Receiver Operating Characteristic Analysis (II)

11.6 Method of Generating "Smooth" ROC Curves

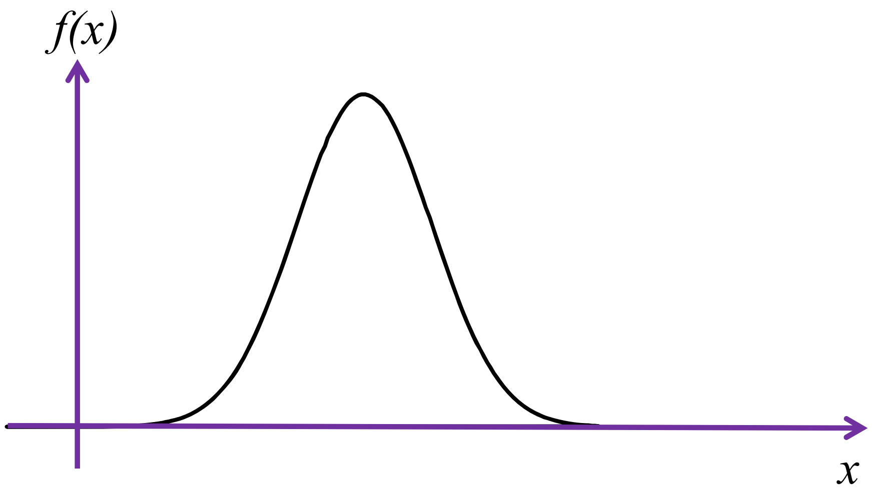
(1) Introduction

- Recall Handout #11 ROC Part I, we have learned the method of generating an empirical ROC curve with discrete rating scales.
- These discussions and exercises provide a conceptual understanding of ROC analyses.
- In the following, we will study the algorithm of generating conventional "smooth" ROC curves based on binormal distribution model, with maximum likelihood estimation.

(2) Review of Statistics: Normal Distribution and Standard Normal Distribution

(a) The basics of normal distribution

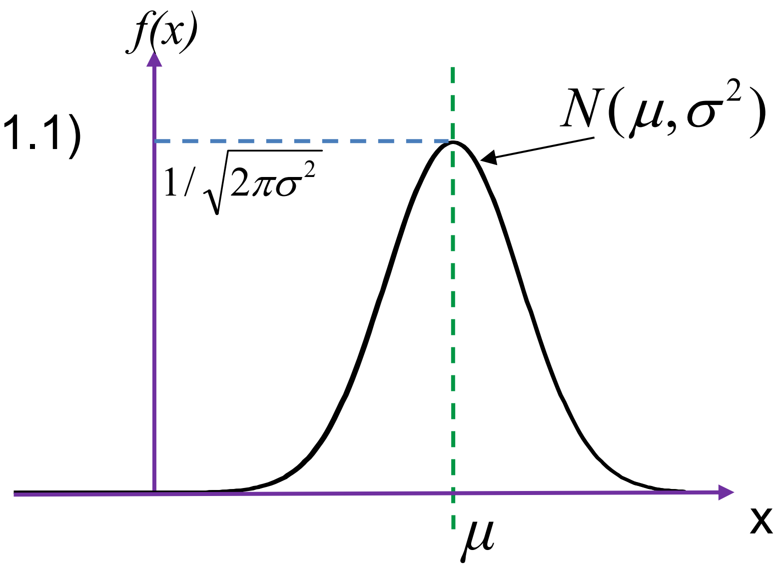
- Perhaps the most common distribution used in statistical practice is the normal distribution (or Gaussian distribution), the familiar bell-shaped curve, as seen in following figure.
- Many clinical measurements follow normal or approximately normal distributions.



(b) The probability density function

- The normal distribution is a continuous probability distribution that describes data that cluster around a **arbitrary center (mean or average)** μ, with **variance** σ^2, abbreviated as $N(\mu, \sigma^2)$.
- **The probability density function** for such distribution is given by the formula:

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \times e^{-(x-\mu)^2/2\sigma^2} \qquad (11.1)$$



where:

