INTRODUCTION TO ROC CURVE ANALYSIS WITH APPLICATIONS IN FUNCTIONAL GENOMICS

Presented by:
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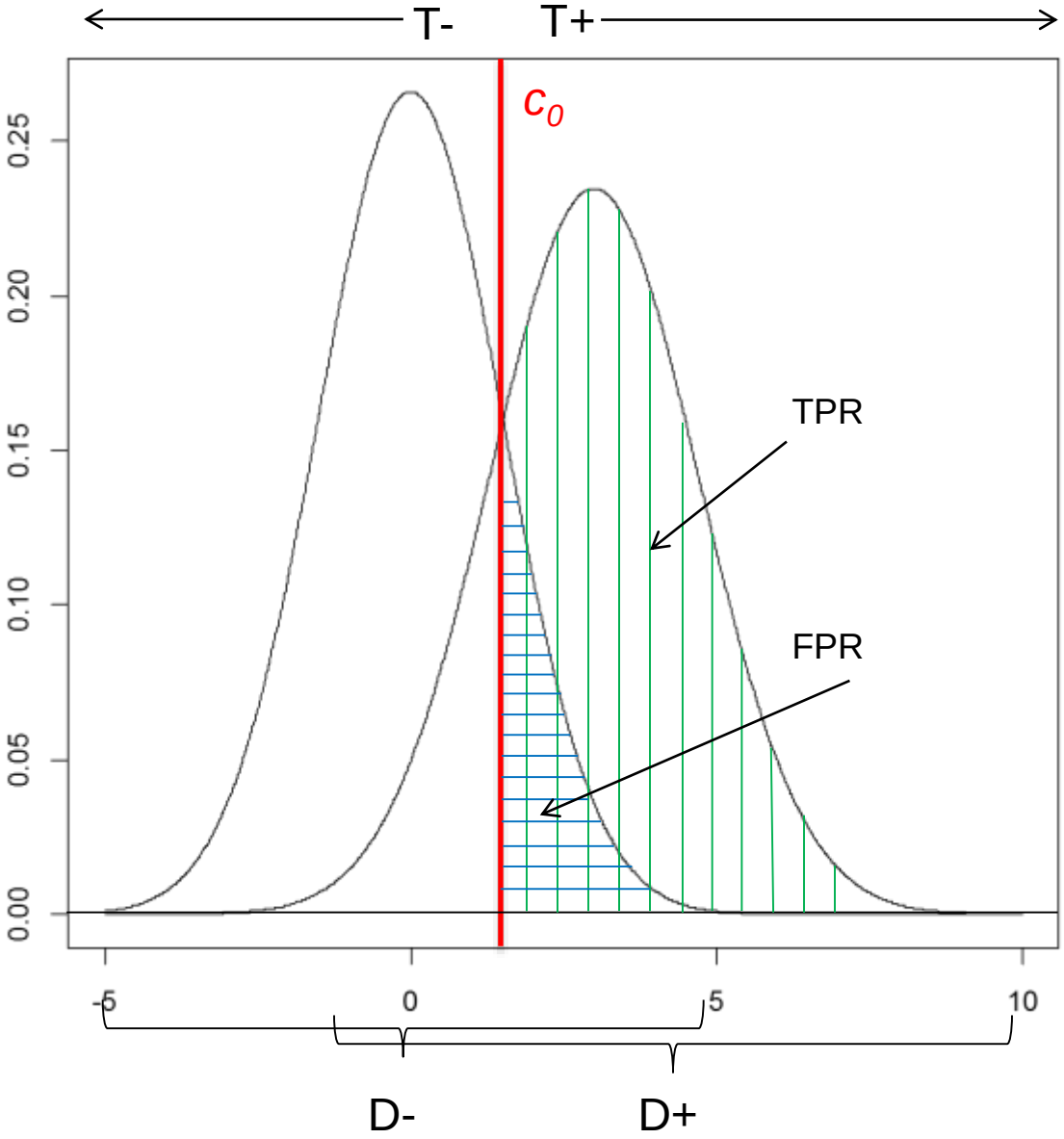
OUTLINE

- Introduction
  - Parametric ROC Curve
  - Non-Parametric ROC Curve
- Examples
  - Single Cutoff-Point: Single mutation
  - Continuous outcome: Gene expression levels
  - Discreet outcome: Gene ranks
- Extensions
  - ‘Non-Proper’ ROC Curves
  - Multi-class ROC Analysis

ROC CURVES

- ROC = Receiver-operator characteristic (signal detection)
- Purpose: evaluation of classification model that predicts binary group membership
  - Model can be based on supervised or unsupervised methods, but 'true' group membership (as determined by 'gold standard') is known
- Depict tradeoffs between sensitivity and specificity over a range of cutoff values. In terms of disease:
  - Sensitivity (True positive rate [TPR]): identification of those who truly have the disease (D+) as having the disease (T+)
  - Specificity (True negative rate [TNR]): identification of those that do not actually have the disease (D-) as not having the disease (T-)
  - The value [1-Specificity] (False positive rate [FPR]) is used in graphs
    - Ideal classification models have high TPR while maintaining low FPR
    - TPR and FPR increase/decrease together


T-
T+
c_0
TPR
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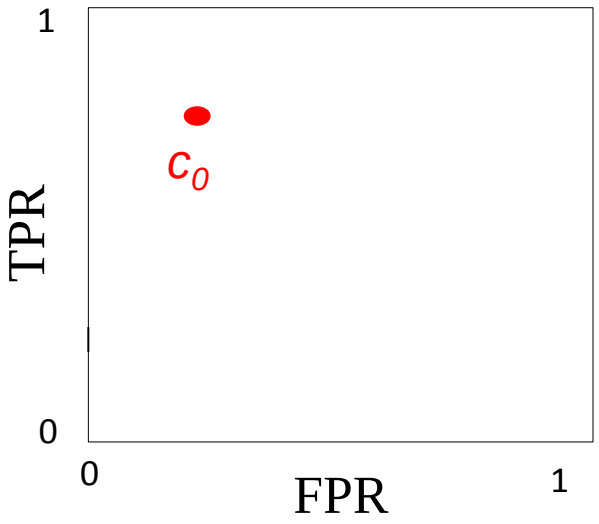
D-
D+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TPR
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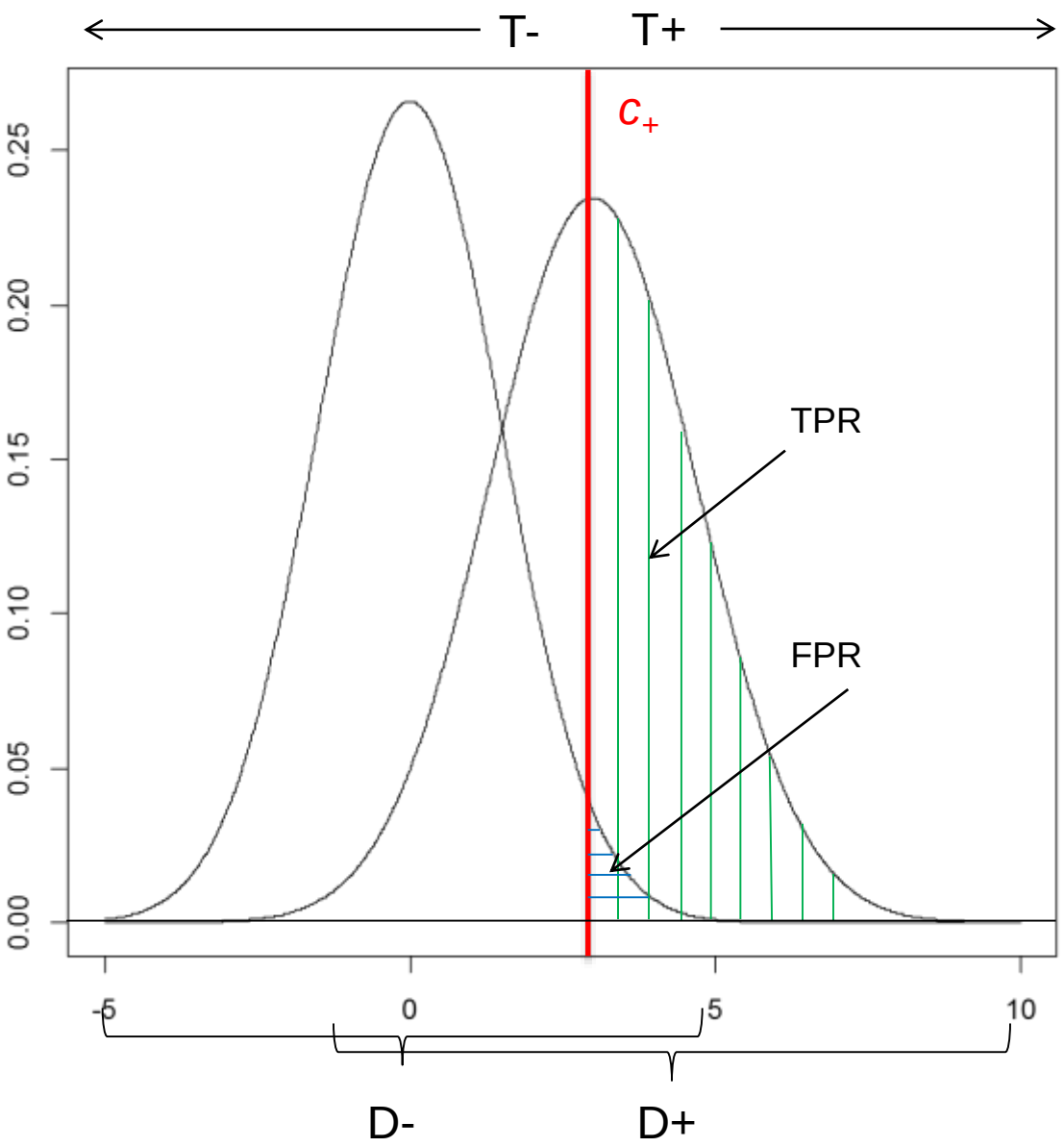
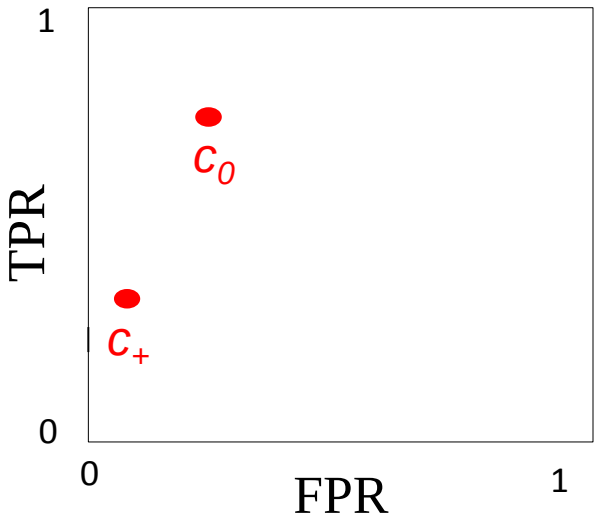
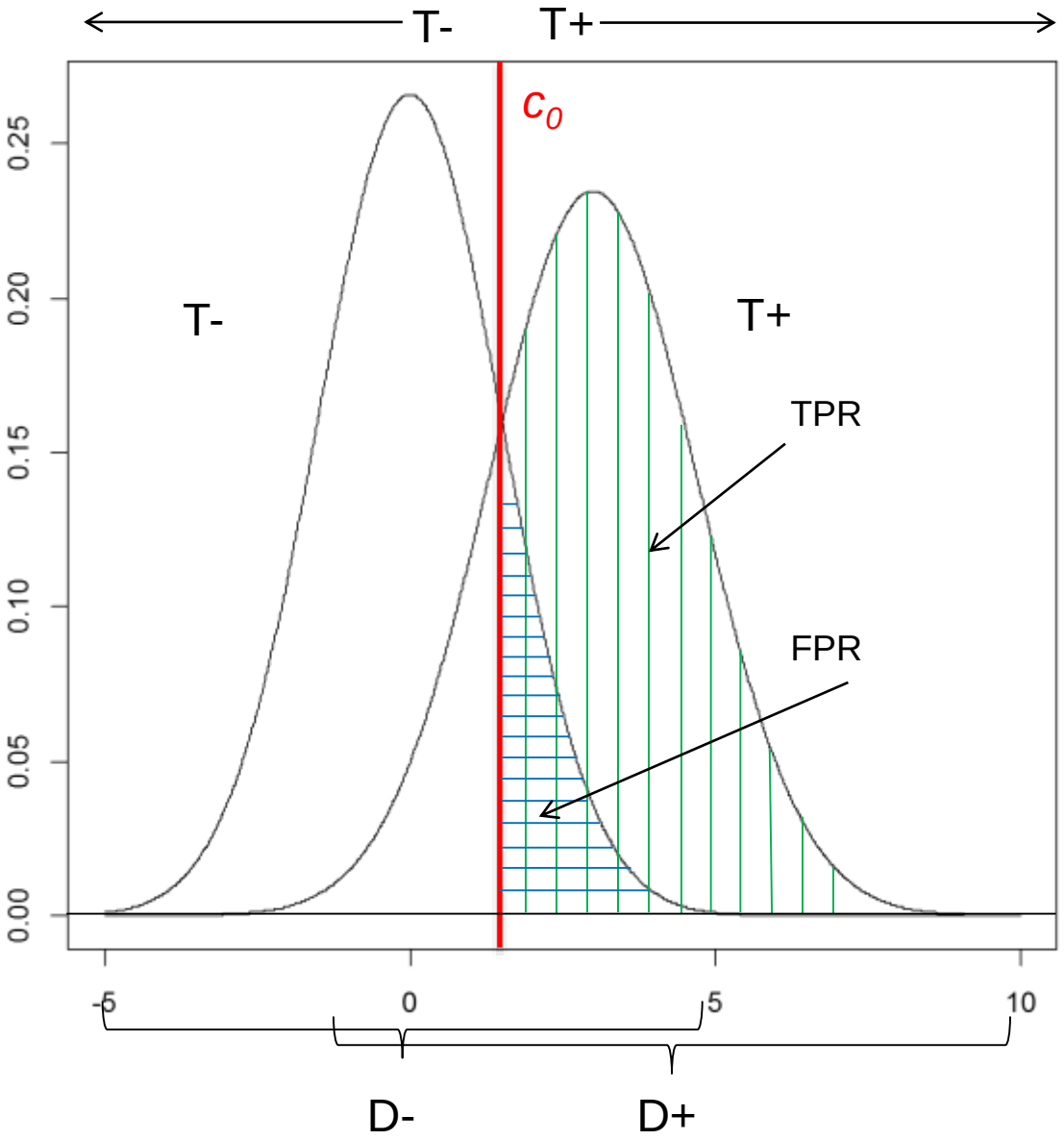




- Increasing the cutoff point (making the test *more conservative*) decreases TPR and FPR
  - ➢ Less false alarms, but also less true positives identified


