



iRoeMetz

User Manual 2016

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1. Introduction

iRoeMetz is a Java application that simulates **Multi-Reader Multi-Case** reader studies. The model for the scores comes from a 1992 paper by Roe and Metz [1] . The application also estimates the total variance of AUC and its variance components [2] and can calculate the true variances and components through numerical integration [3].

The simulated experiments (ROC scores) can be saved to validate analysis methods or to explore characteristics of summary statistics (as in sizing a study).

For an in-depth explanation of iMRMC/ROC reader studies, refer to section 1 of the iMRMC user guide titles "Introduction to ROC Reader Studies".

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2. Getting Started

iRoeMetz is available for Windows, Mac and Linux OS.

Download Java

The software is written in Java. It requires Java Runtime Environment(JRE) 1.8 and higher version.

User can check the JAVA version from <http://java.com/en/download/testjava.jsp>

User can download JRE from [ORACLE](https://www.oracle.com/in/java/technologies/javase-downloads.html) website.

Download iMRMC

Go to <https://github.com/DIDSR/iMRMC/releases> to download and save the latest version of iRoeMetz file.

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3. Run iRoeMetz

iRoeMetz software can be run under 2 models, GUI interface and command line. Both of them are available on Windows, Mac and Linux operation systems.

In **GUI interface**, users can manually input or load simulation parameters, and use buttons to manage software.

In **command line**, users can only load parameter from input file, and iRoeMetz will automatically do simulation and statical analysis.

Study parameters include **four** parts:

1. **Model Parameters:** Means of 2 modalities; variance components for readers, cases, modalities and interactions.
2. **Study Size:** Number of readers and cases in each trial.
3. **Study Design:** Defines whether the study is fully crossed or split-plot. User can also specify whether readers or cases are paired across.
4. **Random generator seed and number of Monte Carlo trials:** Sets number for study trials and Random Number Generator seed (RNG), with it user could redo the simulation.

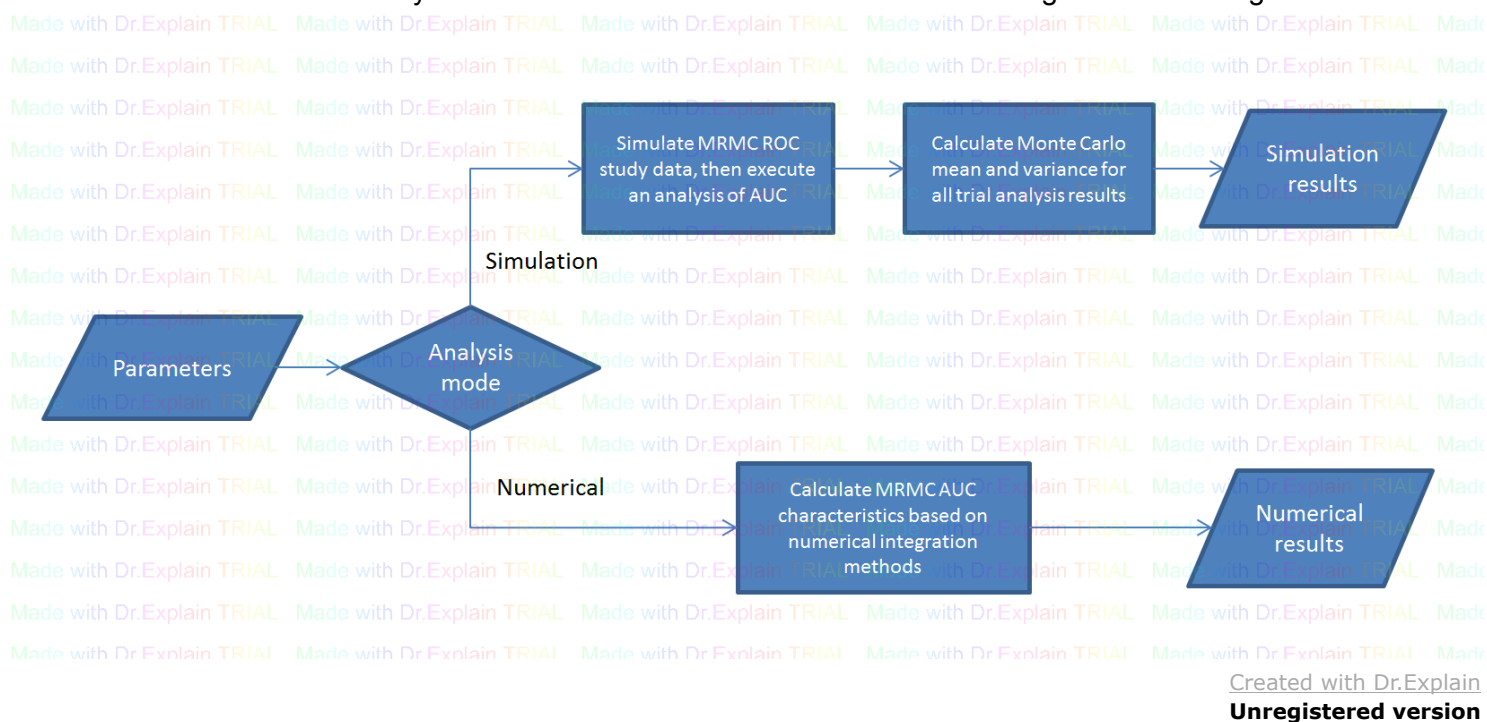
The software provides two kinds of statistical analyses **Simulation Experiments** and **Numerical Integration**.