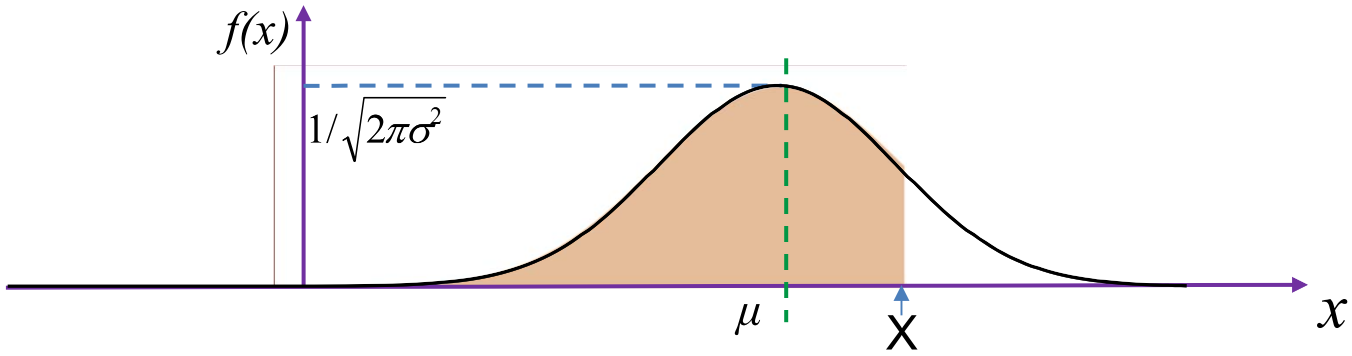
μ: is mean or expectation of the normal distribution.

σ: is standard deviation

σ²: is variance

(c) The cumulative distribution function (CDF)

- The **cumulative distribution function (CDF)** of the normal distribution gives **the area** under the probability density function, from **-∞** to **X.** It equals to **probability**.



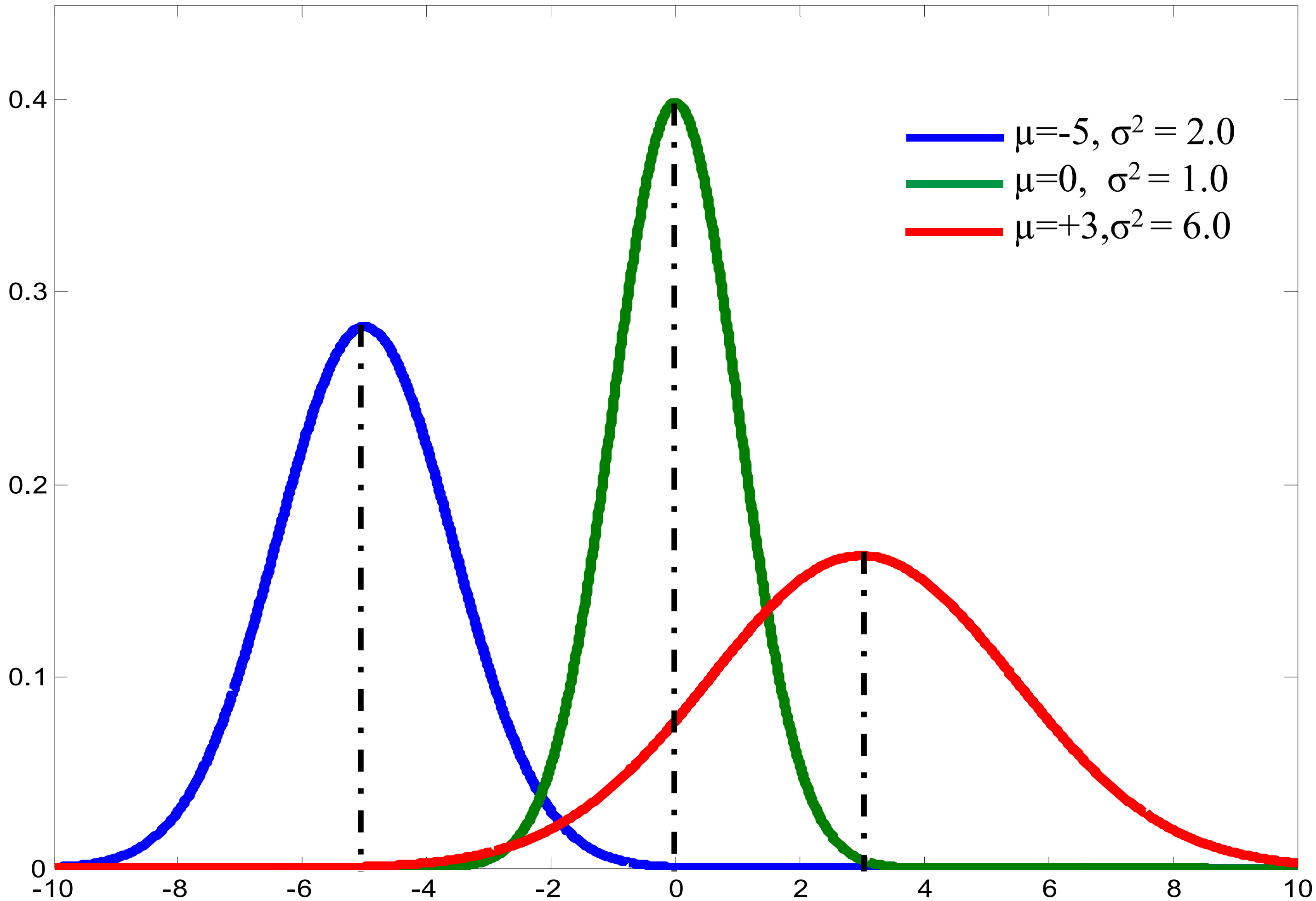
- It can be computed as an integral of the probability density function:

$$\Phi(X) = \int_{-\infty}^{X} \frac{1}{\sqrt{2\pi\sigma^2}} \times e^{-(x-\mu)^2/2\sigma^2} \times dx \qquad (11.2)$$

