Models in Medicine IV

ROC Analysis: Methods and Practical Applications

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1

The six levels of diagnostic efficacy:

(Fryback & Thornbury, *Med Decis Making*, 1991)

1) Technical quality: MTF, NPS, H&D curve, etc.

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4

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5

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6

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7

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8

Why is receiver operating characteristic (ROC) analysis necessary?

… because of the limitations of other available methods for evaluating diagnostic accuracy

9

An inadequate index:

Detection rate ("sensitivity")

- When used alone, does not reveal how test performs on actually-negative cases

10

A traditional but inadequate index:

Percent correct ("Dx accuracy")

- depends strongly on disease prevalence
- does not reveal relative frequencies of FN and FP errors

11

A pair of indices:

"Sensitivity" and "Specificity"

- Sensitivity: Probability of calling an actually-positive case "Positive"
- Specificity: Probability of calling an actually-negative case "Negative"

12

"Sensitivity" and "Specificity":

- independent of disease prevalence (if Dx test is used in a constant way)
- implicitly reveal relative frequencies of FP and FN errors

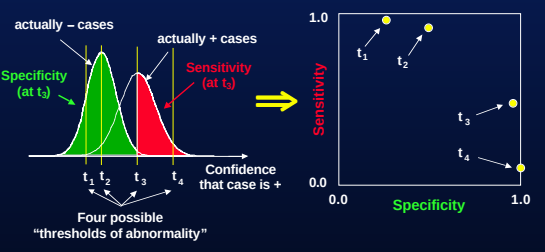
13

Problems in comparing Dx tests in terms of Sensitivity and Specificity:

- Sensitivity and Specificity of each test depend on the particular "threshold of abnormality" adopted for that test
- Often, one test is found to have higher Sensitivity but lower Specificity than the other

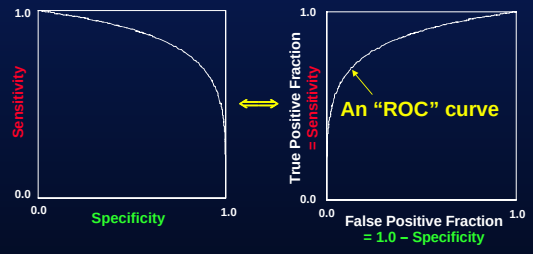
14

Dependence of Sensitivity and Specificity on "threshold of abnormality":



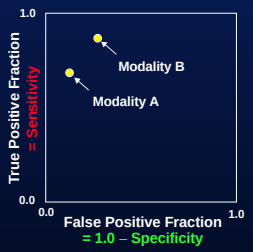
15

A curve is swept out as the "threshold of abnormality" (t) is varied continuously:



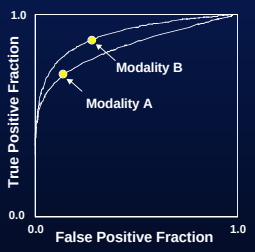
16

A dilemma: Which modality is better?



17

The dilemma is resolved after ROC curves are determined (one possible scenario):



Conclusion:

Modality B is better, because it can achieve:

- **higher TPF at same FPF, or**
- **lower FPF at same TPF**

18

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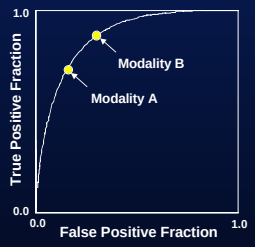
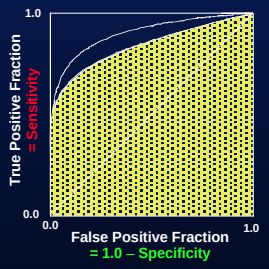


Conclusion:

Modalities are equivalent, because same combinations of TPF and FPF are available

19

The ROC "Area Index" (A_z):



A_z =

guessing ➡ $A_z = 0.5$

perfect ➡ $A_z = 1.0$

20

Interpretations of ROC area (A_z):

- Sensitivity (TPF) averaged over all Specificities (or FPFs) — i.e., average ROC curve height
- Specificity averaged over all Sensitivities
- Probability of distinguishing correctly between a randomly selected actually-positive case and a randomly selected actually-negative case

However ...