Simulation Experiments:

For each trial the software simulates a multiple reader, multiple case ROC reader study based on study parameters, then executes an MRMC analysis of AUC from the data. Finally it estimates the Monte Carlo mean and variance for all trial analyses.

Numerical Integration:

Software directly calculates the MRMC AUC characteristics using numerical integration methods.



GUI interface

On **Linux**, run iRoeMetz GUI using the command: `java -jar iRoeMetz-v3p0.jar`

On **Windows and Mac**, User can use given above command or double click the icon to launch iRoeMetz GUI.

The figure is the main **iRoeMetz GUI interface**. Users can use input boxes, buttons and check boxes to operate the software.

1. User can manually input simulation parameters and settings such as reader variance, study size and design, random number generator seed and number of trials. User can also use "Populate Components from File"/"Save Components to File" to load or save these parameters and settings.

2. Click "Perform Simulation Experiments" or "Do Numerical Inegration" button to do simulation or numerical analysis.

Optional: User could click "Output Raw Data"(8) to choose a directory to save simulated MRMC studies ROC scores for each trial.



1 Study Parameter

Input Means:

μ_A : 1.0 μ_B : 1.0

Input Variances Independent to Modality:

v_{R0} : 0.166 v_{C0} : 0.166 v_{RC0} : 0.166 v_{R1} : 0.166 v_{C1} : 0.166 v_{RC1} : 0.166

Input Variances Specific to Modality A:

v_{AR0} : 0.166 v_{AC0} : 0.166 v_{ARC0} : 0.166 v_{AR1} : 0.166 v_{AC1} : 0.166 v_{ARC1} : 0.166

Input Variances Specific to Modality B:

v_{BR0} : 0.166 v_{BC0} : 0.166 v_{BRC0} : 0.166 v_{BR1} : 0.166 v_{BC1} : 0.166 v_{BRC1} : 0.166

1. **Input Means:** Means for modalities A and B.

2. **Input Variances independent to Modality:**

v_{R0} , v_{C0} and v_{RC0} are reader and case variances and covariance for nondiseased cases;

v_{R1} , v_{C1} and v_{RC1} are for diseased cases. These six variance components do not depend on modality.

3. **Input Variances Specific to Modality A/ Input Variance Specific to Modality B:**

Variances and covariances for Modalities A and B.

Note: The original Roe and Metz model specified non-diseased variance components to be the same as diseased components.

2 Study Size

Input Experiment Size:

N0: 20 N1: 20 Nr: 4

N0: Number of nondiseased cases**N1:** Number of diseased cases**Nr:** Number of readers**3 Study Design**

Study Design: # of Split-Plot Groups 1 Paired Readers? Yes No Pair Normal Cases? Yes No Pair Disease Cases? Yes No

1. Set the number of split-plot groups

2. Check whether the readers and normal/disease cases are paired

4 Clear Fields

Clear Fields

1. Clears the study parameter and study size setting.

2. Sets the number of split-plot groups to 1.

3. Marks the readers and cases to paired.

5 Load Fields

Populate Components from File

Navigate to and load study parameters, study size and study design from a properly formatted ".irm" input file.

Example input files are available at https://github.com/DIDSR/iMRMC/tree/gh-pages/000_iRoeMetz/inputFiles**6 Export Fields**

Save Components to File

Exports study parameters, study size and study design to file.

7 Number of trials and RNG seed

Simulation Experiments:

Seed for RNG 946910207 # of MC Trials 10 Use MLE?

Sets a random generator seed, number of simulation trials, and MLE flag

8 Export Simulated Study Results (Optional)

Output Raw Data

Select which directory the simulated MRMC studies ROC scores will be saved. If users don't want to export those files to their local disk, don't set the directory.

9 Does the Simulation Analysis

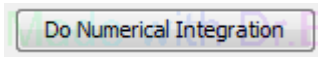
Perform Simulation Experiments

Does the simulation, displays results in a window: Monte Carlo mean and variance

10 Do Numerical Analysis

Download iRoeMetz at <https://github.com/DIDSR/iMRMC/releases>

GUI interface



Does the Numerical analysis and display the results in a window.

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Simulation Results: MC means window

The Monte Carlo mean and variance results are the average and variance of each trial analysis results. This window has very similar format as iMRMC analysis results window. Users can use the **"Export Analysis Result"** button to save results to their disk.