- The total area under the normal distribution is 1:

$$\Phi(\infty) = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi\sigma^2}} \times e^{-(x-\mu)^2/2\sigma^2} \times dx = 1$$

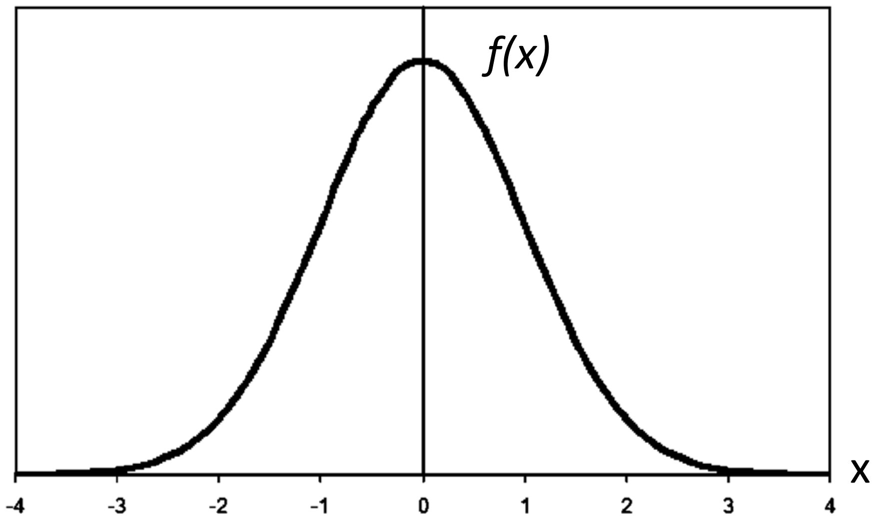
❖ The following figure shows a few **normal distributions** with different mean and variance values.



(d) The standard normal distribution

- **The standard normal distribution** is a special case of **normal distribution** with **mean** μ=0 and **variance** σ^2 =1, can be abbreviated as $N(0, 1)$.
- **The probability density function** of standard normal distribution can be described as:

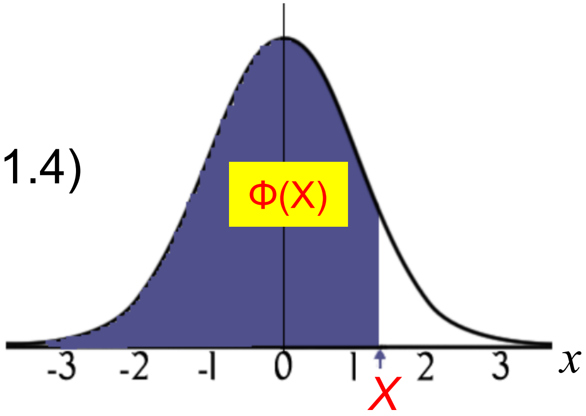
$$f(x) = \frac{1}{\sqrt{2\pi}} \times e^{-x^2/2} \qquad (11.3)$$



(e) The CDF of standard normal distribution

❖ The **cumulative distribution function (CDF)**, Φ(X), of the standard normal distribution can be computed as:

$$CDF = \Phi(X) = \int_{-\infty}^{X} \frac{1}{\sqrt{2\pi}} \times e^{-x^2/2} \times dx \quad (11.4)$$

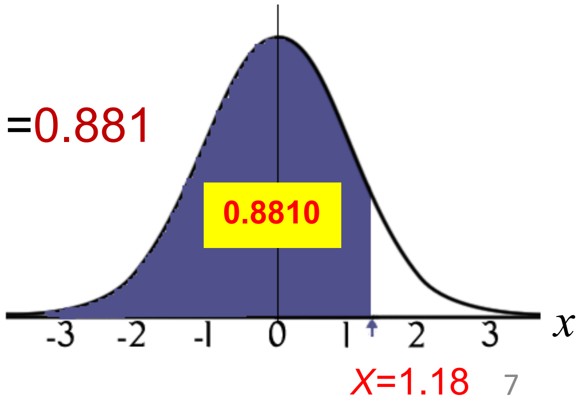


❖ The value of CDF can be determined by using Excel or Matlab, by following commands.