T-
T+
c_0
T-
T+
TPR
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0.25
0.20
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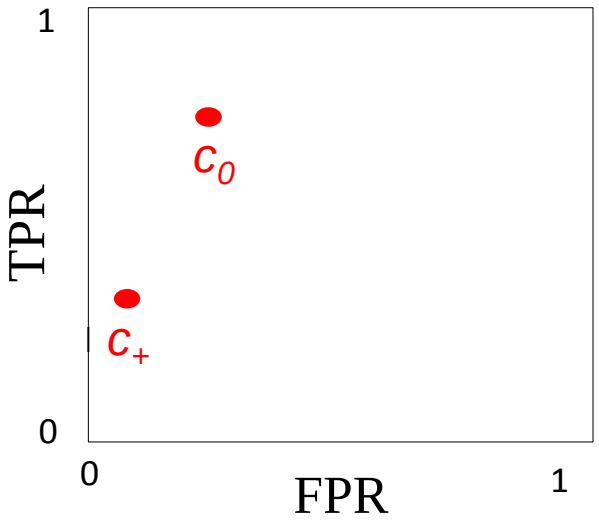
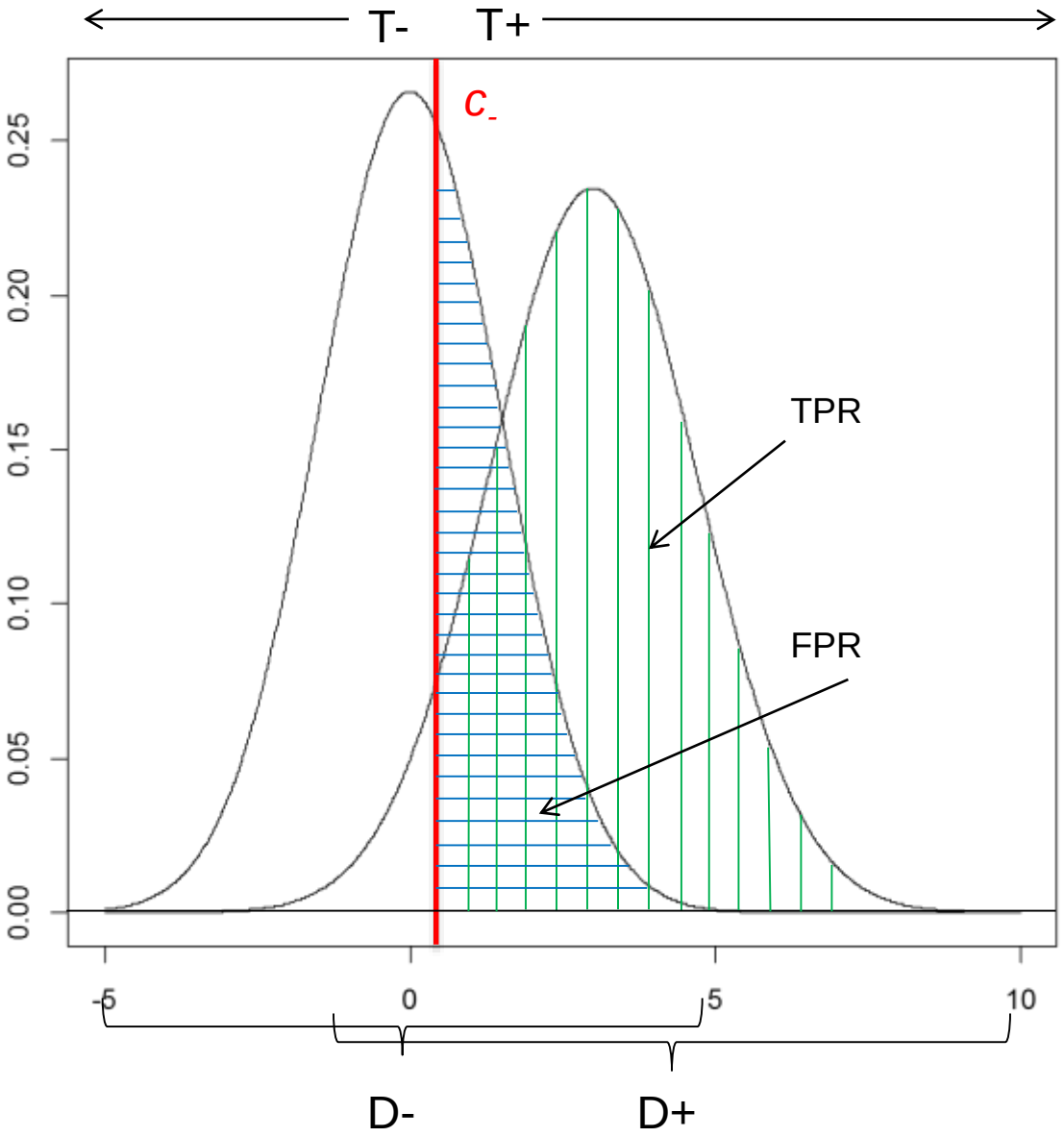
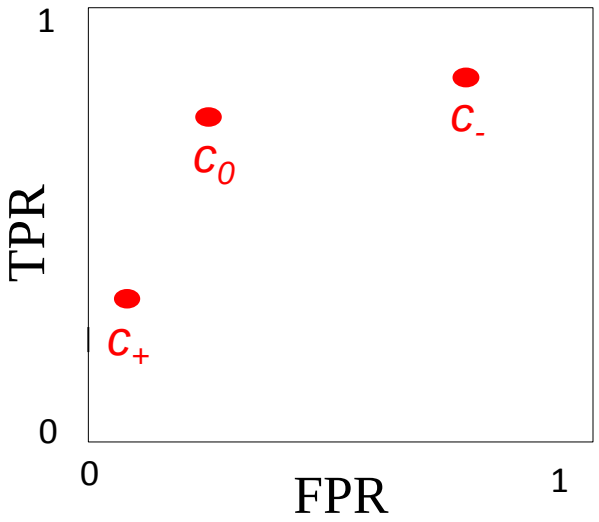
D-
D+


1
c_0
TPR
c_+
0
0
FPR
1

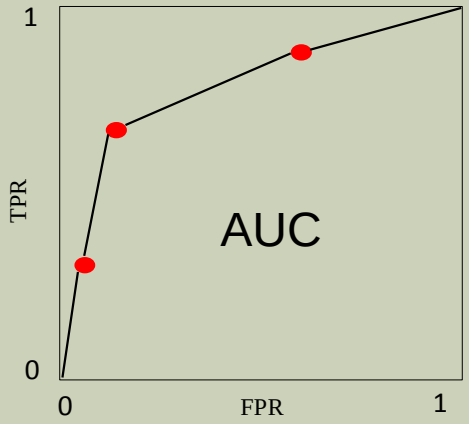




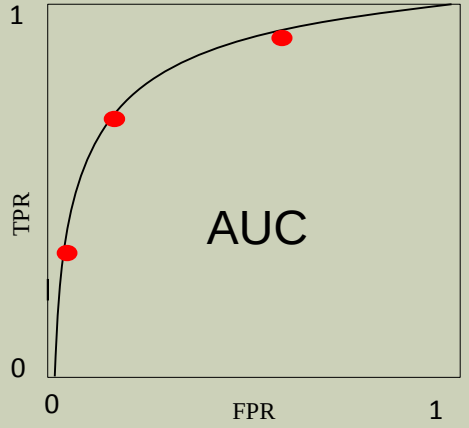
- Decreasing the cutoff point (making the test *less conservative*) increases both TPR and FPR
  - ➢ More false alarms, but also more true positives identified

AUC

Non-Parametric



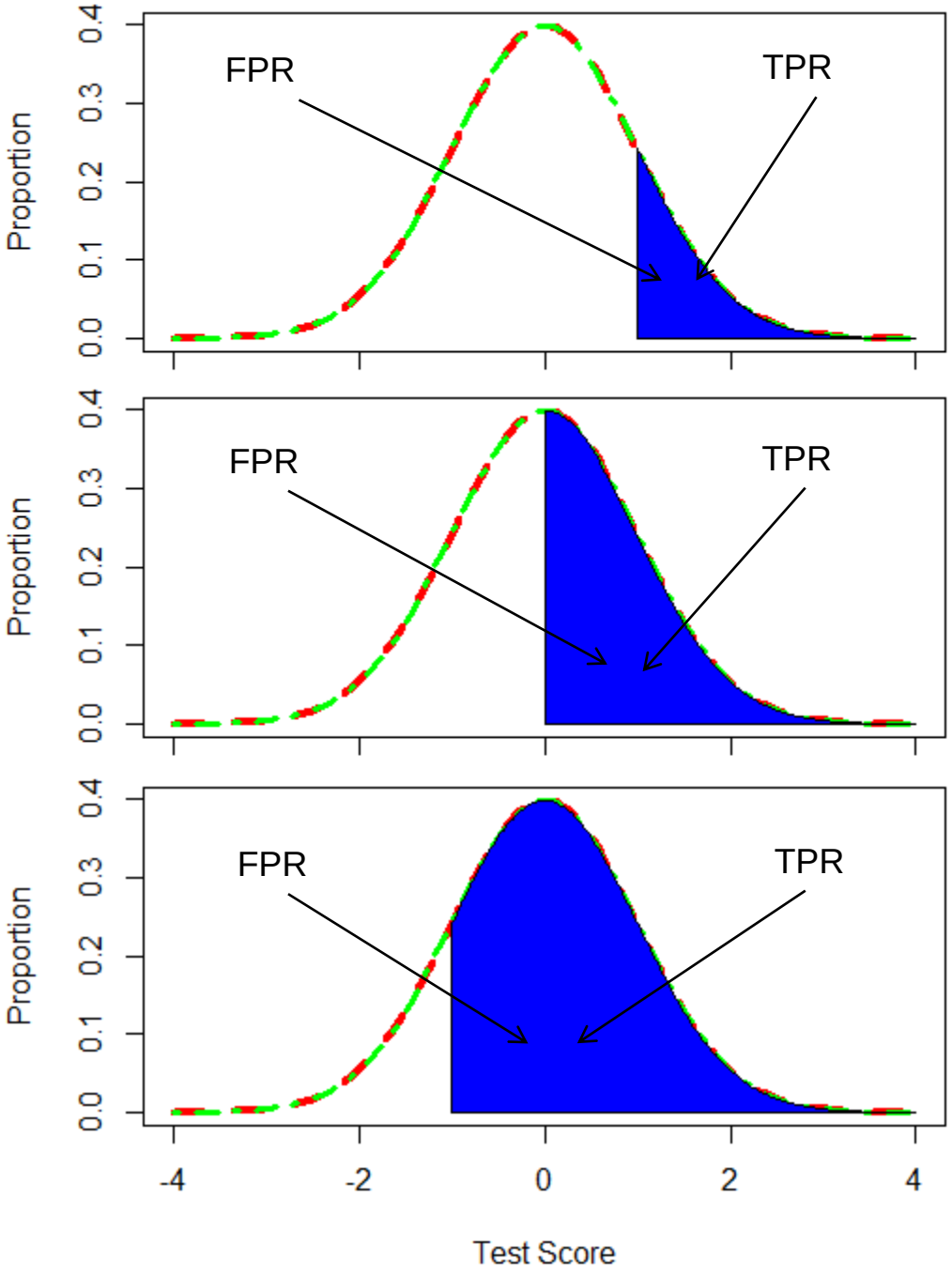
Parametric

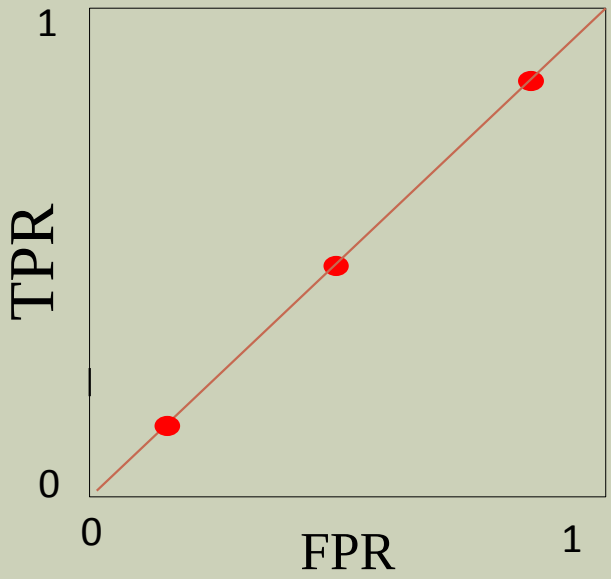


The area under the ROC curve (AUC) is a statistical summary of overall accuracy

- **Equivalent to the probability that a test (or classification model) will correctly classify a random pair of observations when one is from the D+ group and the other is from the D- group**

  → measure of how well the populations are separated by the classification model





- AUC Values range: 0.5 – 1.0
  - 0.5 - test is no better than a random class assignment
  - 1.0 - perfect class prediction

PARAMETRIC CALCULATION (NORMAL DISTRIBUTION)

Let X_0 and X_1 be test scores for 2 different populations of interest (such as no disease versus disease).

If $X_0 \sim N(\mu_0, \sigma_0)$ and $X_1 \sim N(\mu_1, \sigma_1)$, then

$$\text{AUC} = \Phi\left(\frac{a}{\sqrt{1+b^2}}\right)$$

Where $a = \frac{\mu_1 - \mu_0}{\sigma_1}$, $b = \frac{\sigma_0}{\sigma_1}$, and Φ is the cumulative normal distribution function.

I think it helps to look at the equation a bit differently:

$$\left(\frac{a}{\sqrt{1+b^2}}\right) = \frac{\frac{\mu_1-\mu_0}{\sigma_1}}{\sqrt{1+\left(\frac{\sigma_0}{\sigma_1}\right)^2}} = \frac{\frac{\mu_1-\mu_0}{\sigma_1}}{\sqrt{\left(\frac{\sigma_1}{\sigma_1}\right)^2+\left(\frac{\sigma_0}{\sigma_1}\right)^2}} = \frac{\frac{\mu_1-\mu_0}{\sigma_1}}{\frac{\sqrt{\sigma_1^2+\sigma_0^2}}{\sigma_1}} = \frac{\mu_1-\mu_0}{\sqrt{\sigma_1^2+\sigma_0^2}}$$

It is now readily apparent that AUC:

Increases as distance between means increases.

Decreases when standard deviations increase.

What happens if distance between means is 0?