Simulation Results: MC means

H0: AUC_A - AUC_B = 0.00, two-sided alternative, 95% significance, 4 Readers, 20 Normal cases, 20 Disease cases.
 AUC_A = 0.778, AUC_B = 0.691, AUC_A - AUC_B = 0.088, S.E(total) = 1.007E-1

Large Sample Approx(Normal) p-Value = 0.2151 Conf. Int. = (-0.1096, 0.2849) Reject Null? = No(0.10)
 df(BDG) = 6.92 p-Value = 0.2655 Conf. Int. = (-0.1983, 0.3735) Reject Null? = No(0.10)

Hillis Approx

| | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 |
|----------------|------------|------------|------------|------------|------------|------------|------------|-------------|
| comp MA | 7.78250E-1 | 6.83296E-1 | 6.84329E-1 | 6.44024E-1 | 6.36417E-1 | 6.20397E-1 | 6.19393E-1 | 6.05284E-1 |
| coeff MA | 6.25000E-4 | 1.18750E-2 | 1.18750E-2 | 2.25625E-1 | 1.87500E-3 | 3.56250E-2 | 3.56250E-2 | -3.23125E-1 |
| comp MB | 6.90625E-1 | 5.66362E-1 | 5.76197E-1 | 5.17067E-1 | 5.32500E-1 | 5.05930E-1 | 5.08575E-1 | 4.84044E-1 |
| coeff MB | 6.25000E-4 | 1.18750E-2 | 1.18750E-2 | 2.25625E-1 | 1.87500E-3 | 3.56250E-2 | 3.56250E-2 | -3.23125E-1 |
| comp product | 5.96062E-1 | 5.73566E-1 | 5.77661E-1 | 5.55886E-1 | 5.57875E-1 | 5.48741E-1 | 5.50838E-1 | 5.41706E-1 |
| -coeff product | 1.25000E-3 | 2.37500E-2 | 2.37500E-2 | 4.51250E-1 | 3.75000E-3 | 7.12500E-2 | 7.12500E-2 | -6.46250E-1 |
| total | 1.72969E-4 | 1.21750E-3 | 1.24930E-3 | 1.11274E-2 | 9.96875E-5 | 1.02758E-3 | 9.36641E-4 | -1.91171E-3 |

total var = 1.392E-2

mcVarAUC_A = 1.2694E-2 sqrtMCvarAUC_A = 1.1267E-1,
 mcVarAUC_B = 2.0531E-2 sqrtMCvarAUC_B = 1.4328E-1,
 mcVarAUC_AminusB = 1.3508E-2 sqrtMCvarAUC_AminusB = 1.1623E-1,

Export Analysis Result

1 Monte Carlo Mean of MRMC Analyses

H0: AUC_A - AUC_B = 0.00, two-sided alternative, 95% significance, 4 Readers, 20 Normal cases, 20 Disease cases.
 AUC_A = 0.778, AUC_B = 0.691, AUC_A - AUC_B = 0.088, S.E(total) = 1.007E-1

Large Sample Approx(Normal) p-Value = 0.2151 Conf. Int. = (-0.1096, 0.2849) Reject Null? = No(0.10)
 df(BDG) = 6.92 p-Value = 0.2655 Conf. Int. = (-0.1983, 0.3735) Reject Null? = No(0.10)

Hillis Approx

Each MC trial yields MRMC analysis results. The display above shows the mean over all the trials.

2 Monte Carlo Mean of MRMC Variance Components

| | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 |
|----------------|------------|------------|------------|------------|------------|------------|------------|-------------|
| comp MA | 7.78250E-1 | 6.83296E-1 | 6.84329E-1 | 6.44024E-1 | 6.36417E-1 | 6.20397E-1 | 6.19393E-1 | 6.05284E-1 |
| coeff MA | 6.25000E-4 | 1.18750E-2 | 1.18750E-2 | 2.25625E-1 | 1.87500E-3 | 3.56250E-2 | 3.56250E-2 | -3.23125E-1 |
| comp MB | 6.90625E-1 | 5.66362E-1 | 5.76197E-1 | 5.17067E-1 | 5.32500E-1 | 5.05930E-1 | 5.08575E-1 | 4.84044E-1 |
| coeff MB | 6.25000E-4 | 1.18750E-2 | 1.18750E-2 | 2.25625E-1 | 1.87500E-3 | 3.56250E-2 | 3.56250E-2 | -3.23125E-1 |
| comp product | 5.96062E-1 | 5.73566E-1 | 5.77661E-1 | 5.55886E-1 | 5.57875E-1 | 5.48741E-1 | 5.50838E-1 | 5.41706E-1 |
| -coeff product | 1.25000E-3 | 2.37500E-2 | 2.37500E-2 | 4.51250E-1 | 3.75000E-3 | 7.12500E-2 | 7.12500E-2 | -6.46250E-1 |
| total | 1.72969E-4 | 1.21750E-3 | 1.24930E-3 | 1.11274E-2 | 9.96875E-5 | 1.02758E-3 | 9.36641E-4 | -1.91171E-3 |

Each MC trial yields MRMC variance components. The display above shows the mean over all the trials.

3 Monte Carlo Variances of MRMC Analyses

mcVarAUC_A = 1.2694E-2 sqrtMCvarAUC_A = 1.1267E-1,
 mcVarAUC_B = 2.0531E-2 sqrtMCvarAUC_B = 1.4328E-1,
 mcVarAUC_AminusB = 1.3508E-2 sqrtMCvarAUC_AminusB = 1.1623E-1,

Each MC trial yields MRMC analysis results. The display above shows the variance over all the trials.

4 Export Results to Disk

Export Analysis Result

User will be asked to create a folder on their computer. The software can export 3 files to the folder.