❖ Assume that X=1.18:

In Excel command: =NORMSDIST(1.18); then result =0.881

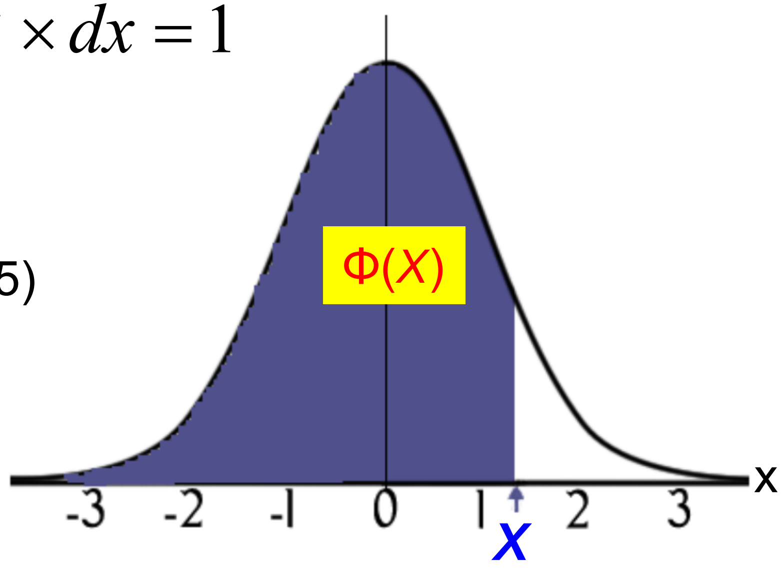
In Matlab program: A=normcdf(1.18); then A =0.8810;



(f) The properties of standard normal distribution

- The total area under the standard normal distribution is 1:

$$\Phi(\infty) = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}} \times e^{-x^2/2} \times dx = 1$$



- Symmetry: for a real number ***X*****,**

$$\Phi(-X) = 1 - \Phi(X) \qquad (11.5)$$

- Inverse Function: for a real number ***X*****,**

$$CDF = \Phi(X)$$

$$\Rightarrow X = \Phi^{-1}(CDF) \qquad (11.6)$$

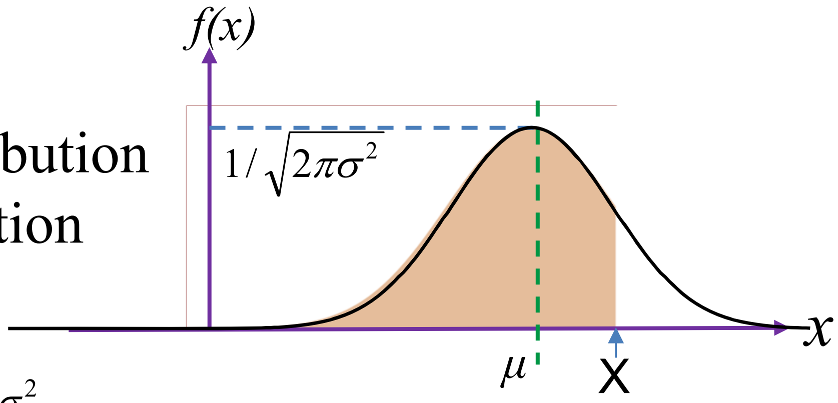
where: Φ^{-1}(CDF) is the inverse function of $\Phi(X)$

- Assume that *CDF*=**0.8810**, the ***X*** value can also be determined by using Excel or Matlab, by following commands.

In Excel command: =NORMSINV(0.8810); then result =1.18

In Matlab program: B=norminv(0.8810); then B =1.1800**;**

(g) Standardize normal distribution



- Recall Eq (11.2), the cumulative distribution function (CDF) of the normal distribution $N(\mu, \sigma^2)$ is described as:

$$\Phi(X) = \int_{-\infty}^{X} \frac{1}{\sqrt{2\pi\sigma^2}} \times e^{-(x-\mu)^2/2\sigma^2} \times dx$$

Let:

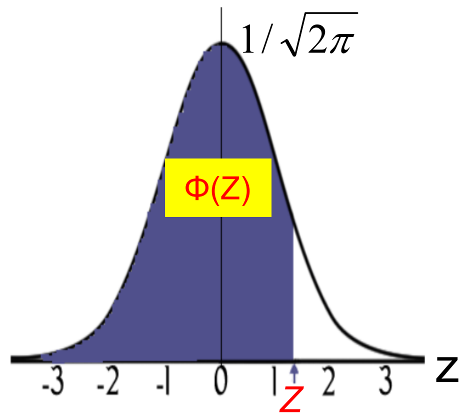
$$z = \frac{x-\mu}{\sigma} \quad \text{and} \quad Z = \frac{X-\mu}{\sigma}$$