“DATA-BASED” NON-PARAMETRIC ROC CURVE

Sort data by score.
Above cutoff point: Predicted Group = 1
Below cutoff point: Predicted Group = 0

	Group	Score
TP	1	10
FN	1	9.4
FN	1	9.2
FN	1	7.6
TN	0	7.4
FN	1	7.3
TN	0	7.1
FN	1	6.5
TN	0	6.3
TN	0	6.2
TN	0	5.6
FN	1	5.4
TN	0	5.3
FN	1	4.7
FN	1	4.6
TN	0	4.2
FN	1	4.1
TN	0	3.9
TN	0	1.8
TN	0	1.5

FPR	TPR
0	0.1

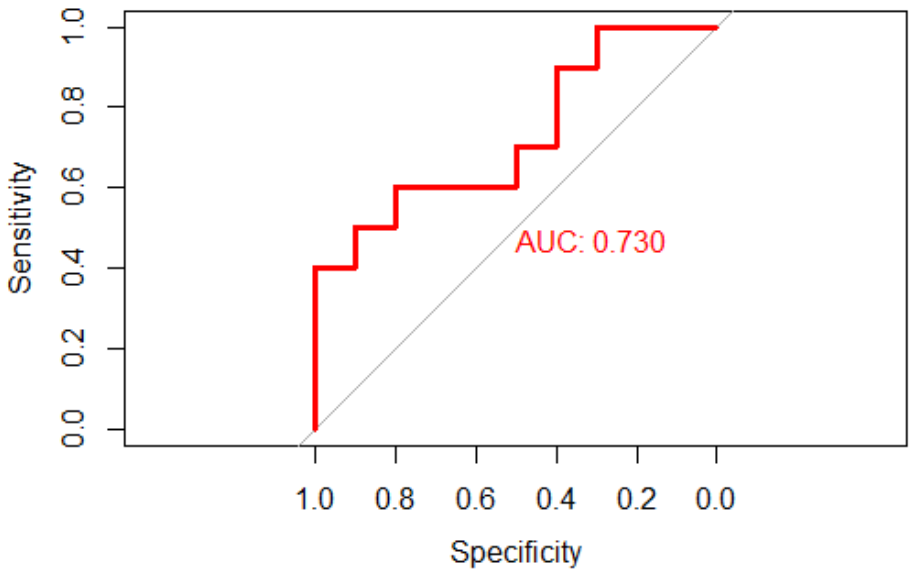
	Group	Score
TP	1	10
TP	1	9.4
TP	1	9.2
TP	1	7.6
FP	0	7.4
FN	1	7.3
TN	0	7.1
FN	1	6.5
TN	0	6.3
TN	0	6.2
TN	0	5.6
FN	1	5.4
TN	0	5.3
FN	1	4.7
FN	1	4.6
TN	0	4.2
FN	1	4.1
TN	0	3.9
TN	0	1.8
TN	0	1.5

FPR	TPR
0	0.1
0	0.2
0	0.3
0	0.4
0.1	0.4

"DATA-BASED" NON-PARAMETRIC ROC CURVE

Above cutoff point: Predicted Group = 1
Below cutoff point: Predicted Group = 0

Group	Score	FPR	TPR
1	10	0	0.1
1	9.4	0	0.2
1	9.2	0	0.3
1	7.6	0	0.4
0	7.4	0.1	0.4
1	7.3	0.1	0.5
0	7.1	0.2	0.5
1	6.5	0.2	0.6
0	6.3	0.3	0.6
0	6.2	0.4	0.6
0	5.6	0.5	0.6
1	5.4	0.5	0.7
0	5.3	0.6	0.7
1	4.7	0.6	0.8
1	4.6	0.6	0.9
0	4.2	0.7	0.9
1	4.1	0.7	1
0	3.9	0.8	1
0	1.8	0.9	1
0	1.5	1	1



Interpretation of AUC = If I randomly select one person from each group, what is the probability that a person from Group(1) has a higher score than the person from Group(0)?

USING RANKS TO BUILD AN ROC CURVE

Group	Score
0	1.5
0	6.2
0	5.3
0	4.2
0	3.9
0	7.1
0	5.6
0	7.4
0	1.8
0	6.3
1	9.2
1	10
1	4.1
1	6.5
1	5.4
1	9.4
1	4.6
1	7.3
1	4.7
1	7.6

Group	Score
1	10
1	9.4
1	9.2
1	7.6
0	7.4
1	7.3
0	7.1
1	6.5
0	6.3
0	6.2
0	5.6
1	5.4
0	5.3
1	4.7
1	4.6
0	4.2
1	4.1
0	3.9
0	1.8
0	1.5

Group	Score	Rank
1	10	1
1	9.4	2
1	9.2	3
1	7.6	4
0	7.4	5
1	7.3	6
0	7.1	7
1	6.5	8
0	6.3	9
0	6.2	10
0	5.6	11
1	5.4	12
0	5.3	13
1	4.7	14
1	4.6	15
0	4.2	16
1	4.1	17
0	3.9	18
0	1.8	19
0	1.5	20

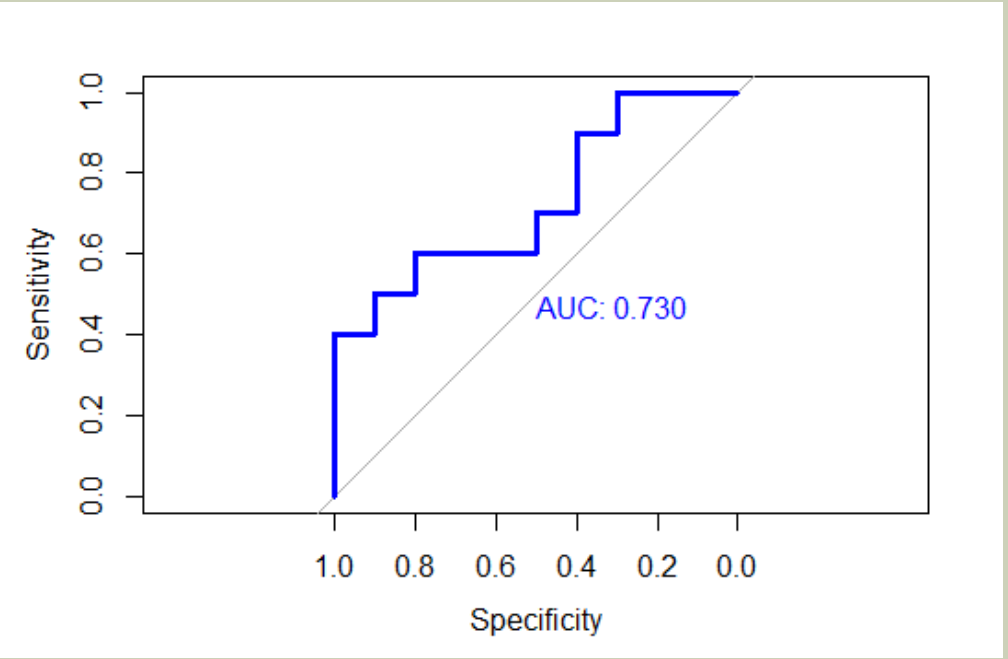
Group	Rank
1	1
1	2
1	3
1	4
0	5
1	6
0	7
1	8
0	9
0	10
0	11
1	12
0	13
1	14
1	15
0	16
1	17
0	18
0	19
0	20

"RANK-BASED" NON-PARAMETRIC ROC CURVE

Above cutoff point: Predicted Group = 1
Below cutoff point: Predicted Group = 0

Group	Rank
1	1
1	2
1	3
1	4
0	5
1	6
0	7
1	8
0	9
0	10
0	11
1	12
0	13
1	14
1	15
0	16
1	17
0	18
0	19
0	20

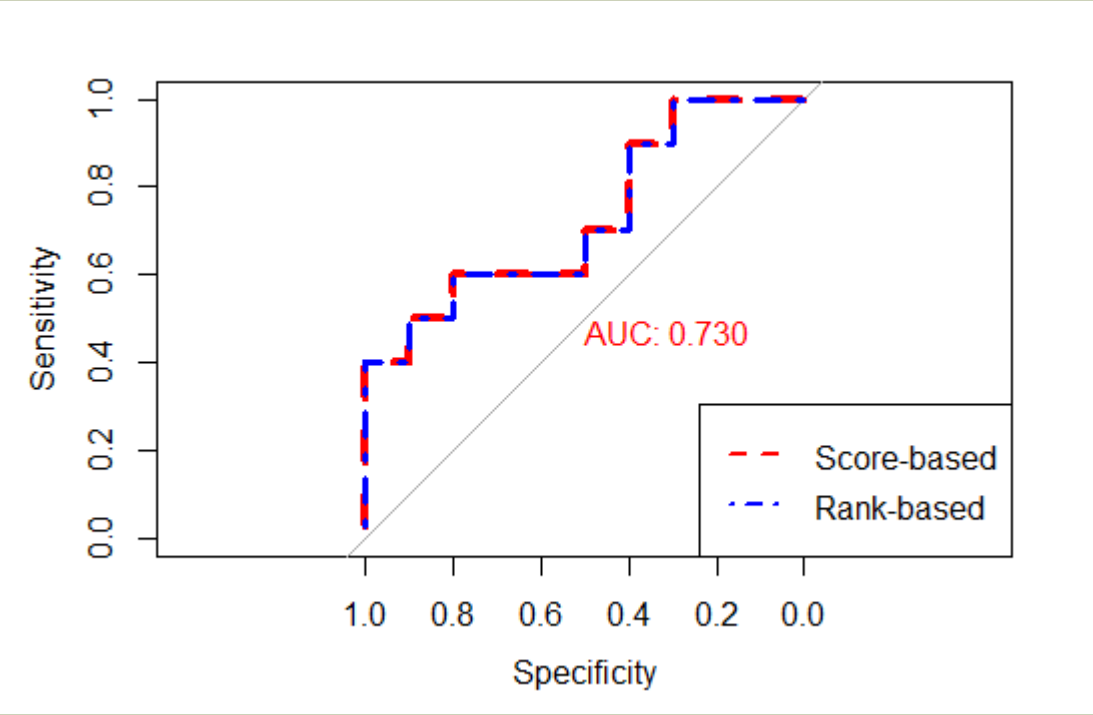
1 - Specificity	Sensitivity
0	0.1
0	0.2
0	0.3
0	0.4
0.1	0.4
0.1	0.5
0.2	0.5
0.2	0.6
0.3	0.6
0.4	0.6
0.5	0.6
0.5	0.7
0.6	0.7
0.6	0.8
0.6	0.9
0.7	0.9
0.7	1
0.8	1
0.9	1
1	1



Interpretation of AUC = If I randomly select one person from each group, what is the probability that a person from Group(1) is ranked higher than the person from Group(0)?

RANK-BASED VS SCORE-BASED NON-PARAMETRIC ROC CURVE

Curves are identical



Non-parametric (or "data–based" or "Empirical") curves are inherently rank-based

"Rankiness" → nice statistical properties without the need to assume a particular distribution

NON-PARAMETRIC CALCULATION

Let X_0 and X_1 be test scores OR ranks based on scores for 2 different populations of interest (such as no disease versus disease).
If there is no distributional assumption for the values of X_0 and X_1, then

$$\text{AUC} = \frac{1}{n_0 n_1} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} I(X_{i1}, X_{j0})$$

$$\text{where } I(X_{i1}, X_{j0}) = \begin{cases} 1 \; if \; X_{i1} > X_{j0} \\ 1/2 \; if \; X_{i1} = X_{j0} \\ 0 \; if \; X_{i1} < X_{j0} \end{cases}$$

AUC is equal to the Mann-Whitney *U* statistic; it compares the sums of ranks.

- Approximately normally distributed for large samples.
- Robust (not sensitive to outliers)

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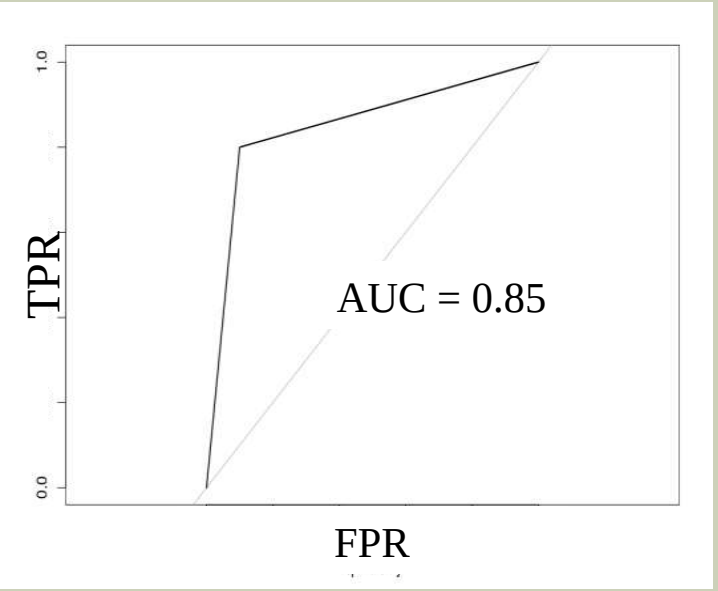
EXAMPLE: SINGLE CUT-POINT, SINGLE MUTATION

True Class Based on Disease Outcome
(0 = Negative for BC , 1 = Positive for BC)

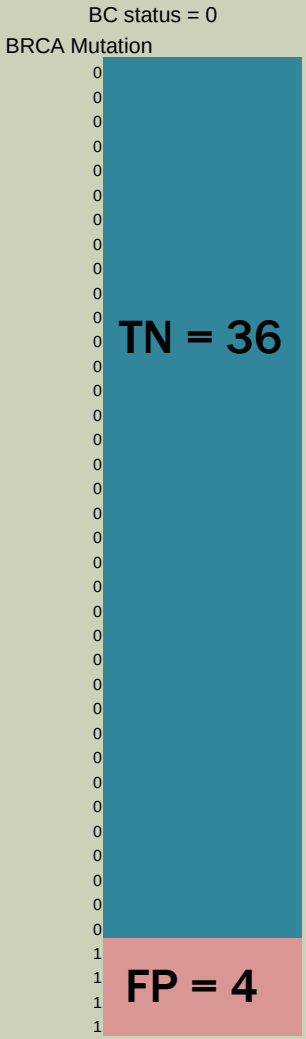
Predicted Class Based on BRCA1 status
(0 = WT, 1 = Mut)

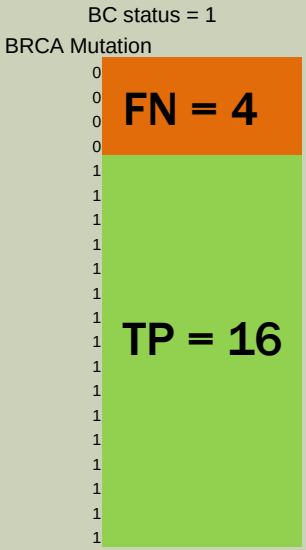
	0	1
0	36 (TN)	4 (FN)
1	4 (FP)	16 (TP)
	40 (P)	20(N)



Sensitivity (TPR)= TP/(TP + FN) =16/(16 +4) = 0.80
Specificity (TNR) = TN/(TN +FP) = 35/(35 + 4) = 0.90
Accuracy = (TP + TN)/(P + N) = (16+36)/(40 +20) = 0.8667
AUC = 0.85