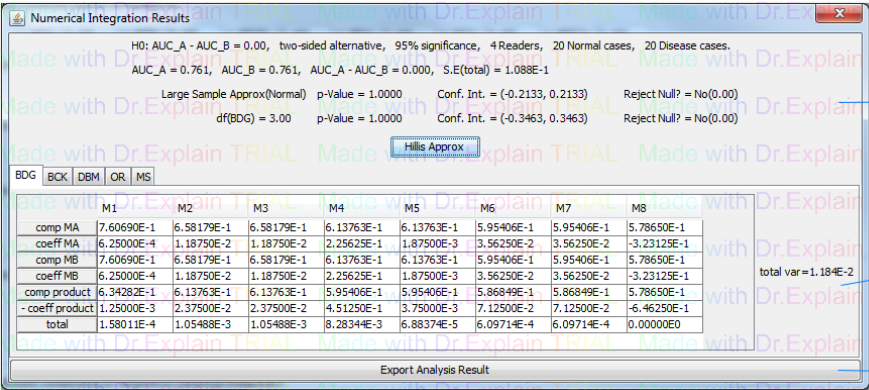
1. **"omrmc" version summary:** Monte Carlo mean and variable results. This version is readable by humans and users can input the file to the iMRMC software as a summary input file.

2. **"csv" version summary:** Monte Carlo mean and variable results. This version is easily read by computer and other software.
3. **"csv" version:** results from all trials.

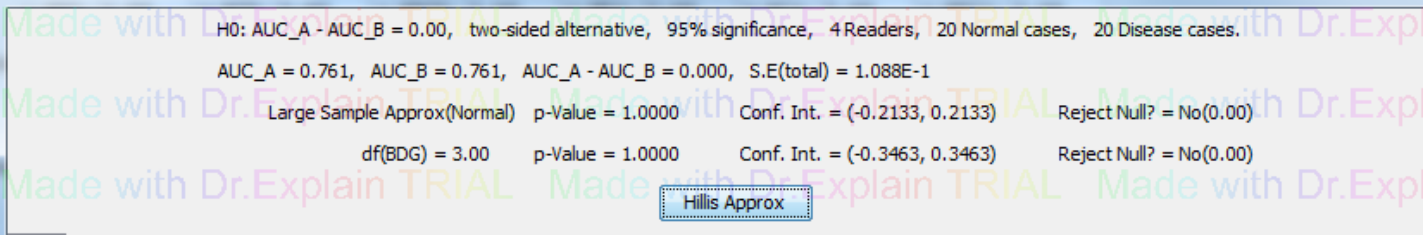
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Numerical Integration Results window

This window displays the numerical analysis results. It has a very similar format as the iMRMC analysis results window. Users can use "Export Analysis Result" button to save results to their disk.

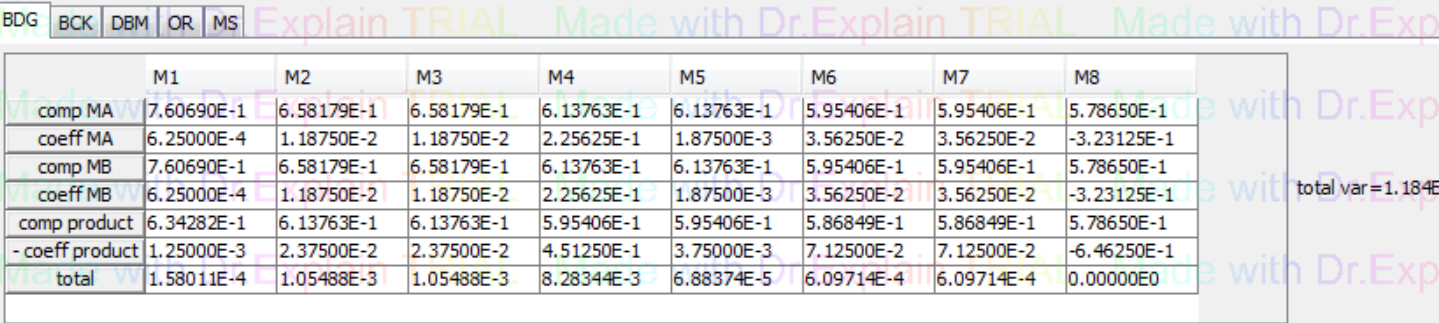


Numerical Calculaions of MRMC Analyses



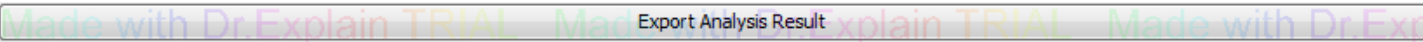
These MRMC analyses results are calculated by numerical intergration. [ref]

Numerical Calculations of MRMC Variance Components



These MRMC analyses variance components are calculated by numerical intergration. [ref]