- The CDF of normal distribution can be expressed in the same formula as the CDF of the standard normal distribution:

$$\Phi(Z) = \int_{-\infty}^{Z} \frac{1}{\sqrt{2\pi}} \times e^{-z^2/2} \times dz \qquad (11.7)$$

or

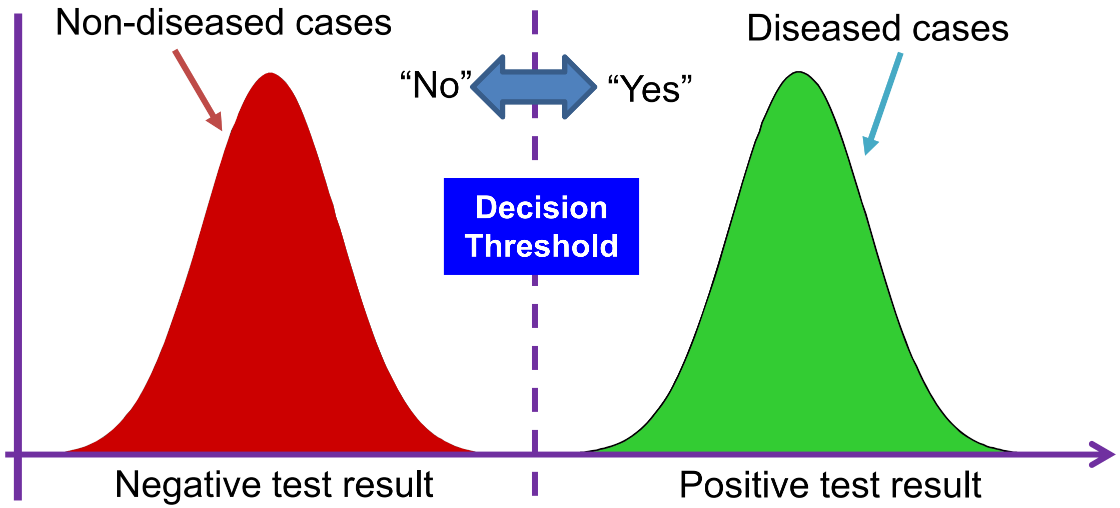
$$\Phi\left(\frac{X-\mu}{\sigma}\right) = \int_{-\infty}^{\frac{X-\mu}{\sigma}} \frac{1}{\sqrt{2\pi}} \times e^{-\left(\frac{x-\mu}{\sigma}\right)^2/2} \times d\left(\frac{x-\mu}{\sigma}\right) \qquad (11.8)$$



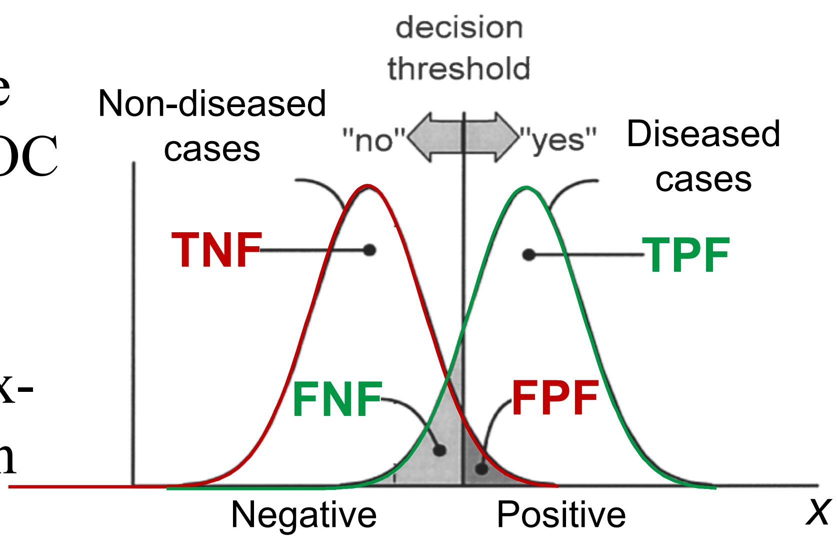
(3) The Binormal Distribution and ROC Analysis

(a) Binormal distribution

- ❖ ROC analysis based on the binormal distribution can be employed to assess clinical diagnosis performance.
- ❖ The binormal distribution includes two normal distributions: one for the test results of those who with **non-diseased cases** and the other for the test results of those who with **diseased cases**.