A CLOSER LOOK AT AUC





Total number of pairwise comparisons :
(TN + FP)(FN + TP) = (40)(20) = 800

Number of times correct ($X_{i1} > X_{j0}$):
TN*TP = 576

Number of ties ($X_{i1} = X_{j0}$):
TP*FP + FN*TN = 64 + 144

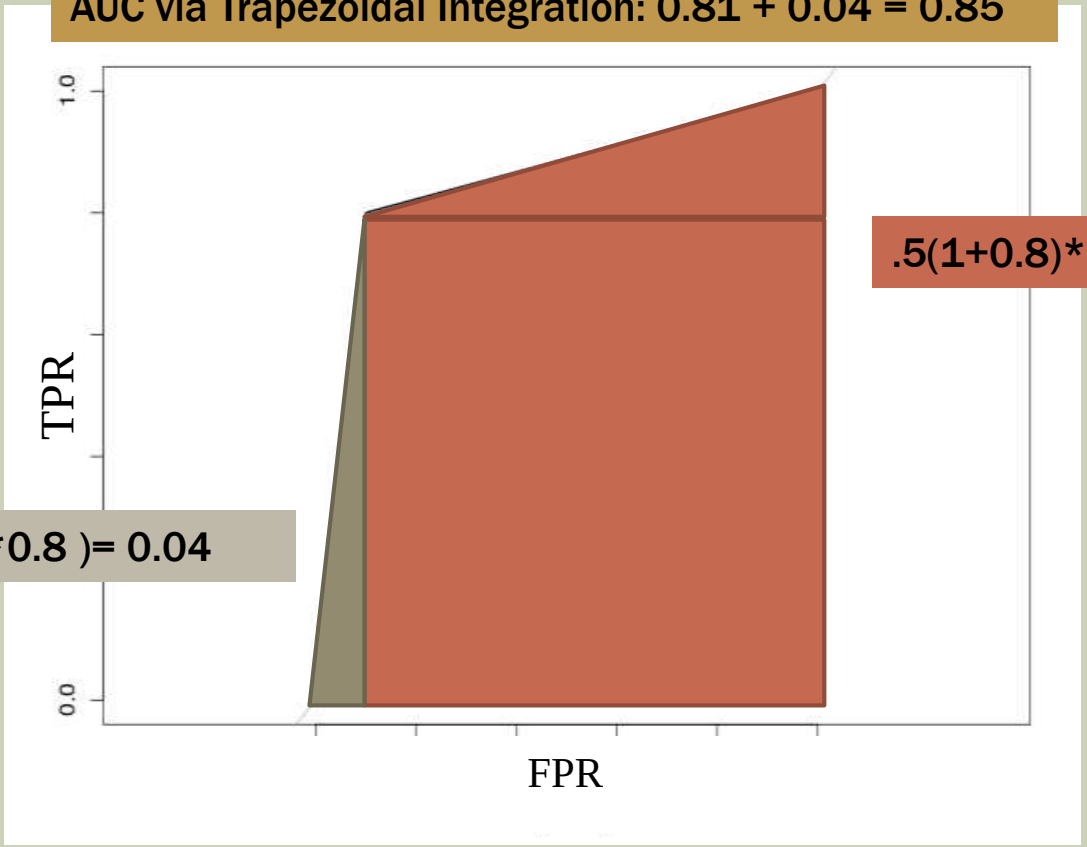
$$\text{AUC} = \frac{576 + \frac{1}{2}(208)}{800} = \frac{680}{800} = 0.85$$

For one cutoff point:

$$\text{AUC} = \frac{2\,(TP*TN)+(TP*FP)+(TP*FN)}{2(TN+FP)(FN+TP)} = \frac{Sens.+Spec.}{2}$$

A GEOMETRIC LOOK AT AUC

AUC via Trapezoidal Integration: 0.81 + 0.04 = 0.85



.5(1+0.8)*0.9 = 0.81

.5(0.1*0.8)= 0.04

*ROC analysis is not typically performed for single cutoff scenarios but hopefully this sheds light on the probabilistic/geometric nature of AUC

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EXAMPLE: CONTINUOUS OUTCOME - GENE EXPRESSION LEVELS

- Hypothetical situation:
  - I read about an cell-line experiment that found certain genes upregulated in MCF-7 (breast cancer) cells. I want to see how the results translate to human BC tumors.
  - I choose two genes and go to the Genomics Portals website to obtain gene expression data

  Dataset: Breast invasive carcinoma from TCGA

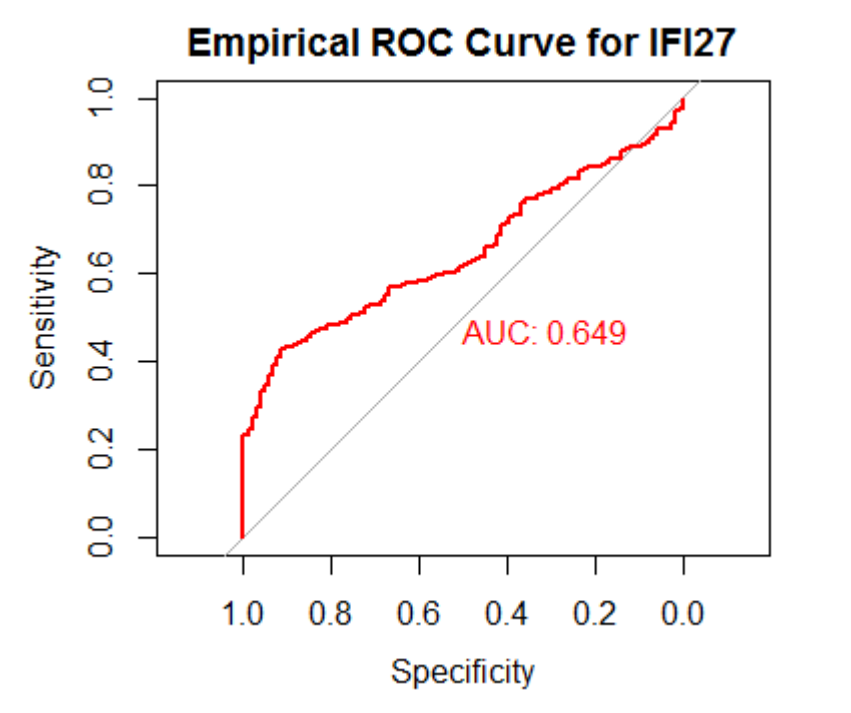
  Pubmed source: TCGA_BRCA_exp_HiSeqV2

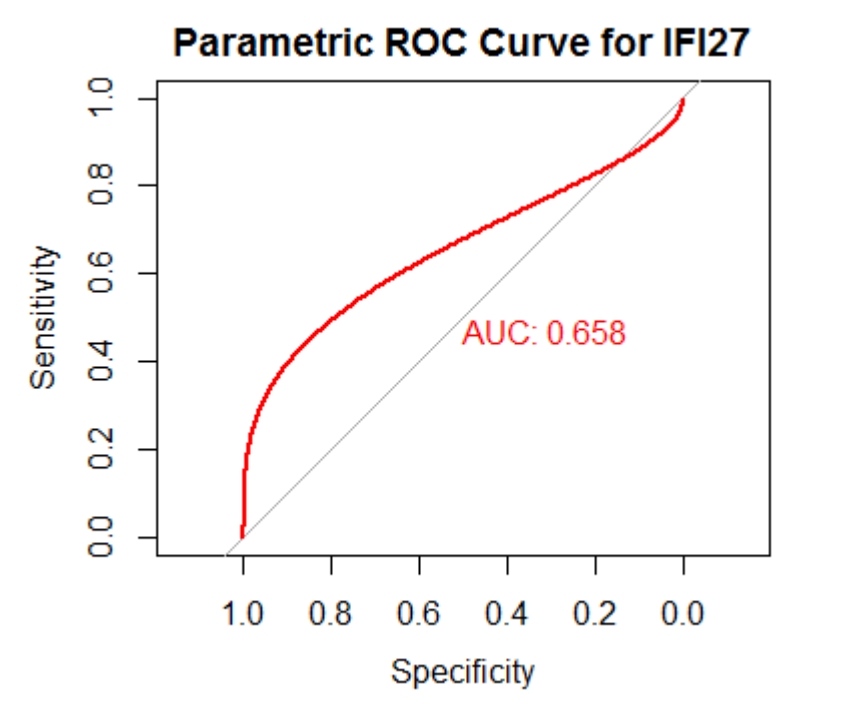
  Genes:
    - IFI27 (interferon, alpha-inducible protein 27) – promotes cell death and is associated with healing
    - FN1 (fibronectin 1) - cell adhesion and migration processes

  - How well do the corresponding gene expression levels discriminate tumor samples from normal tissue samples?

EXAMPLE: CONTINUOUS OUTCOME - GENE EXPRESSION LEVELS

Potential discriminatory gene #1 : IFI27

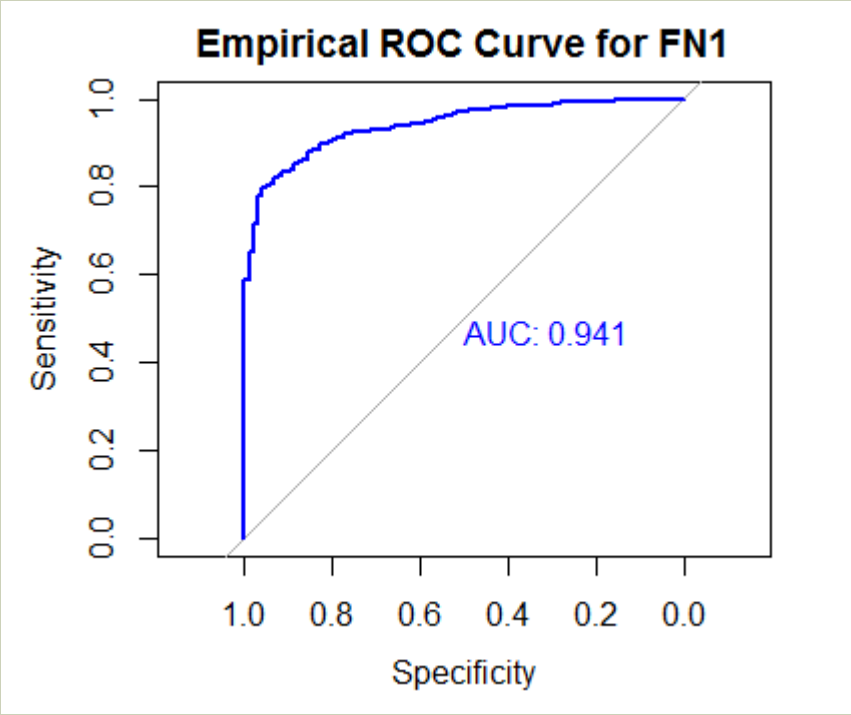


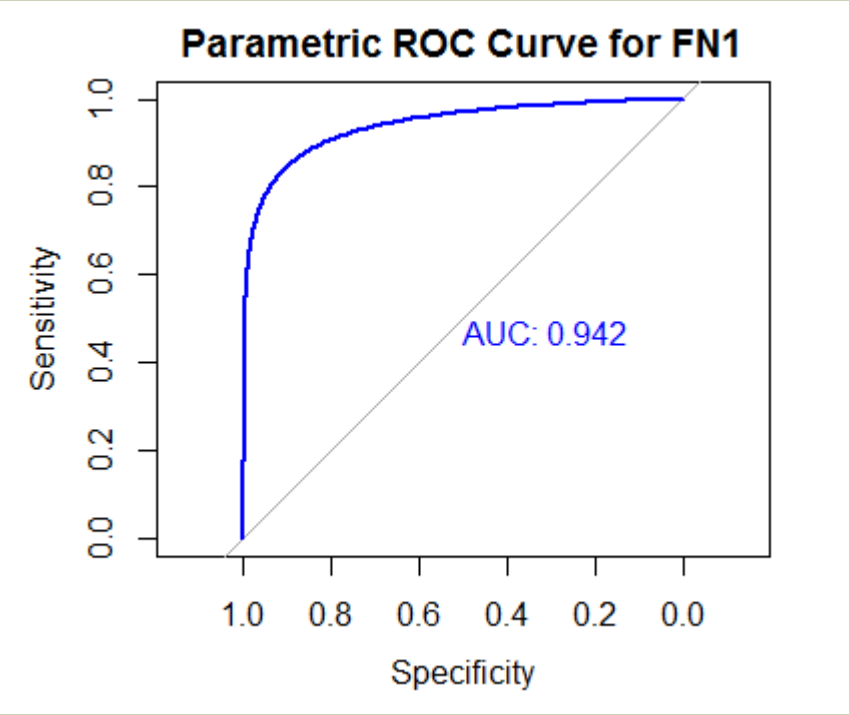


AUC = Probability that that if we randomly select one tumor and one normal sample gene expression for IFI27(tumor) > gene expression for IFI27(normal)

EXAMPLE: CONTINUOUS OUTCOME - GENE EXPRESSION LEVELS

Potential discriminatory gene #2 : FN1

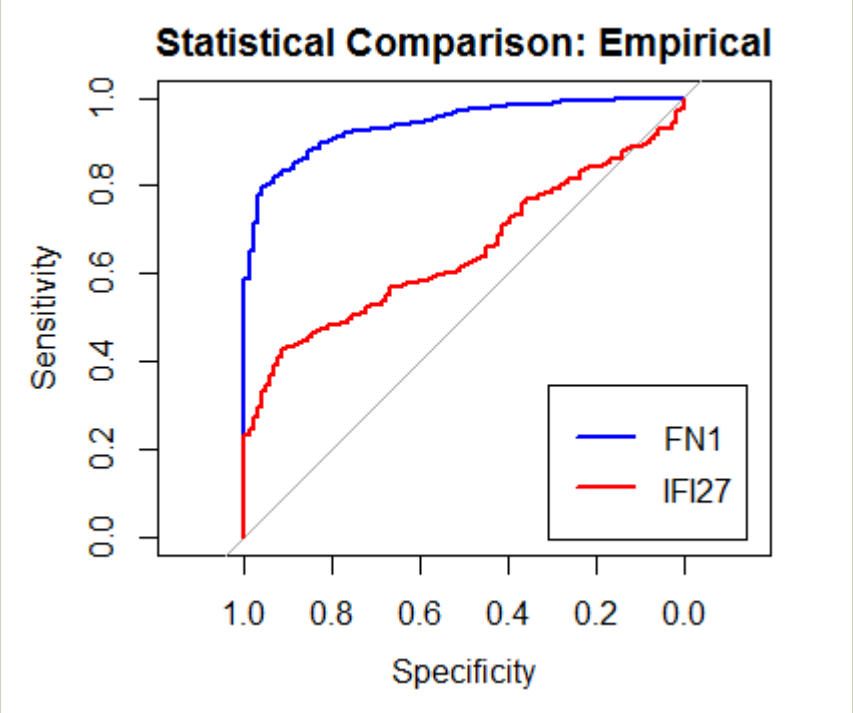


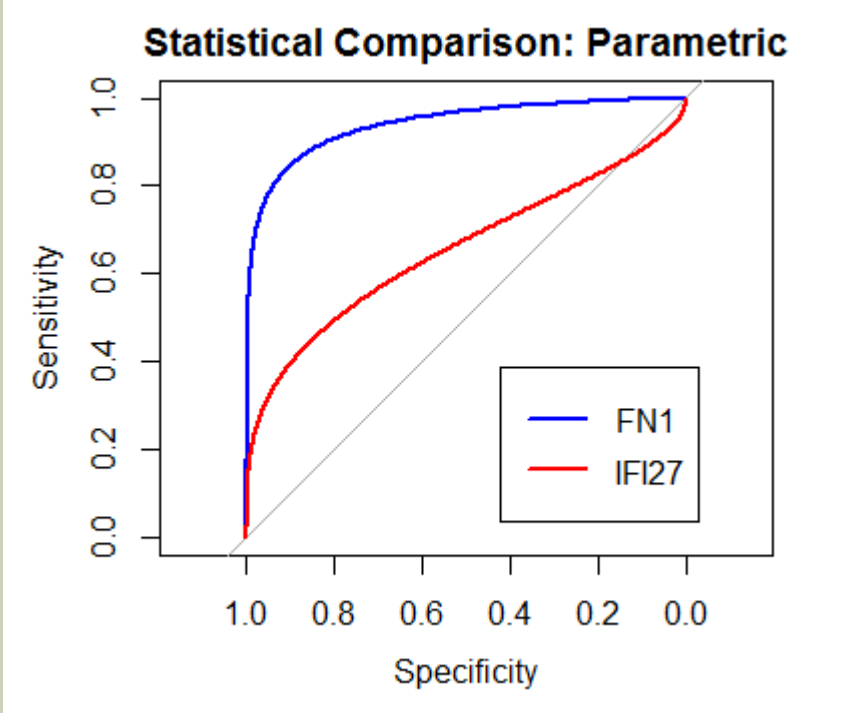


AUC = Probability that that if we randomly select one tumor and one normal sample gene expression for FN1(tumor) > gene expression for FN1(normal)

EXAMPLE: CONTINUOUS OUTCOME - GENE EXPRESSION LEVELS

Is FN1 significantly better at discriminating amongst BC tumor samples than IFI27?