- this global index can be misleading when curves cross and/or there is only one region of interest[1]

Other ROC-based indices of performance

- Partial area below, or to the right of, a segment of the ROC curve (regional)
- TPF at fixed FPF or vice-versa (local)
- Expected utility at optimal operating point (local) — most meaningful but least practical

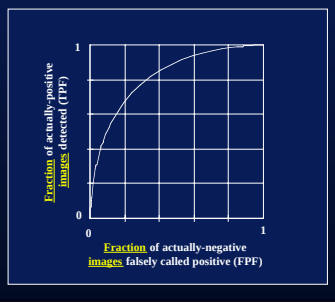
22

Generalized ROC analysis :

- Localization ROC (LROC) analysis
- Free-response ROC (FROC) analysis
- Alternative FROC (AFROC) analysis

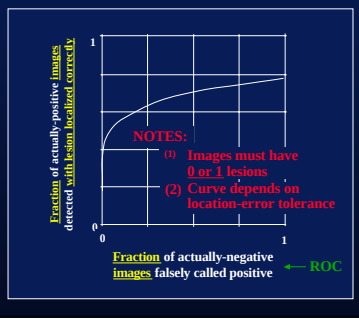
23

Conventional ROC curves:



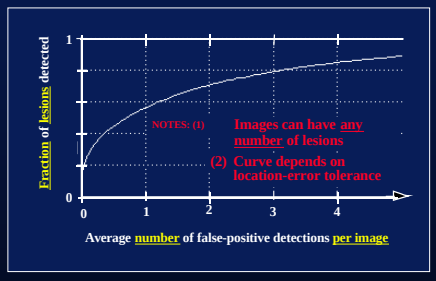
24

LROC (Localization ROC) curves:



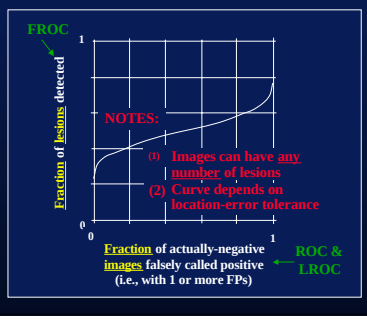
25

FROC (Free-response ROC) curves:



26

AFROC (Alternative FROC) curves



27

Historical background of ROC analysis

- Developed c. 1950 by mathematical psychologists at U of Michigan (Tanner, Birdsall, Swets, Green) to quantify detectability of airplanes by radar
- Quickly applied in experimental sensory psychology, psychophysics and some other fields (e.g., information retrieval)
- Usefulness in medicine — and particularly medical imaging — first pointed out by Lusted c. 1960

28

Historical background (2)

- Methodological developments in ROC analysis during the 1950s and '60s:
  - theory of the binormal model (Birdsall, Swets, Green)
  - advantages of discrete ordinal confidence-ratings over "yes/no" data (Swets)
  - maximum-likelihood curve fitting (Dorfman; Grey & Morgan)

29

Historical background (3)

- ROC analysis first applied rigorously to medical imaging at U of Chicago in early 1970s (Goodenough, Metz, Lusted)
  - interpretation and theoretical justification
  - laboratory experiments (low-contrast disks and spheres on uniform backgrounds in radiography)

30

Historical background (4)

- Methodological extensions of ROC analysis at U of Chicago during 1970s (Goodenough, Metz, Starr):
  - relationship with Shannon information theory
  - effect of search-region size on ROC curve
  - first generalization to a detection-and-localization task: LROC analysis (restricted to 0 or 1 signal)
  - first generalization to multiple signals: "signal counting" (not the way to go!)

31

Historical background (5)

- Other developments in ROC analysis during 1970s:
  - "spreading the gospel" regarding medical applications (McNeil *et al*.; Metz; Swets; others)
  - Wilcoxon statistics of "connect-the-dots" estimates of empirical ROC area (Bamber)
  - FROC analysis: detection-and-localization with *any* number of signals (Bunch *et al*.)

32

Historical background (6)

- Methodological developments in ROC analysis during 1980s:
  - elucidation of sources of bias (Begg *et al*.)
  - first statistical tests for significance of differences between ROC estimates (Hanley & McNeil, Metz & Kronman)
  - first multivariate statistical analysis (Swets & Pickett)
  - Wilcoxon statistics for correlated data (DeLong *et al*.)
  - first advocacy of continuous rating scales (Rockette *et al*.)

33

Historical background (7)

- More methodological developments in ROC analysis during 1980s:
  - partial-area index (McClish)
  - AFROC analysis and curve fitting therein (Chakraborty)
  - ordinal regression (Tosteson & Begg)
  - free software for curve fitting (Dorfman; Metz & Kronman) and statistical testing (Metz & Kronman)
  - introduction of "jackknifing" to estimate and account for correlation in statistical testing (Hanley)

34

Historical background (8)

- Methodological developments during the 1990s:
  - ROC analysis without "truth" (Henkelman *et al*.)
  - first *practical* multivariate statistical analysis of ROC data (Dorfman, Berbaum & Metz)
  - ROC analysis of gains in accuracy from repeated readings (Metz & Shen; Swensson)
  - confidence intervals for ROC analysis (Ma & Hall; Metz)
  - extension of the partial-area index (Jiang *et al*.)