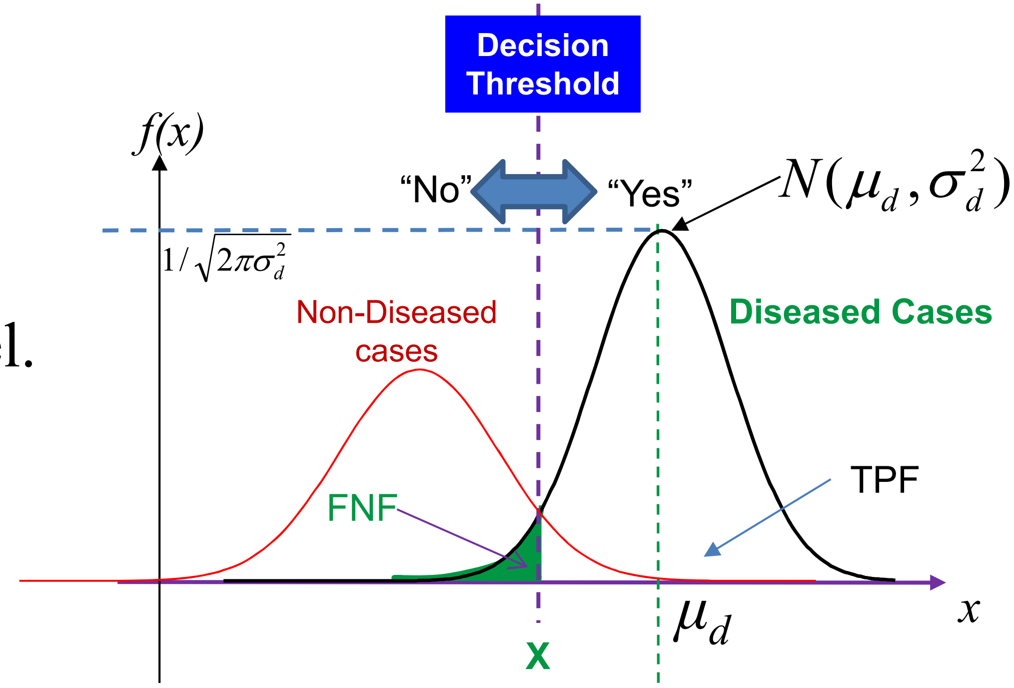


- In most medical imaging applications, overlap occurs between non-diseased and diseased findings, and thus these curves have overlap.
- In such cases, the diagnostician sets his or her own decision threshold. Patients to the right of the decision threshold are considered positive, and patients to the left of the threshold are considered negative.
- When the threshold is set, the **true positive fraction (TPF)**, **true negative fraction (TNF)**, **false positive fraction (FPF)**, and **false negative fraction (FNF)** can be determined.
- These values can be used to compute sensitivity and specificity, which can be employed to define one point on the ROC curve.
- To compute the entire ROC curve, the threshold needs to be swept across the x-axis, which will lead to the computation of many pairs of points needed to draw the entire ROC curve.



(b) The diseased cases

- At first, considering the **diseased cases** normal distribution $N(\mu_d, \sigma_d^2)$ in binormal distribution model.
- Recall Eq.11.8, the **cumulative distribution function** of the diseased cases normal distribution $N(\mu_d, \sigma_d^2)$ can be described in the form of the **standard normal distribution**:



$$\Phi\left(\frac{X-\mu_d}{\sigma_d}\right) = \int_{-\infty}^{\frac{X-\mu_d}{\sigma_d}} \frac{1}{\sqrt{2\pi}} \times e^{-\left(\frac{x-\mu_d}{\sigma_d}\right)^2/2} \times d\left(\frac{x-\mu_d}{\sigma_d}\right) \quad (11.9)$$

❖ Recall discussions about **FNF** and **TPF** (Handout 11.2), **CDF** (Handout 11.6 (2)(c)) and properties of standard normal distribution (Handout 11.6 (2)(f)), we have :

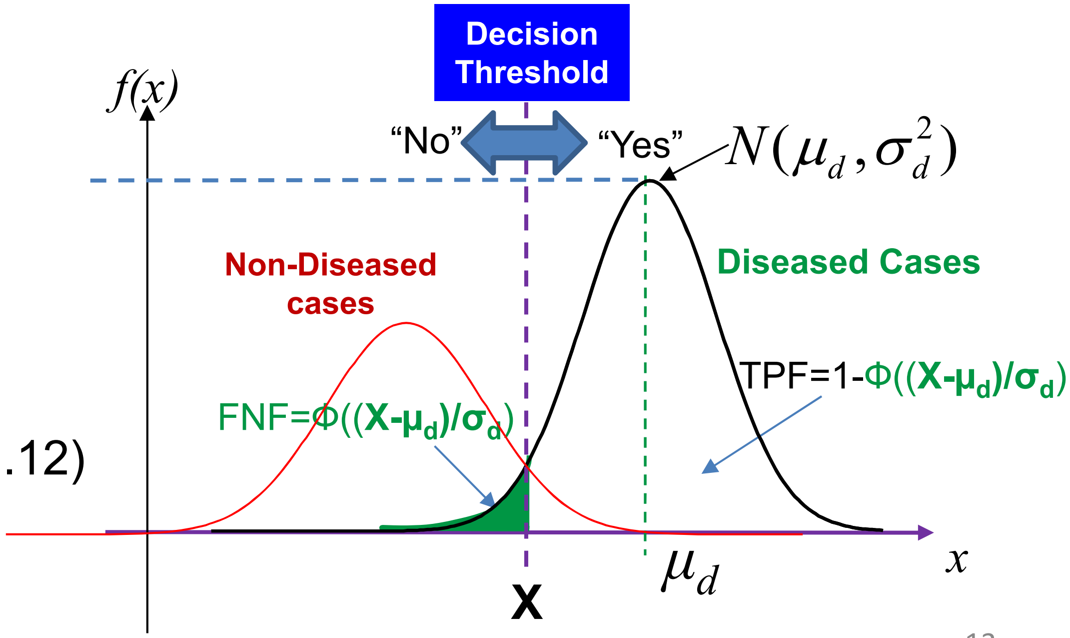
$$FNF = \frac{FN}{FN+TP} = \Phi\left[\frac{X-\mu_d}{\sigma_d}\right] \qquad (11.10)$$