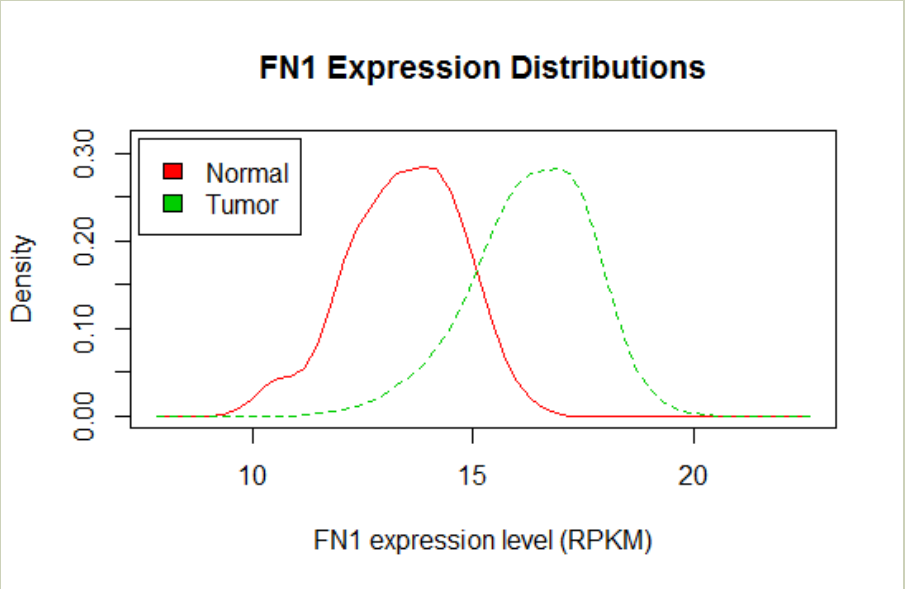


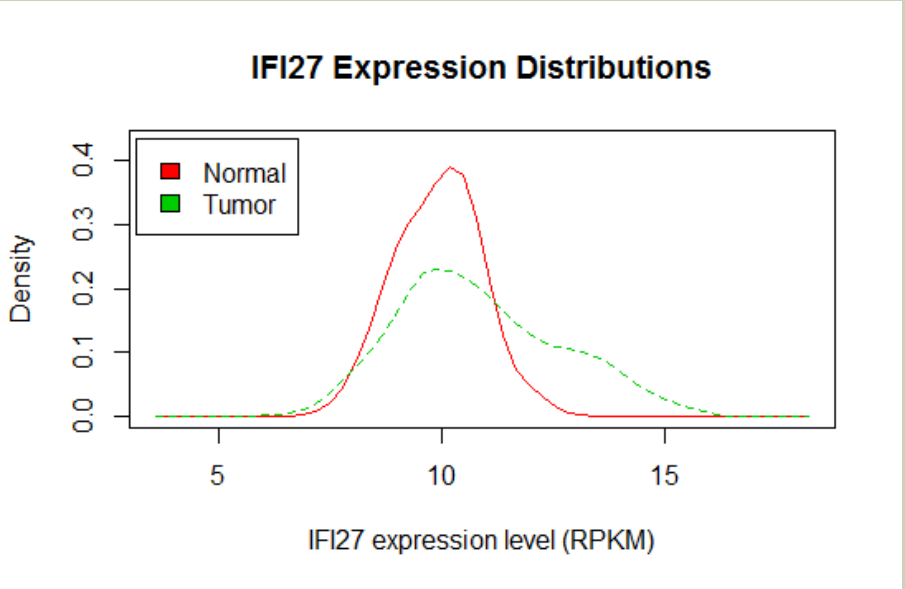
P-value = 1.06 e-46

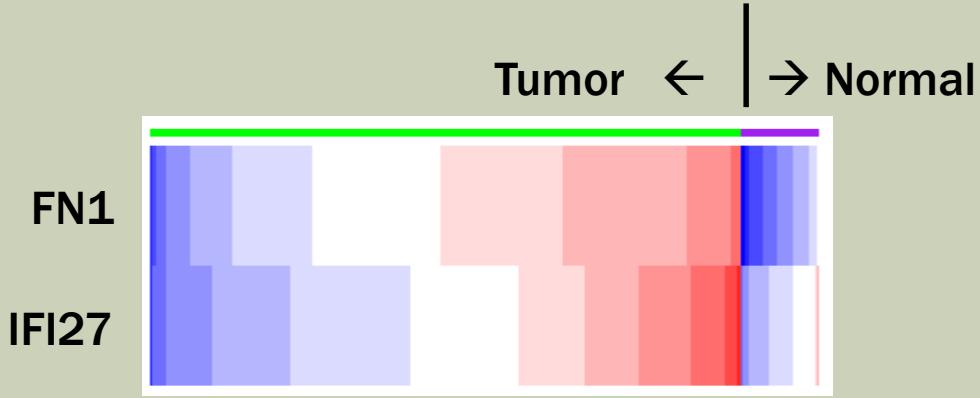
P-value = 4.69 e-42

Note: pROC takes into account correlation between measurements when determining significance

A CLOSER LOOK: DATA DISTRIBUTIONS

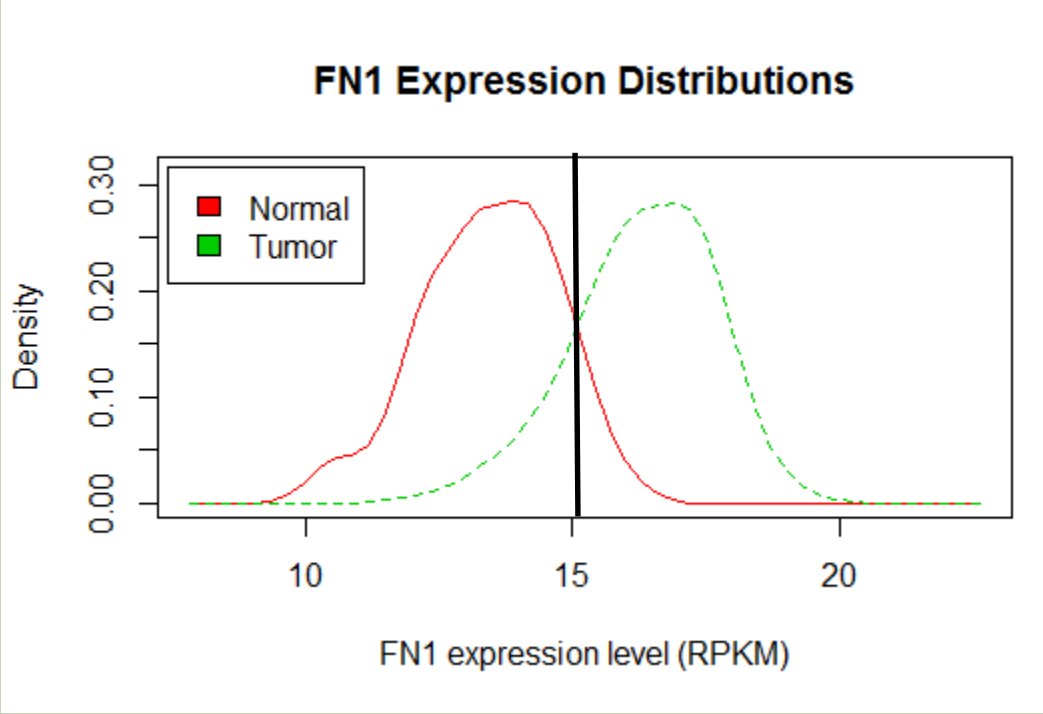


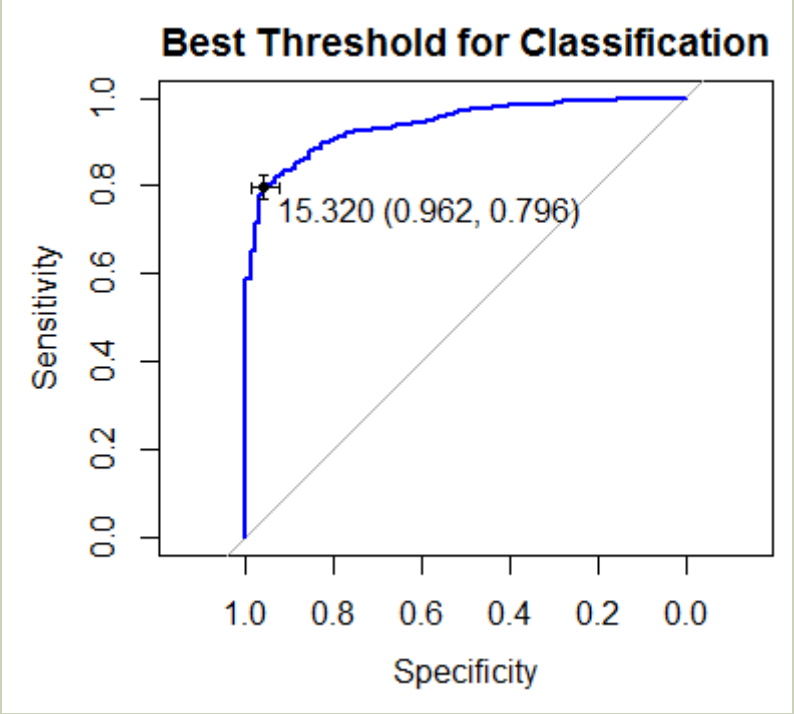




EXAMPLE: CONTINUOUS OUTCOME - GENE EXPRESSION LEVELS

I decide to go with FN1, now I want to know a little more.





OUTLINE

- Introduction
  - Parametric ROC Curve
  - Non-Parametric ROC Curve
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  - Single Cutoff-Point: Single mutation
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EXAMPLE: DISCREET OUTCOME - RANKING OF DE GENES

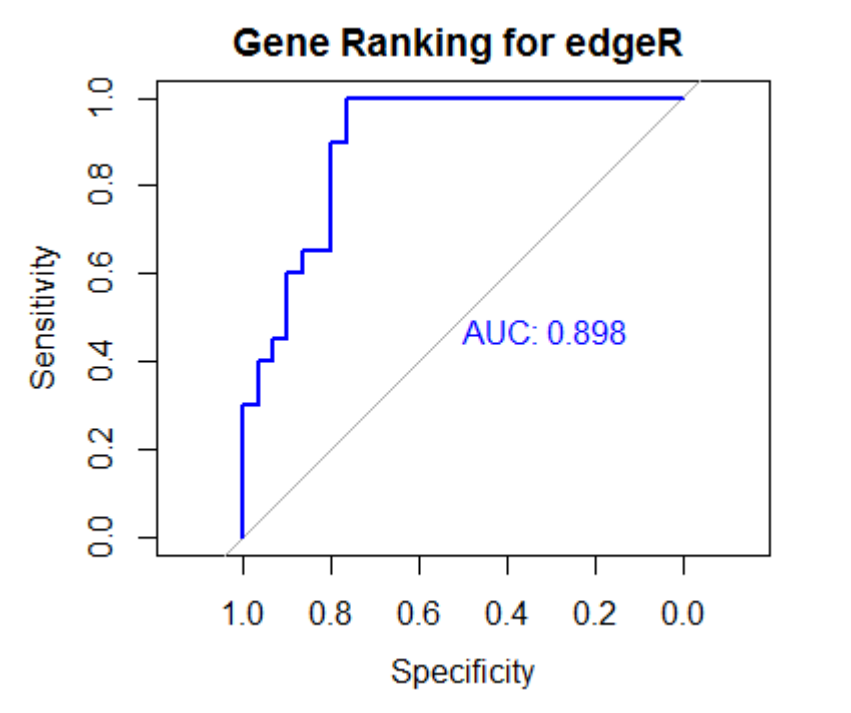
Hypothetical situation:

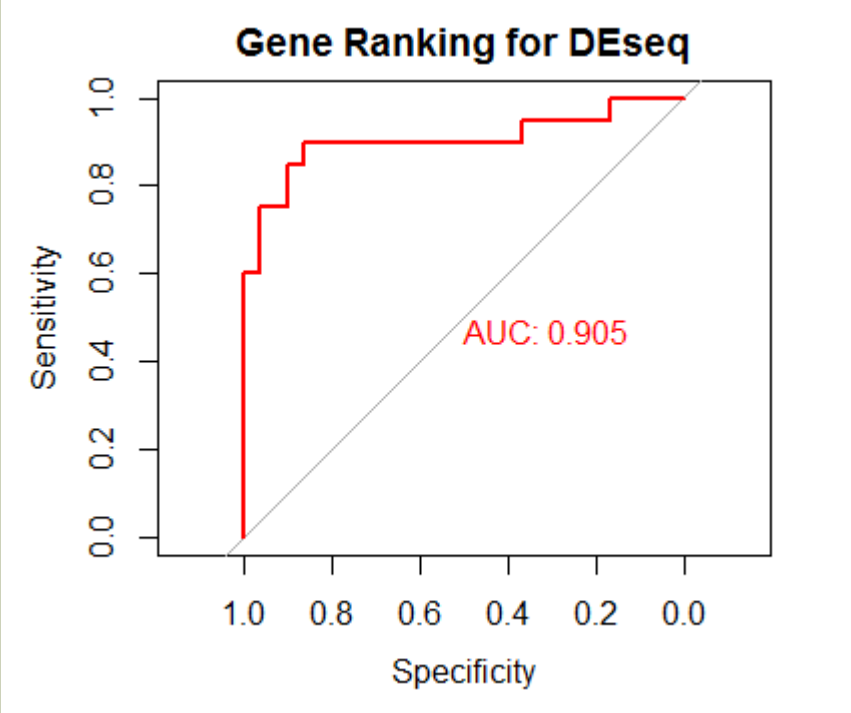
- I have been using DEseq for differential expression analysis. I want to start using edgeR, but I hear it is less conservative than DEseq.
  - Since edgeR is less conservative, I am concerned that it will return more false positives than DEseq.
  - On the other hand, I am concerned that DEseq will return less true positives than edgeR.
  - I construct a simulation data set to represent two groups and expression levels for 50 genes.
    - I choose at random 20 genes to be up- or down-regulated (DE) between groups when I simulate the data
      - (for more detail see Soneson & Delorenzi 2013)
  - I run DE on DEseq and edgeR and then rank the genes by p-value.