Export Results to Disk



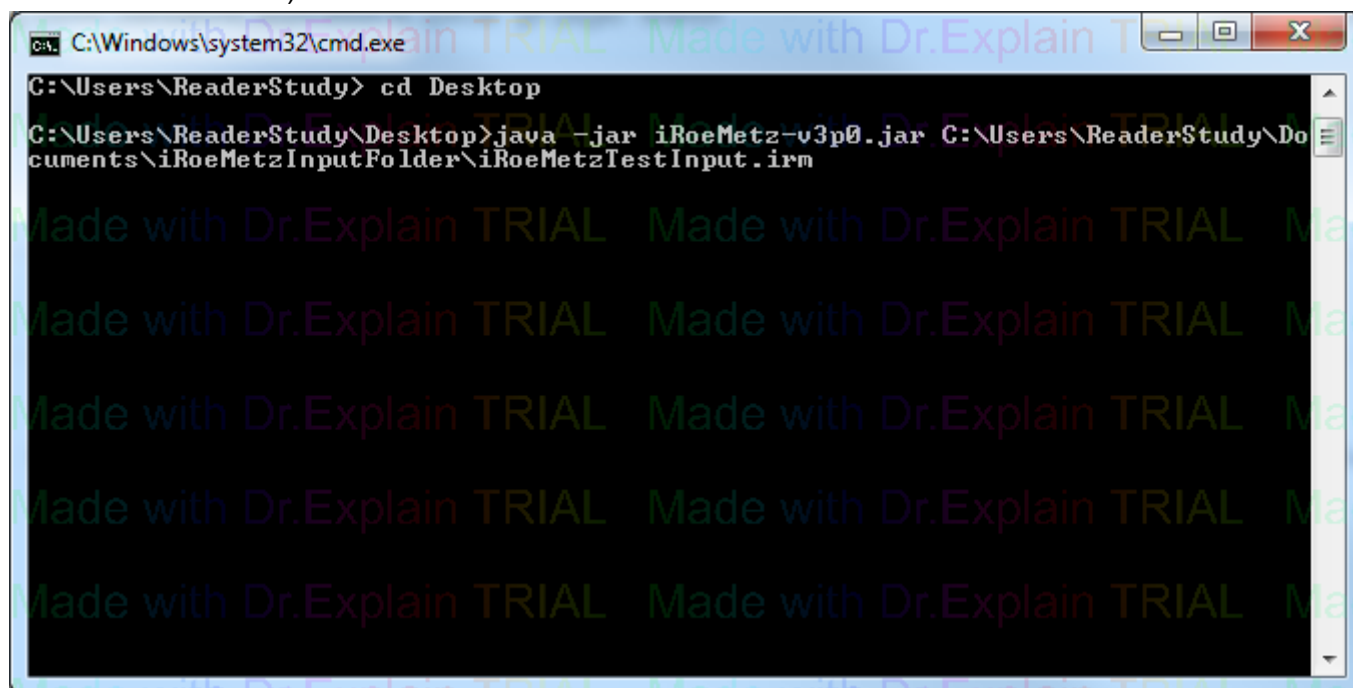
- Users will be asked to create a folder on their computer. The software can export 2 files to the folder
1. **"omrmc" version:** This version is easily read by humans and users can input it to iMRMC software input file.
 2. **"csv" version:** This version is easily read by computers and other software.

Command line

iRoeMetz can be launched and run by command line. The software loads all setting from a specified input file and does the simulation and numerical analysis automatically. With this feature, users can also call iRoeMetz from other softwares.

Users can launch and run iRoeMetz in command line by the following steps:

1. Open up the command window (cmd, terminal) or another compatible software to visit the iRowMetz software saving directory
 2. Type the command "java -jar iRoeMetz-v3p0.jar", along with the full input file name and path
- *In command line version, the input file name and path shouldn't have any space (bad input filename: iRoeMetz Test.irm)



```
C:\Windows\system32\cmd.exe
C:\Users\ReaderStudy> cd Desktop
C:\Users\ReaderStudy\Desktop> java -jar iRoeMetz-v3p0.jar C:\Users\ReaderStudy\Documents\iRoeMetzInputFolder\iRoeMetzTestInput.irm
```