$$TPF = \frac{TP}{FN+TP} = 1 - FNF = 1-\Phi\left[\frac{X-\mu_d}{\sigma_d}\right] = \Phi\left[\frac{\mu_d - X}{\sigma_d}\right] \qquad (11.11)$$

❖ Then

$$\because TPF = \Phi\left(\frac{\mu_d - X}{\sigma_d}\right)$$

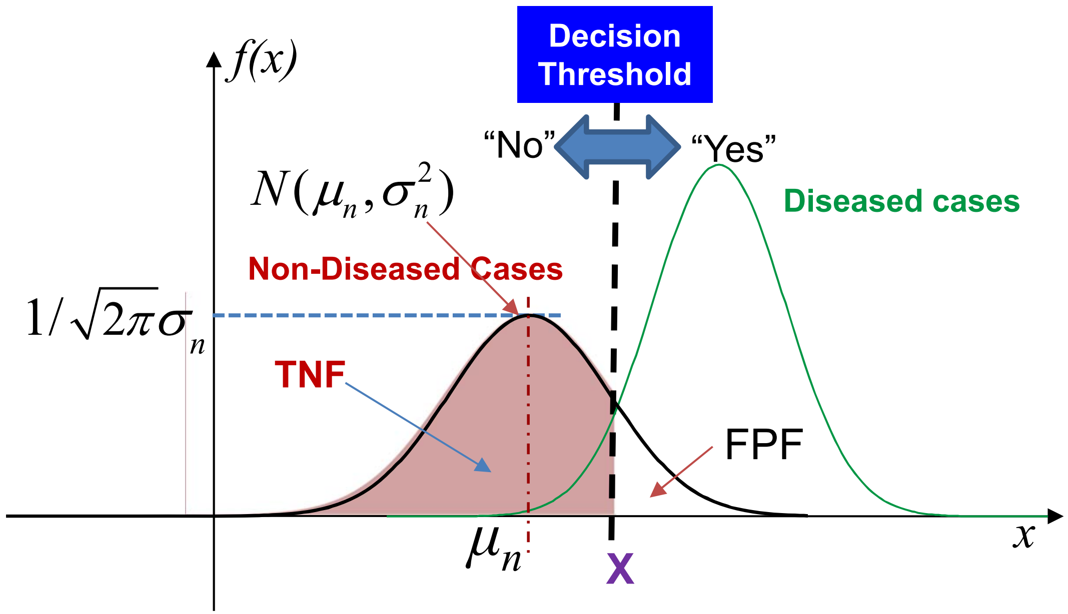
$$\therefore \Phi^{-1}(TPF) = \frac{\mu_d - X}{\sigma_d} \qquad (11.12)$$



(c) The non-diseased cases

❖ Similar to the **disease cases**, the cumulative distribution function of the **non-diseased cases** normal distribution $N(\mu_n, \sigma_n^{\ 2})$ can be described in the form of the **standard normal distribution** as:

$$\Phi\left(\frac{X-\mu_n}{\sigma_n}\right) = \int_{-\infty}^{\frac{X-\mu_n}{\sigma_n}} \frac{1}{\sqrt{2\pi}} \times e^{-\left(\frac{x-\mu_n}{\sigma_n}\right)^2/2} \times d\left(\frac{x-\mu_n}{\sigma_n}\right) \qquad (11.13)$$



