (Bunch *et al.* 1978) and some progress was made in the late 80s and early 90s (Chakraborty *et al.* 1986; Chakraborty 1989; Chakraborty and Winter 1990). The only way to assign a realistic effect size to an FROC figure of merit is to have a model for fitting FROC data that also predicts ROC data. As we have seen, the JAFROC effect size tends to be larger than the corresponding ROC effect size, see Tables 7 and 8. To determine the connection one needs a way of estimating the parameters of a model of visual search that explains free-response and other operating characteristics. Such a model has been introduced (Chakraborty 2006b,a) and a preliminary maximum likelihood estimation method is implemented in the Windows version of the software. We are currently working on enhancements to the estimation procedure for improved reliability. The software currently does not implement any of the ROC curve-fitting methods that are implemented in the University of Iowa and University of Chicago website software. Another direction for improvement is accommodating the LROC paradigm, currently unsupported by any easily accessible software. Since R is an open source platform it is our hope that this software will lead others with interest in this field to contribute to it.

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A. Appendices

A.1. Other free-response figures of merit implemented in RJafroc

Free-response data can be used to infer maximum sensitivity and specificity, corresponding to the highest operating point on the ROC curve, excluding the trivial point at $(1, 1)$. These are defined by

$$\begin{aligned}
\widehat{\theta}_{ij}^{ISe} &= \tfrac{1}{K_2} \textstyle\sum\limits_{k_2=1}^{K_2} \phi\left(max\left(r_{ijk_2 2**}\right)\right) \\
\widehat{\theta}_{ij}^{ISp} &= 1 - \tfrac{1}{K_1} \textstyle\sum\limits_{k_1=1}^{K_1} \phi\left(max\left(r_{ijk_1 1*1}\right)\right)
\end{aligned}$$

The JAFROC FOM is defined as the probability that lesions are rated higher than the highest noise on *normal* images:

$$\widehat{\theta}_{ij}^{JAFROC} = \frac{1}{N_2 K_1} \sum_{k_2=1}^{K_2} \sum_{l_2=1}^{N_{k_2 2}} \sum_{k_1=1}^{K_1} \psi\left(max(r_{ijk_1 1*1}), r_{ijk_2 2l_2 2}\right) \tag{A.1}$$

The corresponding JAFROC1 FOM, which includes the highest noise on abnormal images, is defined by

$$\begin{aligned}
\widehat{\theta}_{ij}^{JAFROC1} = \frac{1}{N_2\left(K_1+K_2\right)} \sum_{k_2=1}^{K_2} \sum_{l_2=1}^{N_{k_2 2}} \Bigg[& \sum_{k_1=1}^{K_1} \psi\left(max(r_{ijk_1 1*1}), r_{ijk_2 2l_2 2}\right) \\
& + \sum_{k'_2=1}^{K_2} \psi\left(max(r_{ijk'_2 2*1}), r_{ijk_2 2l_2 2}\right) \Bigg]
\end{aligned} \tag{A.2}$$

The maximum LLF figure of merit is defined by

$$\widehat{\theta}_{ij}^{\max LLF} = \frac{\sum\limits_{k_2=1}^{K_2} \sum\limits_{l_2=1}^{N_{k_2 2}} \phi\left(r_{ijk_2 2l_2 2}\right)}{N_2} \tag{A.3}$$

Here $\phi\left(x\right) = 1$ is x is finite and $\phi\left(-\infty\right) = 0$. The maximum NLF figure of merit is defined by

$$\widehat{\theta}_{ij}^{\max NLF} = \frac{\sum\limits_{k_1=1}^{K_1} \sum\limits_{k_2=1}^{K_2} \sum\limits_{l_i=1}^{N_{k_t t1}} \phi\left(r_{ijk_t tl_1 1}\right)}{K_1 + K_2} \tag{A.4}$$

An exponentially transformed specificity figure of merit (Popescu 2011) is defined by:

$$\widehat{\theta}_{ij}^{IExpTrnsSp} = \exp\left(-\frac{\sum\limits_{k_1=1}^{K_1}\sum\limits_{l_i=1}^{N_{k_1 1 1}} \phi\left(r_{ijk_1 1 l_1 1}\right)}{K_1}\right) \tag{A.5}$$