EXAMPLE: DISCREET OUTCOME DATA SET-UP

GeneID	DEstatus	rankedgeR	rankDEseq
gene1	1	1	1
gene2	1	2	2
gene3	1	3	3
gene4	1	4	4
gene5	1	5	5
gene6	1	6	6
gene7	1	8	7
gene8	1	9	8
gene9	1	11	9
gene10	1	13	10
gene11	1	14	11
gene12	1	15	12
gene13	1	17	14
gene14	1	20	15
.	.	.	.
.	.	.	.
.	.	.	.
gene37	0	37	35
gene38	0	38	36
gene39	0	39	37
gene40	0	40	39
gene41	0	41	40
gene42	0	42	41
gene43	0	43	42
gene44	0	44	43
gene45	0	45	44
gene46	0	46	46
gene47	0	47	47
gene48	0	48	48
gene49	0	49	49
gene50	0	50	50

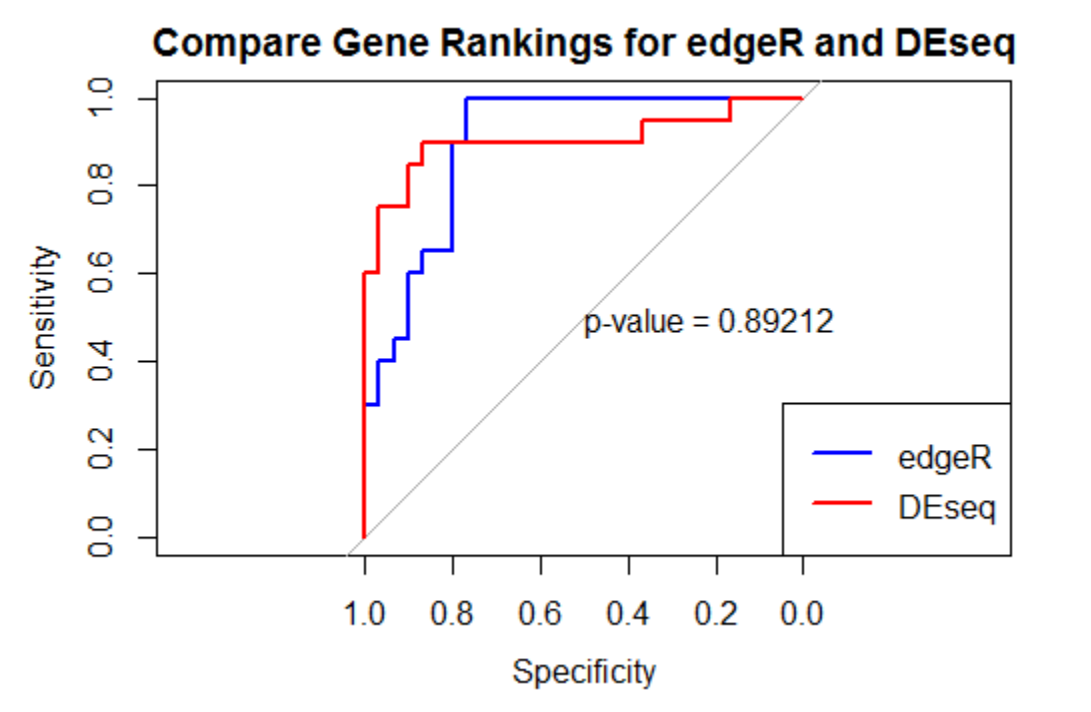
ROC CURVES FOR GENE RANKS





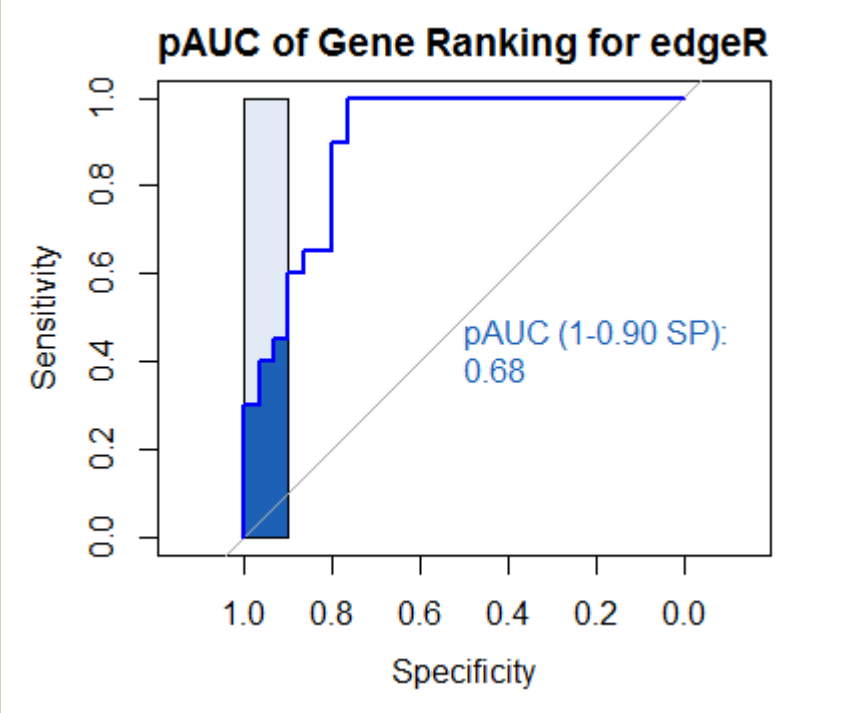
AUC = Probability that that if we randomly select one DE and one non-DE gene:
gene rank(DE gene) > gene rank (non-DE gene)

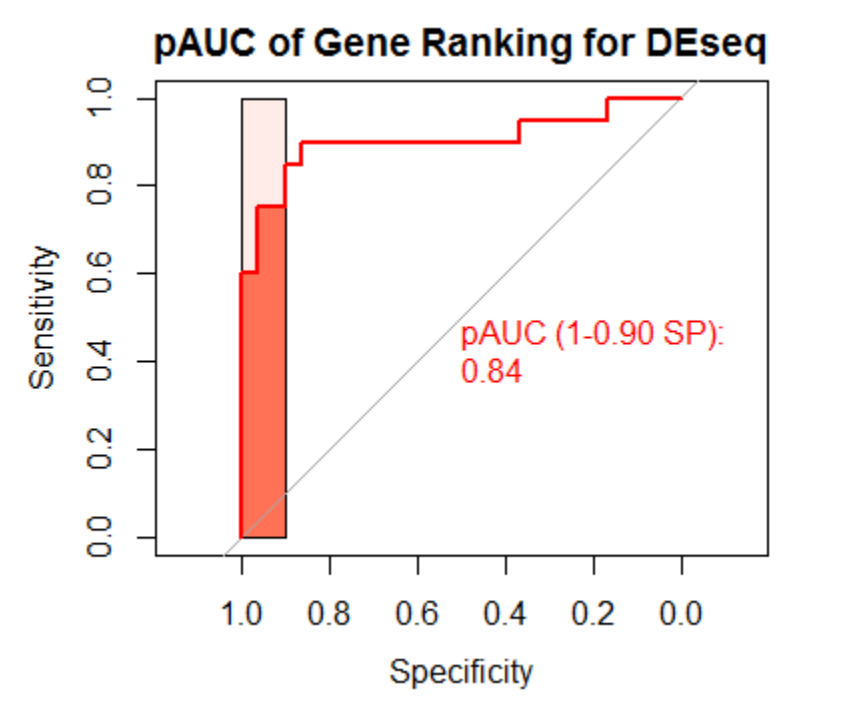
DIFFERENCES IN PERFORMANCE



Is there another way to identify differences in performance?

COMPARISON OVER SPECIFIC FPR

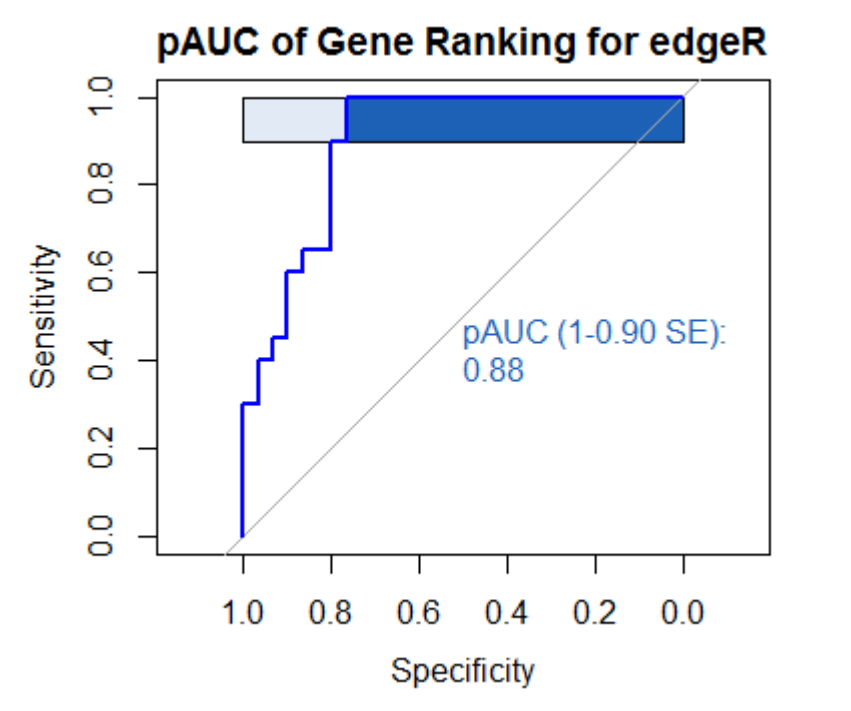


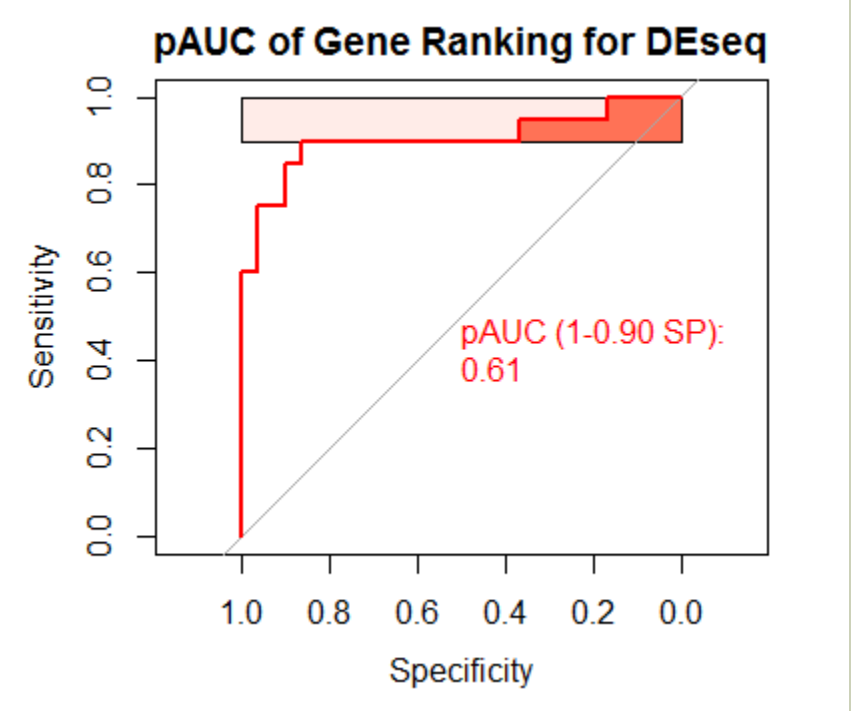


p-value for difference in pAUC= 0.001041

If we are mainly focused on maintaining a low FPR, DEseq outperforms edgeR

COMPARISON OVER SPECIFIC TPR





p-value for difference in pAUC= 0.03188

If we want to identify as many genes as possible, edgeR outperforms DEseq at a lower threshold

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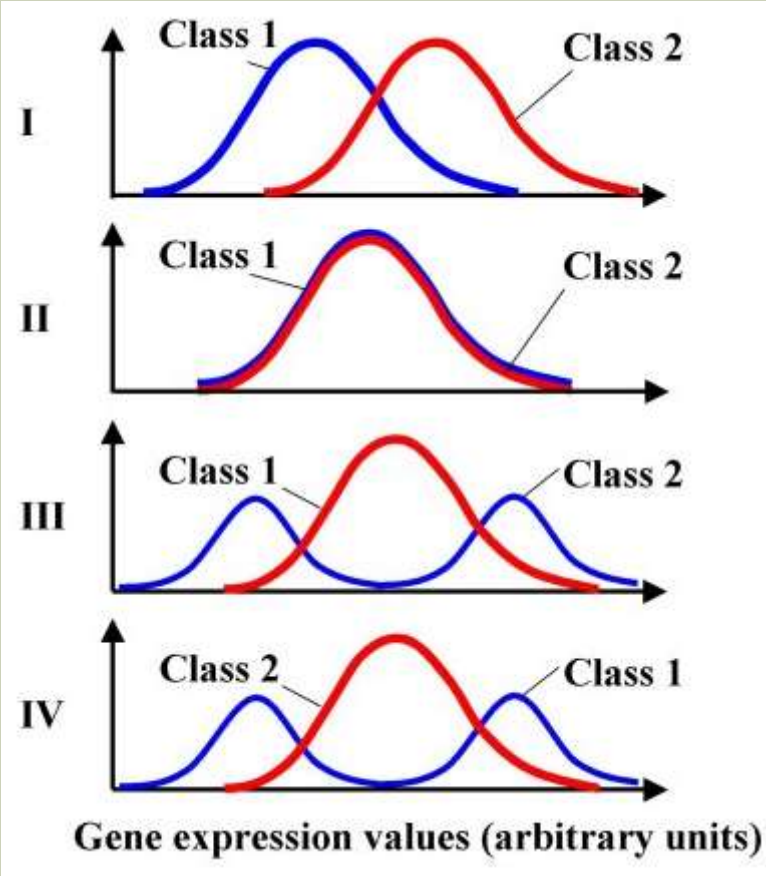
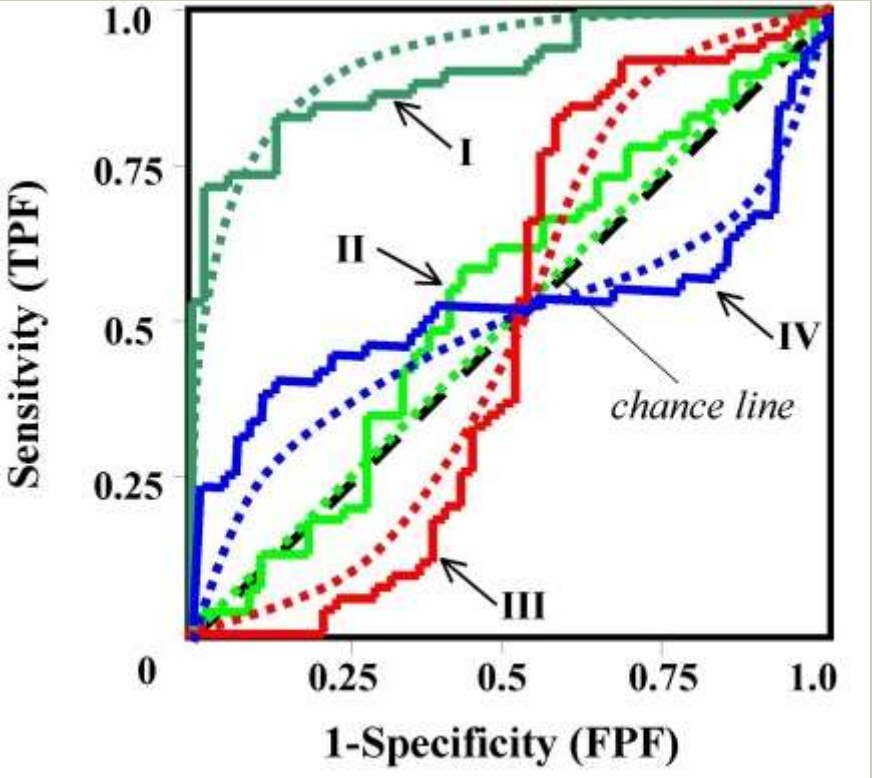
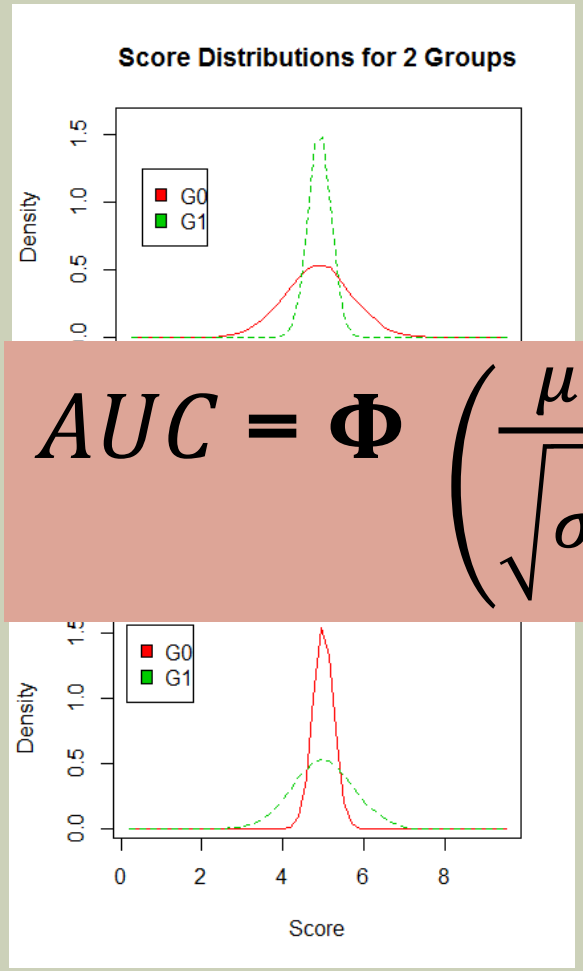
SCENARIOS FOR 'NOT-PROPER' ROC CURVES