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4. Input and Output Files

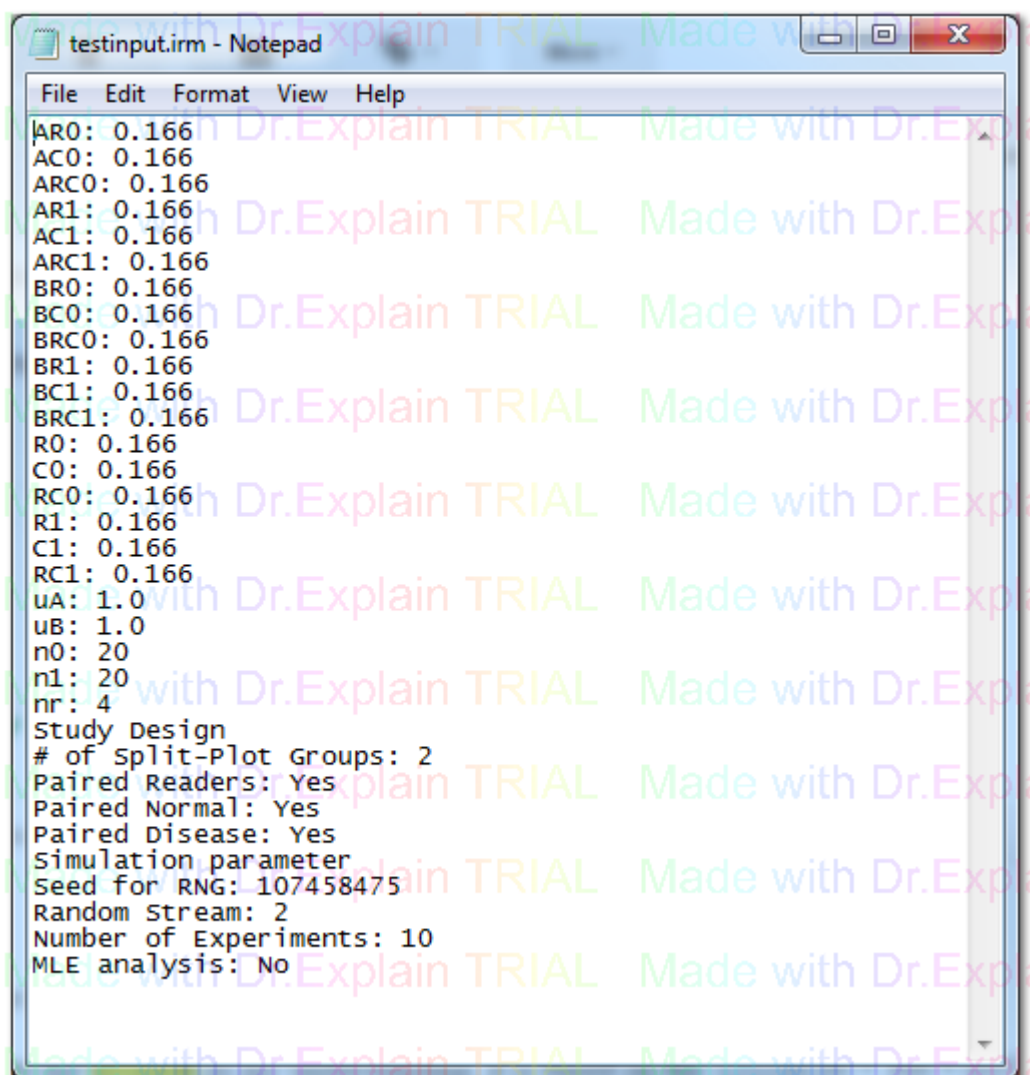
Users can create an ".irm" input file with all the settings with any text editing software, like notepad, and load it to iRoeMetz. iRoeMetz also provides an option to save settings, simulations, and analysis results to their local disk. The software can remember the user's last input and output file directories, and use them as default directories for next load and export processing.

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Input File

Users can manually input model parameters, study size and study design in GUI. They also can load these settings from input file. Input file should in .irm format.

Example: Each parameter should be on one line. Users should follow the format below exactly to generate their own input file.



```
testinput.irm - Notepad
File Edit Format View Help
AR0: 0.166
AC0: 0.166
ARC0: 0.166
AR1: 0.166
AC1: 0.166
ARC1: 0.166
BR0: 0.166
BC0: 0.166
BRC0: 0.166
BR1: 0.166
BC1: 0.166
BRC1: 0.166
R0: 0.166
C0: 0.166
RC0: 0.166
R1: 0.166
C1: 0.166
RC1: 0.166
uA: 1.0
uB: 1.0
n0: 20
n1: 20
nr: 4
Study Design
# of Split-Plot Groups: 2
Paired Readers: Yes
Paired Normal: Yes
Paired Disease: Yes
Simulation parameter
Seed for RNG: 107458475
Random Stream: 2
Number of Experiments: 10
MLE analysis: No
```

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Output File

iRoeMetz can export an ".irm" input file with all current settings, simulated MRMC studys(ROC scores) and analysis results for each trial, Monte Carlo mean and variance results, numerical analysis results.

All Current Settings

iRoeMetz can save all settings into one ".irm file" (model parameters, study size, and study design). The ".irm" input file can be loaded in iRoeMetz later to replicate simulation or numerical analyses.

Simulation Output Files

1. MRMC study (ROC scores) for all trials.

Users have option to save simulated MRMC study results for each trial. These study results are in ".imrmc" format and can be loaded into iMRMC software as raw data(link). *This is only available in GUI mode.*

2. MRMC analysis results from all trials

iRoeMetz can save all trials analysis result into one csv table.

3. Monte Carlo Mean and Variance Results

iRoeMetz can calculate Monte Carlo mean and variance for each trial analysis results (AUCs, Standard Error, Confidence Interval, and Hypothesis test results) and export to disk.

2 Output Modes:

omrmc format: Readable by humans and can be loaded as a summary data(link) on the iMRMC software. *This is only available in GUI mode.*

csv format: Easier to be loaded by other software.

Numerical Output Files

iRoeMetz could use setting variance and study settings calculate MRMC characteristics of AUC(AUCs, Standard Error, Confidence Interval, and Hypothesis test results).

2 Output Modes:

omrmc format: Readable by humans and can be loaded as a summary data on the iMRMC software. *This is only available in GUI mode.*

csv format: Easier to be loaded by other software.

5. Method

This section introduce different study designs and Roe & Metz Model for iRoeMetz software. Paper [Gallas2014_J-Med-Img_v1p031006](#) provides the theoretical foundation and validation for iRoeMetz software.