35

Historical background (9)

- More methodological developments in the '90s:
  - extensions of ordinal regression (Toledano & Gatsonis)
  - elucidation of the meaning of the many correlations and components of variance that arise in *multivariate* ROC analysis (Roe & Metz)
  - maximum-likelihood (ML) fitting of LROC curves (Swensson)
  - use of location information to increase precision in estimating conventional ROC curves (Swensson)

36

Historical background (10)

- Still more methodological developments during the 1990s:
  - statistical analysis of "partially-paired" datasets (Zhou & Gatsonis; Metz, Herman & Roe)
  - "proper" ROC curve-fitting models and algorithms (Dorfman *et al*.; Metz & Pan)
  - ML methods for fitting ROC curves to continuously-distributed data (Metz, Shen & Herman; Zou & Hall)
  - additional free software for curve fitting (Dorfman and Berbaum; Metz, Shen & Herman) and statistical testing (Metz, Shen & Herman)

37

Historical background (11)

- Methodological developments during the '00s:
  - further development of AFROC methodology (Chakraborty)
  - elucidation of biases and variance components in training and testing performance of automated classifiers — e.g., ANNs (Wagner, Chan *et al*.)
  - use of bootstrapping to estimate components of variance and test *multivariate* differences between ROC estimates (Beiden, Wagner, Campbell *et al*.)

38

The "technology" of ROC analysis:

- Sampling images and readers
- Designing the experiment and collecting observer-response data
- Fitting ROC curves to the data
- Testing the statistical significance of apparent differences between ROC curve estimates

39

Selecting meaningful samples of cases and readers

- "Absolute measurement" *vs*. "Ranking" study
  - Absolute measurement: Samples must represent defined clinical populations
  - Ranking: Cases and/or readers can be selected to represent "stressful" subpopulations (e.g., subtle cases and/or expert readers)
    - *—> Generalization of conclusions requires assumptions*
- Criteria for inclusion must be explicit
  - Absolute measurement: Define populations sampled
  - Ranking: Report characteristics of cases and readers employed

40

Designing a study to avoid bias ...

- ... due to absence of subtle disease:
  - Before study is begun, decide criteria for "actually-positive" cases to be included
- ... due to absence of confounding cases:
  - Include clinically-encountered "actually-negative" cases with features that may degrade classifier performance (e.g., cysts in detection of breast cancer)
- ... due to absence of "truth" (verification bias):
  - Establish "truth" for — and include — difficult cases

41

Avoiding bias in assessments of automated classifiers ...

- ... due to training and testing on same cases:
  - Train and test classifier on different cases subsampled independently from same sample (e.g., "leave-one-out" method)
    - *—>Difficult or impossible with rule-based classifiers*
- ... due to misinterpretation of meaning and precision of evaluation study's result:
  - Changing number of training cases changes both true classification accuracy and precision with which true classification accuracy (for a given number of training cases employed) can be estimated
  - Changing number of test cases changes only precision

42

Avoiding bias in CAD studies...

- ... from failure to consider how CAD will be used:
  - If CAD is to aid human observer, then performance of aided observer must be measured
    - —> *Better computer detection scheme may not complement human observer best*
    - —> *Computer-human interface is crucial*
- ... from failure to consider higher-level efficacy:
  - Does/will CAD change patient outcomes?
  - Is/will CAD be cost effective?
    - —> *Data are needed — faith is not enough!*

43

Practical issues in designing human observer studies

- Use a continuous or nominally continuous ("100-point") rating scale
- Use a block design to avoid "reading-order" effects
- In clinical studies, don't underestimate the difficulty of establishing "truth" without introducing bias

44

Current controversies:

- Advantages/disadvantages of discrete *vs*. continuous or nominally continuous ("100-point") confidence-rating scales?
- Advantages/disadvantages of conventional ROC *vs*. FROC/AFROC methodology?
  - realism
  - adequacy of information obtained
  - availability of robust curve-fitting and statistical techniques
  - statistical power

45

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46

ROC curve fitting

- Some functional form with adjustable parameters must be assumed for the ROC curve — usually the "binormal" model
- The assumptions of conventional least-squares curve fitting aren't valid here, so maximum-likelihood (ML) estimation should be used instead
- Free software is available (listed later)

47

ROC curve fitting (continued)

The conventional "binormal" curve-fitting model ...

- assumes that all ROC curves plot as straight lines on "normal deviate" axes (z_{TPF} *vs*. z_{FPF})
- equivalently, assumes that the two underlying distributions *can be* transformed to normal by a generally unknown transformation ("semi-parametric")
- has been shown valid in a broad variety of situations

but ...