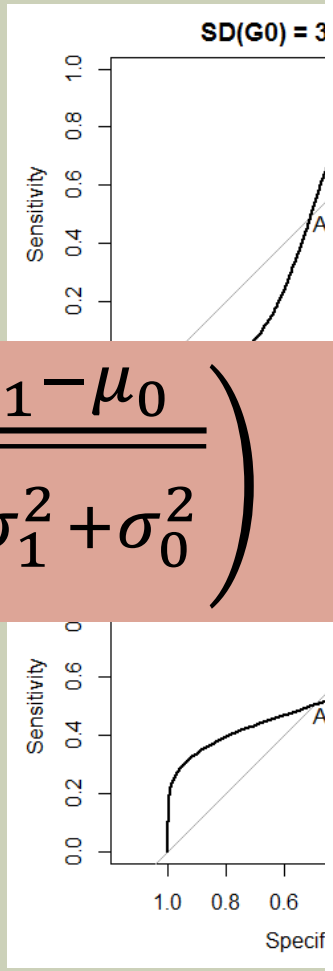


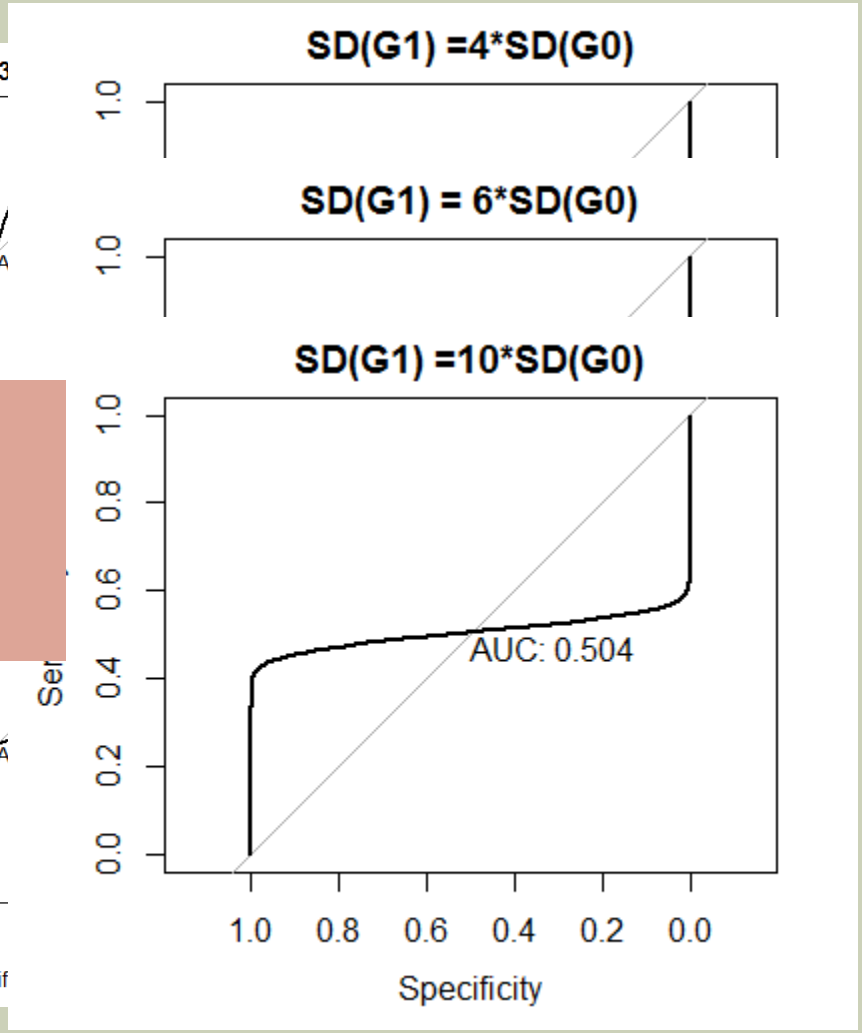
Parodi *et al. BMC Bioinformatics* 2008 9:410 doi:10.1186/1471-2105-9-410

SIMPLIFIED SCENARIO: SAME MEAN, DIFFERENT SD'S



$$AUC = \Phi\left(\frac{\mu_1 - \mu_0}{\sqrt{\sigma_1^2 + \sigma_0^2}}\right)$$





ANALYSIS WITH NOT-PROPER ROCS

- Rationale: If there is no difference in mean measurement between groups, we are 'constrained' to have AUC = 0.50
  - Useful if difference in measurements between groups is not reflected by an *overall* difference in means.
  - Can account for bimodal distributions, 'nested' distributions
  - May capture unique aspects of biological variability
- ABCR = area between the ROC curve and the rising diagonal
- *TNRC* = Test for Not-proper ROC Curves

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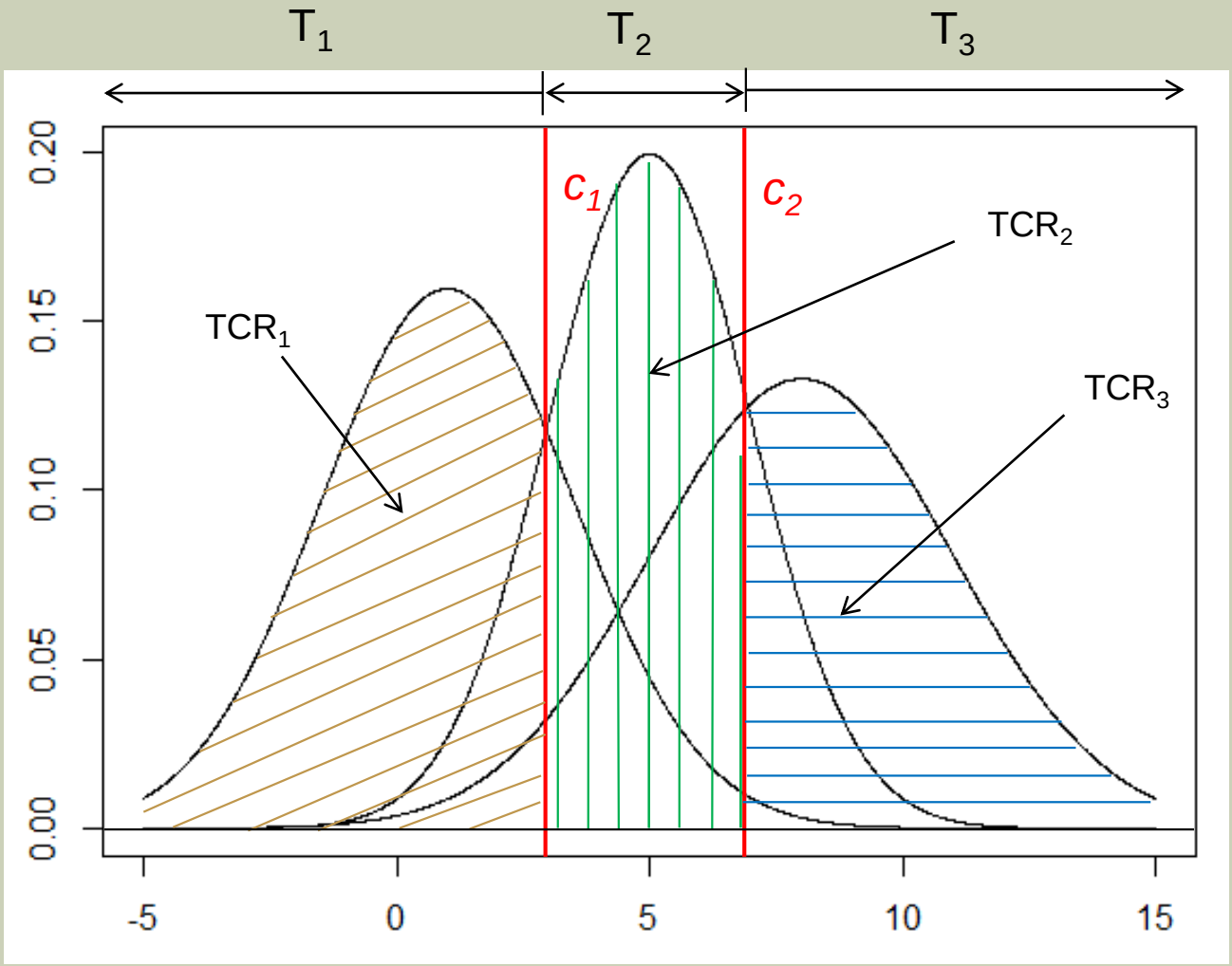
MULTI-CLASS ROC

- Oftentimes, category labels are made binary for ease of interpretation and/or analysis
  - Ex) [cancer, no cancer], [normal, abnormal], [positive, negative]
- Traditional ROC methods adhere to this 'rule'
  - If there is more than one class we are interested in, we have to 'force dichotomization' by combining two [or more] classes
    - Ex) Types of breast cancer (LA, LB, HER2, Basal) would all be classified as cancer if compared to normal
- Multi-class ROC methods are natural extensions of traditional methods
  - Instead of area [under the curve], we are interested in volume under the surface (VUS, 3-classes) or hypervolume under the manifold (HUM, more than three classes)
  - Baseline value for comparison:

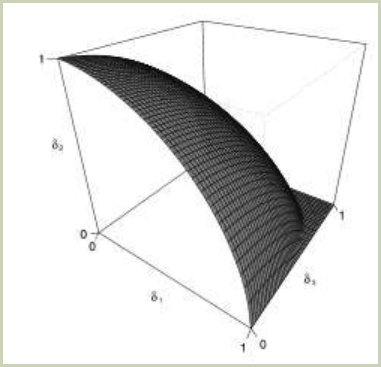
$$\frac{1}{k!} \text{ where k = number of classes}$$



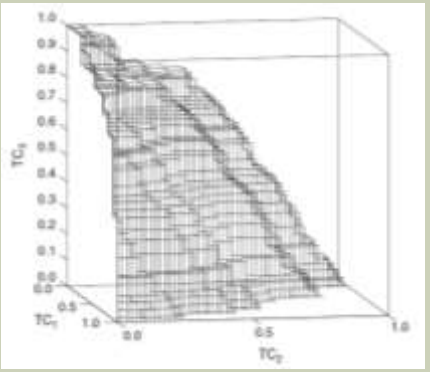
Instead of TPR and FPR, we are concerned with the **three** true classification rates (TCR) for any two cutoff points (c_1, c_2), where $c_1 < c_2$

VOLUME UNDER THE SURFACE

- Each possible pair of cutoff points yields a triplet of true classification rates
  - Triplet is coordinates for point in 3-D space
  - Points are plotted and connected to form an ROC surface

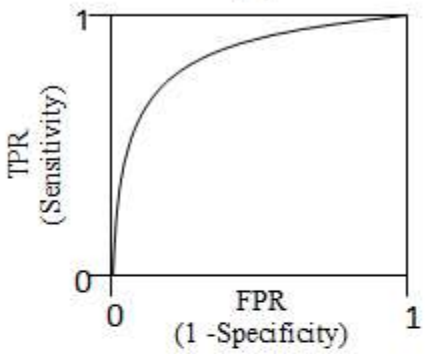
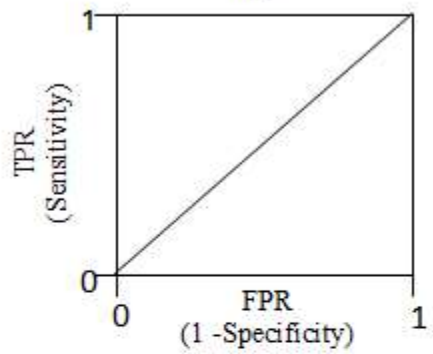
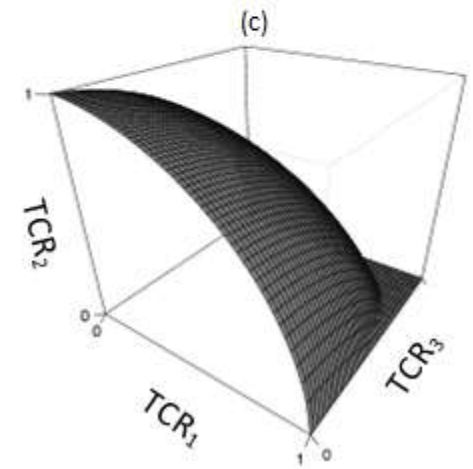
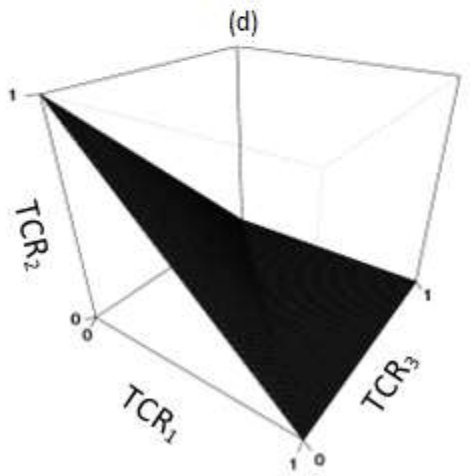


Parametric (Kang & Tian 2013)



Non-Parametric (Nakas & Yiannoutsos 2004)

  - Volume under the ROC surface (VUS) is analogous to AUC
  - VUS of $\frac{1}{6}$ (≈ 0.167) indicative of random class assignment

	Good Classification	Classification no better than random assignment
2-Way ROC	(a)  	(b) 
	AUC = 0.80	AUC = 0.50
3-Way ROC	(c)  	(d) 
	VUS = 0.54	VUS = 0.17

Note: (c) and (d) adapted from (Kang & Tian 2013)

EXAMPLE: MICROSATELLITE INSTABILITY IN COLON CANCER

- Microsatellite instability (MSI) has been associated with colon cancer. Results from a panel of genetic markers are used to determine MSI status on three levels:
    1. MSS: microsatellite stable, no markers detected
    2. MSI-L: MSI-Low; at least 1 but < 30% across panel
    3. MSI-H: MSI-High; > 30% mutation rate across panel
  - I read a paper (*Molecular Cancer* 2007, 6:54) that says they found a gene that is upregulated in MSI-H vs. MSS-type tumors (they dichotomized their data)
    - I want to see if these findings also apply to tumor samples and extend to a three-level classification system.