These are summarized in Table A.1:

Table A.1

Paradigm	Description of FOM	Symbol	Comments
FROC	Highest rating inferred sensitivity	$\widehat{\theta}_{ij}^{ISe}$	Case-level inferred sensitivity
	Highest rating inferred specificity	$\widehat{\theta}_{ij}^{ISp}$	Case-level inferred specificity
	Exponentially transformed specificity	$\widehat{\theta}_{ij}^{IExpTrnsS}$	Popescu suggestion
	JAFROC	$\widehat{\theta}_{ij}^{JAFROC}$	Does not use weighting
	JAFROC1	$\widehat{\theta}_{ij}^{JAFROC1}$	Does not use weighting
	Maximum ordinate of FROC	$\widehat{\theta}_{ij}^{maxLLF}$	Lesion-level ”sensitivity”
	Maximum abscissa of FROC	$\widehat{\theta}_{ij}^{maxNLF}$	Lesion-level ”inverse specificity”, lower values preferred

A.2. Special cases of DBMH analysis

Fixed-reader random-case (FRRC) analysis

When readers are treated as a fixed effect, the appropriate F statistic for testing the null hypothesis is

$$F_{DBM|R} = \frac{MS_Y\left(T\right)}{MS_Y\left(TC\right)} \tag{A.6}$$

This is distributed as an F statistic with $ndf = I - 1$, and $ddf = (I-1)(K-1)$:

$$F_{DBM|R} \sim F_{I-1,(I-1)(K-1)} \tag{A.7}$$

The critical value of the statistic is $F_{1-\alpha;I-1,(I-1)(K-1)}$ which is that value such that fraction $(1-\alpha)$ of the distribution lies to the left of the critical value. The null hypothesis is rejected if the observed value of the F statistic exceeds the critical value:

$$F_{DBM|R} > F_{1-\alpha;I-1,(I-1)(K-1)} \tag{A.8}$$

The p-value of the test is the probability that a random sample from the distribution exceeds the observed value:

$$p = \mathrm{P}\left(F > F_{DBM|R} | F \sim F_{I-1,(I-1)(K-1)}\right) \tag{A.9}$$

The $(1-\alpha)$ confidence interval is given by:

$$CI_{1-\alpha} = \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet}\right) \pm t_{\alpha/2;(I-1)(K-1)} \sqrt{\frac{2}{JK} MS_Y\left(TC\right)} \tag{A.10}$$

Random-reader fixed case (RRFC) analysis

When cases are treated as a fixed effect, the appropriate F statistic for testing the null hypothesis is

$$F_{DBM|C} = \frac{MS_Y\left(T\right)}{MS_Y\left(TR\right)} \tag{A.11}$$

This is distributed as an F statistic with $ndf = I - 1$, and $ddf = (I-1)(J-1)$:

$$F_{DBM|C} \sim F_{I-1,(I-1)(J-1)} \tag{A.12}$$

The critical value of the statistic is $F_{1-\alpha;I-1,(I-1)(J-1)}$ which is that value such that fraction $(1-\alpha)$ of the distribution lies to the left of the critical value. The null hypothesis is rejected if the observed value of the F statistic exceeds the critical value:

$$F_{DBM|C} > F_{1-\alpha;I-1,(I-1)(J-1)} \tag{A.13}$$

The p-value of the test is the probability that a random sample from the distribution exceeds the observed value:

$$p = \mathrm{P}\left(F > F_{DBM|C} | F \sim F_{I-1,(I-1)(J-1)}\right) \tag{A.14}$$

The $(1-\alpha)$ confidence interval is given by:

$$CI_{1-\alpha} = \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet}\right) \pm t_{\alpha/2;(I-1)(J-1)} \sqrt{\frac{2}{JK} MS_Y\left(TR\right)} \tag{A.15}$$