- can yield inappropriate shapes when cases are few and/or when data scale is discrete and operating points are poorly-distributed (–> "proper" models)

48

Statistical significance tests for differences between ROC curves

Ways that "difference" can be quantified:

- Area index A_z (global)
- TPF at a given FPF (local)
- FPF at a given TPF (local)
- Partial area index ("regional")
- Both parameters of binormal model ("bivariate")
- Cost/Benefit (at optimal operating points)

49

Statistical significance tests (cont')

Different statistical tests take different kinds of variation taken into account (and, thus, allow different generalizations):

- **Reader variation only** (a "significant" result applies to readers in general … but only to the particular cases used in the experiment)
- **Case-sample variation only** (result applies to cases in general … but only to the particular reader[s] used)
- **Both** (result applies to readers and cases in general)

⇒ Note: *Conventional statistical tests cannot be applied directly in most situations*

50

Current statistical tests ...

… that take only reader variation into account:

- paired or unpaired Student's *t* test of differences in any index ... at least in principle

51

Current statistical tests...

… that take only case-sample variation into account:

- non-parametric Wilcoxon/Mann-Whitney tests of differences in total ROC area [only] (Hanley & McNeil; DeLong *et al*.)
- non-parametric tests of differences in any index … at least in principle (Wieand *et al*.)
- semi-parametric tests of differences in any index … at least in principle (Metz *et al*.)

52

Current statistical tests...

… that take both sources of variation into account (and are applicable to differences in any index, at least in principle):

- semi-parametric tests (Swets & Pickett; Dorfman, Berbaum & Metz; Toledano & Gatsonis; Obuchowski)
- bootstrapping approach (Beiden, Wagner & Campbell)

53

Free software for ROC analysis:

- **Metz** (University of Chicago; >5000 registered users)
  - **ROCFIT and LABROC**: fit a single ROC using the binormal model
  - **INDROC**: tests difference between independent ROC estimates
  - **CORROC2 and CLABROC**: test diff. between correlated ROCs
    - → difference in A_z
    - → difference in TPF at given FPF
    - → diff. in both binormal ROC curve parameters ("bivariate" test)
  - **ROCKIT:** integrates and extends the five programs above
  - **PROPROC**: fits a single ROC using the "proper" binormal model
  - **LABMRMC**: does a jackknife-ANOVA test for difference in A_z (data collected on continuous and/or discrete scale)
- **Dorfman and Berbaum** (University of Iowa)
  - **RSCORE2** and **RSCORE4**: fit a single ROC using binormal model
  - **MRMC**: Jackknife-ANOVA test for diff. in A_z (discrete scale only)

54

All University of Chicago software for ROC curve fitting and statistical testing can be downloaded from the World Wide Web without charge from:

`http://xray.bsd.uchicago.edu/krl/roc_soft.htm`

—> Please note new URL

55

Current controversies:

- Best way to fit ROC curves to "degenerate" data?
  - RSCORE4 (*ad hoc*)
  - bigamma model (restricts curve shape too much?)
  - "proper" binormal model (computationally intensive, no statistical tests for differences so far)
  - "contaminated" binormal model (restricts curve shape too little?)
- Validity/robustness of current techniques for fitting FROC/AFROC curves and testing the statistical significance of differences thereof?
- Most appropriate index/indices for comparisons?

56

Relationship between ROC analysis and Cost/Benefit analysis:

- Different "operating points" on an ROC curve provide different frequencies of TP, FP, TN, and FN decisions (which depend on disease prevalence).
- If utilities can be assigned to the various kinds of correct and incorrect decisions and if prevalence is known, then the optimal operating point can be found on any ROC curve.
- The maximized utility found in this way quantifies the "value" of a diagnostic test in terms of its ROC.
- See reading list for details.

57

Needs for the future:

- Develop stratified-sampling methodology
- Establish validity/robustness of data-analysis techniques for free-response paradigms
  - curve fitting
  - statistical testing of differences
- Develop "MRMC" methods for statistical analysis of data from incompletely-balanced experimental designs, particularly ...
  - when observers don't read the same cases
  - when data are correlated within cases

58

Needs for the future (continued):

- Develop highly efficient approaches well-suited to exploratory analyses
  - Key need is to control for decision-threshold effects
  - Other biases may be acceptable if sufficiently small
- Generalize ROC analysis to handle >2 decision alternatives
  - Must provide an appropriate compromise between complexity and practicality
  - Approaches proposed to date are *not* adequate

59

Overview:

- Diagnostic efficacy can be addressed at six levels
- "Diagnostic Accuracy" (Level-2 efficacy) is measured best by ROC analysis

60

Overview (continued):

- Many kinds of bias must be avoided in evaluation studies
- Some generalized forms of ROC analysis are available (and particularly well-suited to evaluation of CAD techniques). However, methodology for curve fitting and statistical testing is not fully developed and/or validated.

61

An incomplete list of recommended literature on ROC methodology

BACKGROUND:

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62

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63

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- Wagner RF, Beiden SV, Campbell G, Metz CE, Sachs WM. Assessment of medical imaging and computer-assist systems: lessons from recent experience. Academic Radiol 2002; 8: 1264.

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65

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