Gene: SECTM1

Data: Colon adenocarcinomas from TCGA

Pubmed source= TCGA_COAD_exp_HiSeqV2

EXAMPLE: MICROSATELLITE INSTABILITY IN COLON CANCER

[Edited] Raw Data Summary:

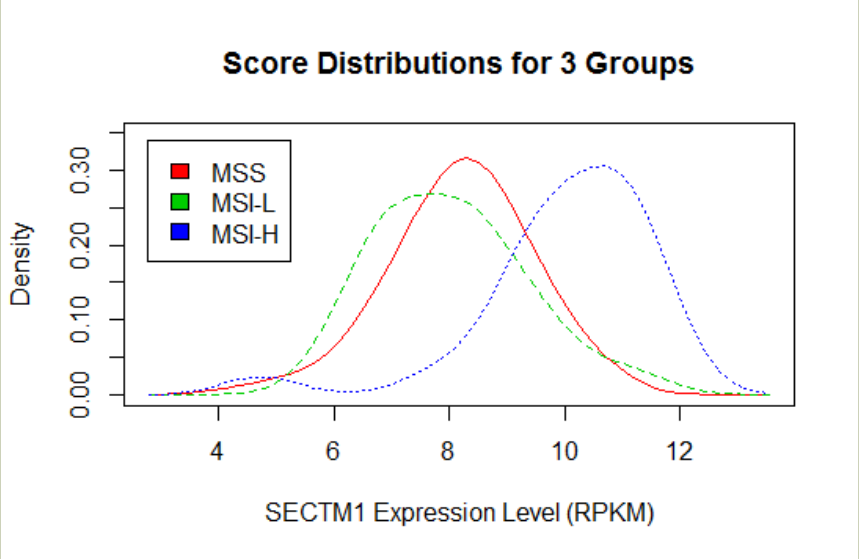
		n	mu	sd
Level 1:	MSS	98	8.21	1.17
Level 2:	MSI-L	25	8.03	1.29
Level 3:	MSI-H	25	10.05	1.49

VUS=0.3419, 95% CI=[0.2258, 0.457]

Best cut-points: lower(c_1)=8.0439, upper(c_2)=9.3773

The group correct classification probabilities are

MSS	MSH-L	MSH-H
0.4184	0.6429	0.8000



VUS = Probability that if we choose at random one MSS, MSI-L and MSI-H sample:

$$SECTM1_{MSS} < SECTM1_{MSI\text{-}L} < SECTM1_{MSI\text{-}H}$$

EXAMPLE: MICROSATELLITE INSTABILITY IN COLON CANCER

[Edited] Raw Data Summary:

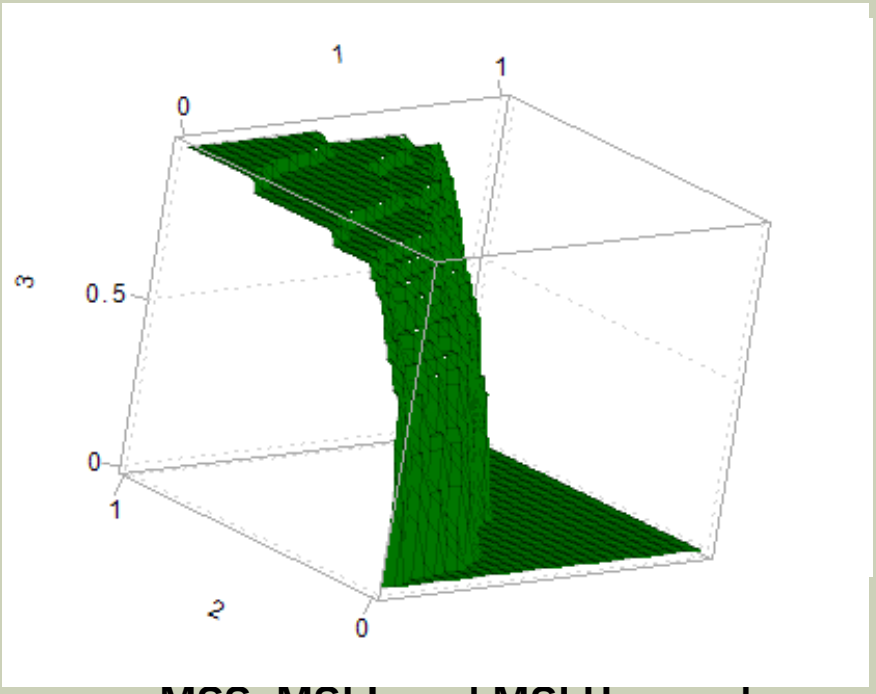
		n	mu	sd
Level 1:	MSI-L	25	8.03	1.29
Level 2:	MSS	98	8.21	1.17
Level 3:	MSI-H	25	10.05	1.49

VUS(new)=0.4692, 95% CI=[0.3289, 0.6017]
VUS(old)=0.3419

Best cut-points: lower(c_1)=7.4214, upper(c_2)=9.3773

The group correct classification probabilities are

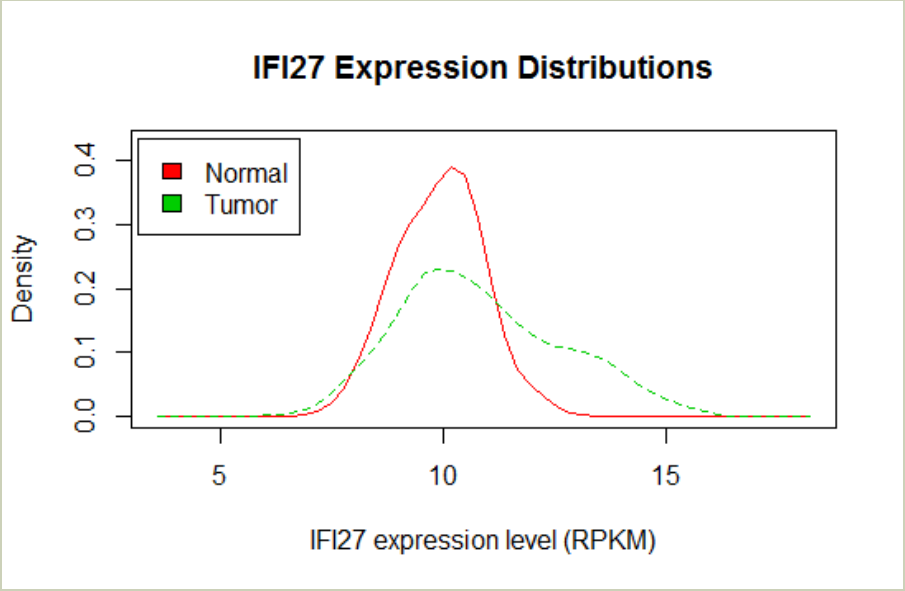
MSS	MSH-L	MSH-H
0.4184	0.4400	0.8000



VUS = Probability that if we choose at random one MSS, MSI-L and MSI-H sample:

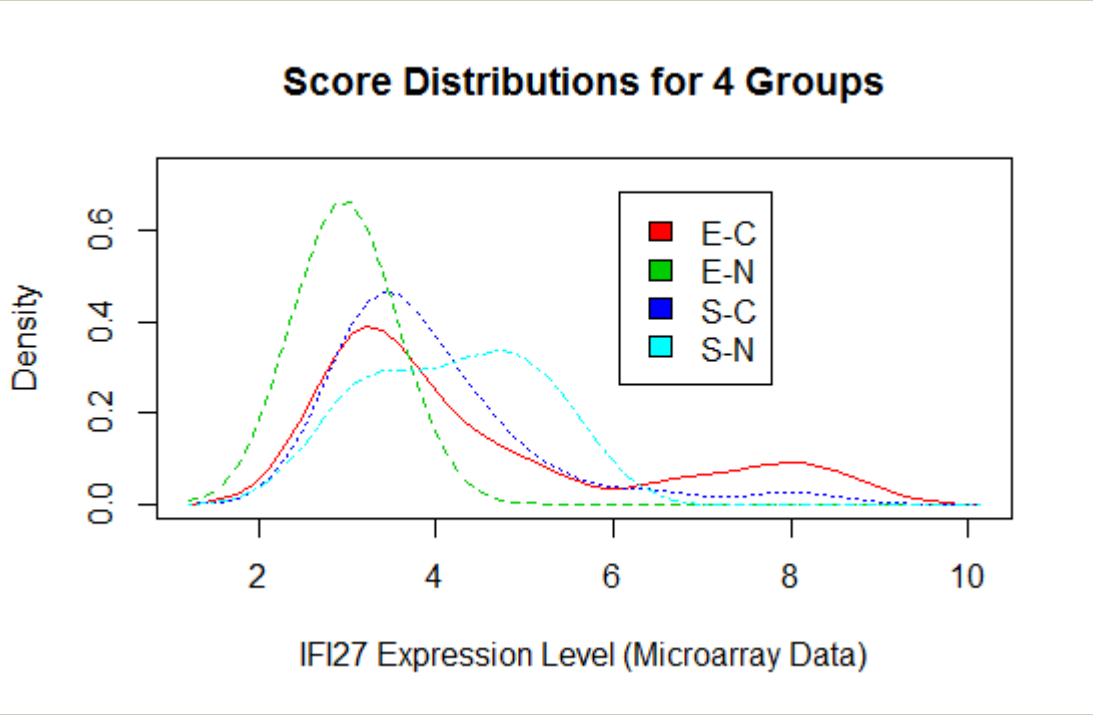
$$SECTM1_{MSI\text{-}L} < SECTM1_{MSS} < SECTM1_{MSI\text{-}H}$$

SOMETHING TO CONSIDER: REMEMBER IFI27?



- The original AUC was not very impressive, but levels are moderately higher in tumors
  - Brief literature review yields info that IFI27 upregulation has been implicated in epithelial cancer cells.
  - Can we gain further insight if we stratify by cell type?
  - We can't do this with the TCGA data, but Genomics Portal has a different data set I can use
    - Tumor and normal tissue samples classified as either epithelial or squamous
    - PubMed source= GSE10797,

SOMETHING TO CONSIDER: REMEMBER IFI27?



- Heterogeneity of BC adds 'noise' to the ROC analysis
  - Keeping in mind small sample size, a few sources in this case include:
    - Higher levels of IFI27 measured in normal stromal cells
    - An 'island' of cancerous epithelial cells with marked IFI27 upregulation

J Surg Res. 2015 Jan;193(1):255-64. doi: 10.1016/j.jss.2014.06.055. Epub 2014 Jul 5.

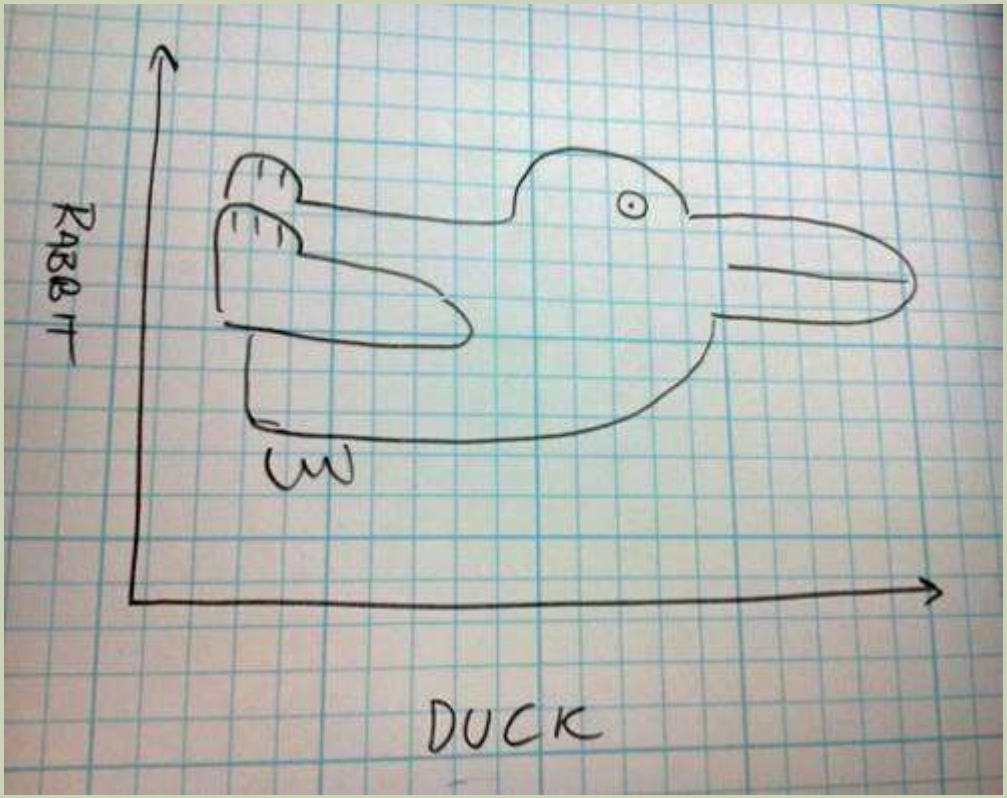
Interferon alpha-inducible protein 27 promotes epithelial-mesenchymal transition and induces ovarian tumorigenicity and stemness.

Li S[1], Xie Y[2], Zhang W[3], Gao J[4], Wang M[1], Zheng G[1], Yin X[1], Xia H[5], Tao X[6].

SUMMARY OF ROC ANALYSIS

- Flexible tool for evaluating classification models
  - Provides statistical and graphical measures of overall accuracy
  - Yields optimal cutoff values for prediction
- Some considerations for use in functional genomics:
  - Heterogeneity of biological data
    - We are using relatively simple methods but dealing with appreciably complex phenomena
  - Unequal sample sizes for groups
    - Generally more cancer samples than normal samples
    - More genes are non-DE vs DE (when considering ranking systems)
- This is only the tip of the iceberg!
  - Bayesian methods, semi-parametric methods, misclassification costs, training/validation issues, multivariable models…

QUESTIONS?



http://stats.stackexchange.com/questions/423/what-is-your-favorite-data-analysis-cartoon?page=2&tab=votes#tab-top