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Study Design

iRoeMetz provides options to do fully-crossed or split-plot study and paired or unpaired data study.

Fully-crossed study

"Fully crossed" refers to the data collection: all the readers rate all the cases in both modalities with respect to confidence of disease.

Split-plot study

In split-plot study, we separate reader, non-disease cases and disease cases into several groups. Each group of readers only read specific groups of non-disease and disease case.

Paired data study

In paired data study, readers and cases are same across two modalities.

Unpaired data study

In unpaired study, readers or cases are different across two modalities.

Example Study

Figure 1 is an example of paired split-plot group study design. We design a split plot study with 4 groups of readers, non-disease cases and disease cases. Each group of readers only read a quarter of whole non-disease and disease cases. And readers and cases in both modalities are same.

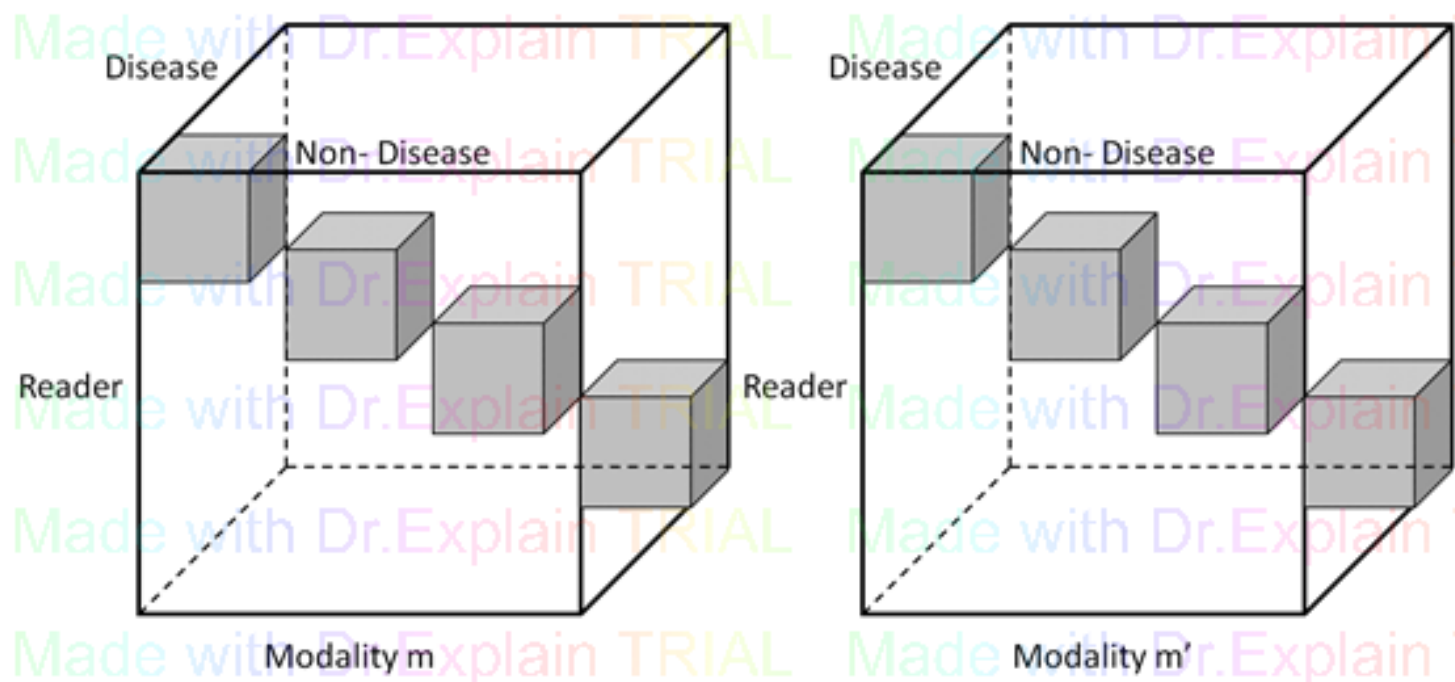


Figure 1. Paired split plot study with 4 groups of readers, non-disease cases and disease cases

Figure 2 is an unpaired reader paired case study design with 4 split plot groups. Two modalities have different readers, but same diseased and non-diseased case.