A.3. Special cases of ORH analysis

Fixed-reader random-case (FRRC) analysis

When readers are treated as a fixed effect, the appropriate F statistic for testing the null hypothesis is

$$F_{OR|R} = \frac{MS\left(T\right)}{\left[\widehat{Var} - \widehat{Cov}_1 + (J-1)\,H\left(\widehat{Cov}_2 - \widehat{Cov}_3\right)\right]} \tag{A.16}$$

This is distributed as an F statistic with $ndf = I - 1$, and $ddf = \infty$, or equivalently a chi-square distribution with I-1 degrees of freedom:

$$F_{OR|R} \sim F_{I-1,\infty} = \chi^2_{I-1} \tag{A.17}$$

The critical value of the statistic is $F_{1-\alpha;I-1,\infty} = \chi^2_{1-\alpha;I-1,}$ which is that value such that fraction $(1-\alpha)$ of the distribution lies to the left of the critical value. The null hypothesis is rejected if the observed value of the F statistic exceeds the critical value:

$$F_{OR|R} > F_{1-\alpha;I-1,\infty} = \chi^2_{1-\alpha;I-1,} \tag{A.18}$$

The p-value of the test is the probability that a random sample from the distribution exceeds the observed value:

$$p = \mathrm{P}\left(F > F_{OR|R} | F \sim F_{I-1,\infty}\right) \tag{A.19}$$

The $(1-\alpha)$ confidence interval is given by:

$$CI_{1-\alpha} = \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet}\right) \pm t_{\alpha/2;\infty}\sqrt{\frac{2}{J}\left[\widehat{Var} - \widehat{Cov}_1 + (J-1)\,H\left(\widehat{Cov}_2 - \widehat{Cov}_3\right)\right]} \tag{A.20}$$

Random-reader fixed case (RRFC) analysis

When cases are treated as a fixed effect, the appropriate F statistic for testing the null hypothesis is:

$$F_{OR|C} = \frac{MS\,(T)}{MS\,(TR)} \tag{A.21}$$

This is distributed as:

$$F_{OR|C} \sim F_{I-1,(I-1)(J-1)} \tag{A.22}$$

The critical value of the statistic is $F_{1-\alpha;I-1,(I-1)(J-1)}$ which is that value such that fraction $(1-\alpha)$ of the distribution lies to the left of the critical value. The null hypothesis is rejected if the observed value of the F statistic exceeds the critical value:

$$F_{DBM|C} > F_{1-\alpha;I-1,(I-1)(J-1)} \tag{A.23}$$

The p-value of the test is the probability that a random sample from the distribution exceeds the observed value:

$$p = \mathrm{P}\left(F > F_{DBM|C} | F \sim F_{I-1,(I-1)(J-1)}\right) \tag{A.24}$$

The $(1-\alpha)$ confidence interval is given by:

$$CI_{1-\alpha} = \left(\widehat{\theta}_{i\bullet} - \widehat{\theta}_{i'\bullet}\right) \pm t_{\alpha/2;(I-1)(K-1)}\sqrt{\frac{2}{J} MS\,(TR)} \tag{A.25}$$

A.4. Details of ROI simulator

Since it is based on the Roe-Metz simulator for ROC data, we begin by describing the ROC data simulator for MRMC studies. For each modality, it consists of two unit variance distributions separated by an amount that determines AUC in that modality. The readers and cases are modeled by random samples and there is an error term that depends on treatments, readers and cases. The Roe and Metz model is (Roe and Metz 1997):

$$Z_{ijk_tt} = \mu_t + \tau_{it} + C_{k_tt} + R_{jt} + (\tau C)_{ik_tt} + (\tau R)_{ijt} + (RC)_{jk_tt} + \varepsilon_{ijk_tt} \tag{A.26}$$

The fixed effects in the simulator are described by

$$\begin{aligned} &\mu_1 = 0; \mu_2 = \mu \\ &\tau_{i,1} = 0; \tau_{1,2} = 0; \tau_{2,1} = \tau \end{aligned} \tag{A.27}$$