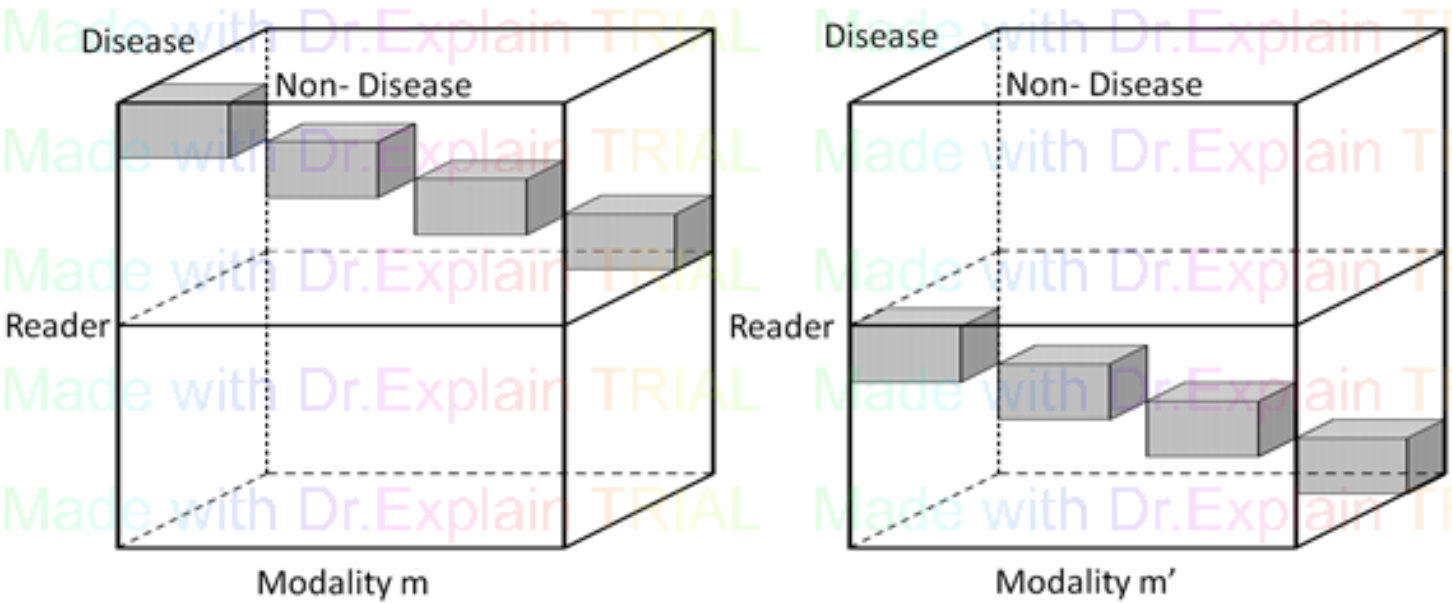


Figure 2. Unpaired readers, paired cases study with 4 split plot groups

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Roe & Metz Model

Generalized Roe & Metz Model

iRoeMetz is an implementation of the updated Roe & Metz simulation model for creating reader ratings for diseased and non-diseased cases in two modalities[4]. This generalized model accounts for 18 variances as opposed to the six variances in the original model. The original six variances were of readers, cases, the interaction between readers and cases, and the interaction of modality with the three aforementioned variances. The generalized model takes these existing six and then accounts for the interaction of them against truth and differing modalities.

Simulation

We simulate the reading score with the following equations

$$\begin{aligned}t_{0A} &= 0 + \sigma_{R0}^2 + \sigma_{C0}^2 + \sigma_{RC0}^2 + \sigma_{AR0}^2 + \sigma_{AC0}^2 + \sigma_{ARC0}^2 \\t_{0B} &= 0 + \sigma_{R0}^2 + \sigma_{C0}^2 + \sigma_{RC0}^2 + \sigma_{BR0}^2 + \sigma_{BC0}^2 + \sigma_{BRC0}^2 \\t_{1A} &= \mu_A + \sigma_{R1}^2 + \sigma_{C1}^2 + \sigma_{RC1}^2 + \sigma_{AR1}^2 + \sigma_{AC1}^2 + \sigma_{ARC1}^2 \\t_{1B} &= \mu_B + \sigma_{R1}^2 + \sigma_{C1}^2 + \sigma_{RC1}^2 + \sigma_{BR1}^2 + \sigma_{BC1}^2 + \sigma_{BRC1}^2\end{aligned}$$

The first two are nondiseased case scores for modality A and B. The other two are diseased case scores. Experiments are simulated by taking normally distributed random variables of the corresponding variance. The t-matrices produced by these equations can be used to estimate the components of variance and their respective decompositions, and to create simulated MRMC reading scores.

The random variables are created by using a pseudo-random number generator known as the Mersenne Twister. This method of random number generation is particularly suited to Monte Carlo trials, and is faster and more efficient than Java's standard library pseudo-random number generator.

iRoeMetz has the ability to perform numerous simulations at once based on the same input variances. The effect is that the average estimated components of variance over a large number of simulations approaches the calculated components of variance. iRoeMetz scales to multi-core CPUs, providing a speed benefit when performing numerous simulations.

Calculation

Given the variances, means and experiment size, the components of variance can be calculated via numerical integration.

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Reference

- [1] Roe, Cheryl A., and Charles E. Metz. "Dorfman-Berbaum-Metz method for statistical analysis of multireader, multimodality receiver operating characteristic data: validation with computer simulation." *Academic radiology* 4.4 (1997): 298-303.
- [2] Gallas, Brandon D., et al. "A framework for random-effects ROC analysis: biases with the bootstrap and other variance estimators." *Communications in Statistics—Theory and Methods* 38.15 (2009): 2586-2603.
- [3] Gallas, Brandon D., and Stephen L. Hillis. "Generalized Roe and Metz receiver operating characteristic model: analytic link between simulated decision scores and empirical AUC variances and covariances." *Journal of Medical Imaging* 1.3 (2014): 031006-031006.
- [4] Metz, C. E., "Basic principles of ROC analysis." *Semin Nucl Med* 1978 Oct;8(4):283-98.

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