The random effects are described by

$$\begin{aligned} &C_{k_tt} \sim N\left(0, \sigma_C^2\right) \\ &R_{jt} \sim N\left(0, \sigma_R^2\right) \\ &(\tau C)_{ik_tt} \sim N\left(0, \sigma_{\tau C}^2\right) \\ &(\tau R)_{ijt} \sim N\left(0, \sigma_{\tau R}^2\right) \\ &(RC)_{jk_tt} \sim N\left(0, \sigma_{RC}^2\right) \\ &\varepsilon_{ijk_tt} \sim N\left(0, \sigma_\varepsilon^2\right) \end{aligned} \tag{A.28}$$

To preserve the unit variance character of the model, the following constraint is applied:

$$\sigma_C^2 + \sigma_{\tau C}^2 + \sigma_{RC}^2 + \sigma_\varepsilon^2 = 1 \tag{A.29}$$

Since ROI data is a special case of FROC data, we denote the ROI rating by $r_{ijk_ttl_ss}$ where on$l_1 = 1, 2, \ldots, Q$ non-diseased cases, where Q is the number of ROIs (or “quadrants”) on every case, and on diseased cases $l_2 = 1, 2, ..., q_{k_2}$, where q_{k_2} is the number of diseased ROIs on diseased case $k_2 2$, and $l_1 = 1, 2, \ldots, Q - q_{k_2}$ on diseased case $k_2 2$.

The ROI model is defined by:

$$\begin{aligned} Z_{ijk_tt} = \mu_t + \tau_{it} + C_{k_tt} + R_{jt} + (\tau C)_{ik_tt} + (\tau R)_{ijt} + (RC)_{jk_tt} \\ + (CL)_{k_ttl_ss} + (\tau CL)_{ik_ttl_ss} + (RCL)_{jk_ttl_ss} + \varepsilon_{ijk_ttl_ss} \end{aligned} \tag{A.30}$$

The idea is to split up each term containing the case factor into two terms, one containing the case factor, and the other an additional location factor L (for location) with levels defined by , such that the net case variance is unaltered. The following two terms do not contain the case factor and hence do not need to be split.

$$\begin{aligned} &R_{jt} \sim N\left(0, \sigma_R^2\right) \\ &(\tau R)_{ijt} \sim N\left(0, \sigma_{\tau R}^2\right) \end{aligned}$$

The following term containing only the case factor is split up as follows [the term () controls the correlation between the samples from the different locations on the same case]:

$$\begin{aligned} &C_{k_t t} \sim N\left(0, \rho_C \sigma_C^2\right) \\ &(CL)_{k_t t l_s s} \sim N\left(0, (1-\rho_C)\sigma_C^2\right) \end{aligned}$$

Likewise, the treatment-case factor is split up as follows:

$$\begin{aligned} &\tau C_{i k_t t} \sim N\left(0, \rho_{\tau C} \sigma_{\tau C}^2\right) \\ &(\tau CL)_{i k_t t l_s s} \sim N\left(0, (1-\rho_{\tau C})\sigma_{\tau C}^2\right) \end{aligned}$$

The reader-case factor is split up as follows:

$$\begin{aligned} &RC_{j k_t t} \sim N\left(0, \rho_{RC} \sigma_{RC}^2\right) \\ &(RCL)_{j k_t t l_s s} \sim N\left(0, (1-\rho_{RC})\sigma_{RC}^2\right) \end{aligned}$$

Finally, the error term is split up as follows:

$$\begin{aligned} &\varepsilon_{ijk_t t} \sim N\left(0, \rho_\varepsilon \sigma_\varepsilon^2\right) \\ &(\varepsilon L)_{ijk_t t l_s s} \sim N\left(0, (1-\rho_\varepsilon)\,\sigma_\varepsilon^2\right) \end{aligned}$$

For the simulated data the following values, selected from Table 1 in the Roe and Metz paper, were used:

$$\begin{aligned} &\sigma_R^2 = 0.2; \sigma_{\tau R}^2 = 0.005; \\ &\sigma_C^2 = 0.7; \sigma_{\tau C}^2 = 0.05; \sigma_{RC}^2 = 0.2; \sigma_\varepsilon^2 = 0.05; \end{aligned}$$

The correlation parameters were set as follows:

$$\rho_C = 0.1; \rho_{RC} = 0.1; \rho_{\tau C} = 0.9; \rho_\varepsilon = 0.9;$$

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