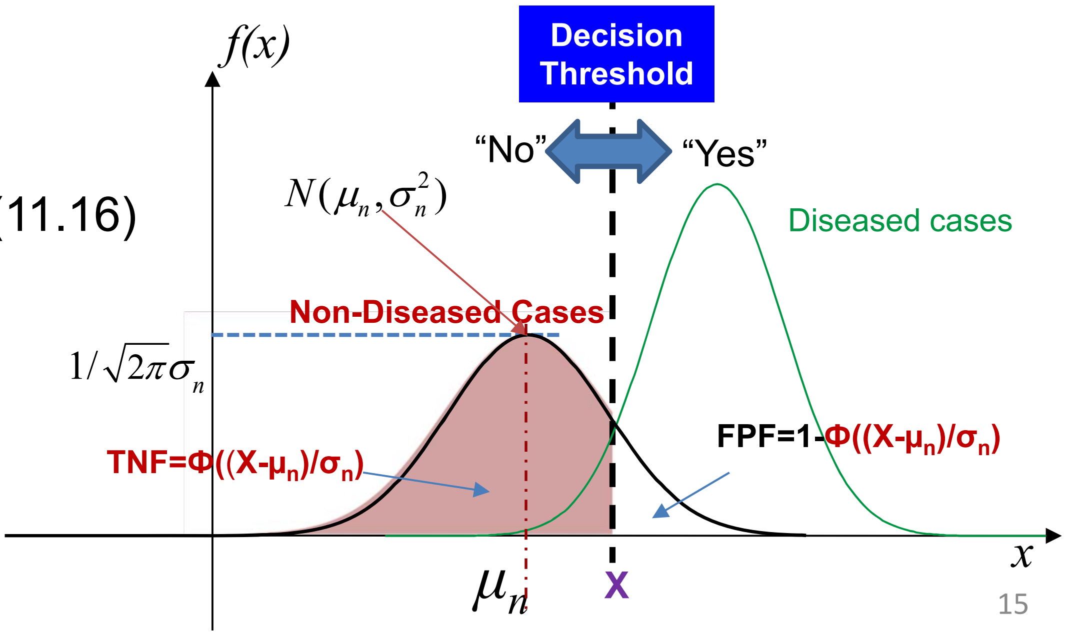
❖ Also, we have:

$$TNF = \frac{TN}{TN + FP} = \Phi\left[\frac{X - \mu_n}{\sigma_n}\right] \qquad (11.14)$$

$$FPF = \frac{FP}{TN + FP} = 1 - TNF = 1 - \Phi\left[\frac{X - \mu_n}{\sigma_n}\right] = \Phi\left[\frac{\mu_n - X}{\sigma_n}\right] \qquad (11.15)$$

❖ Therefore:

$$\Phi^{-1}(FPF) = \frac{\mu_n - X}{\sigma_n} \qquad (11.16)$$

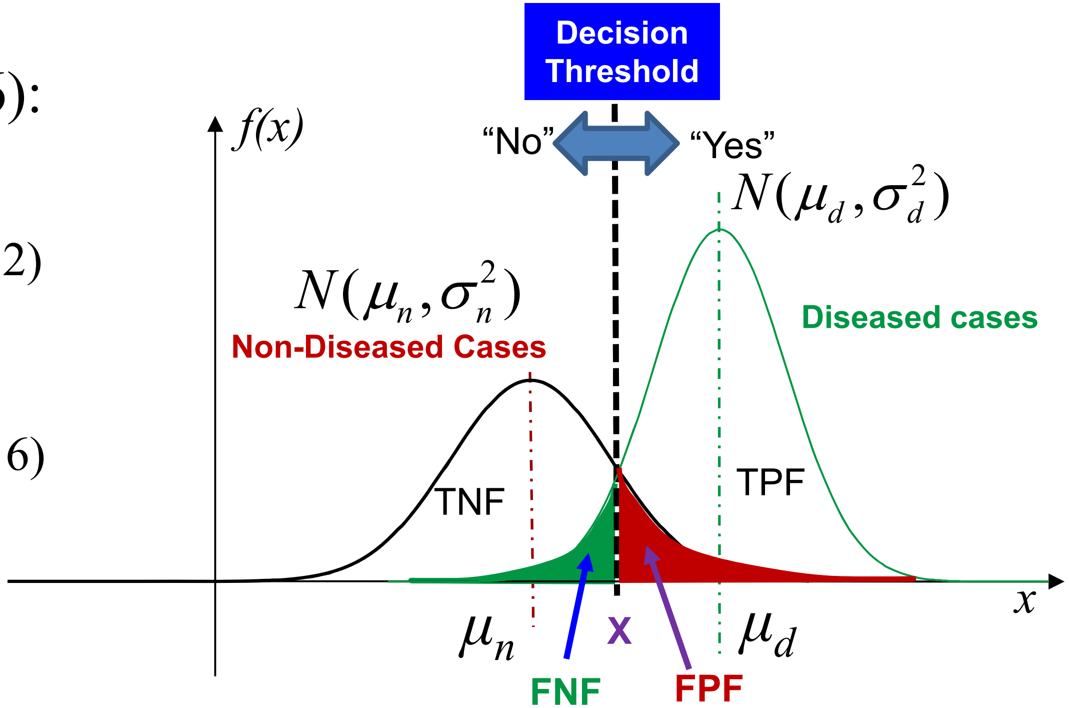


(d) Two important parameters: *a* and *b*.

❖ Recall eq. (11.12) and (11.16):

$$\Phi^{-1}(TPF) = \frac{\mu_d - X}{\sigma_d} \quad (11.12)$$

$$\Phi^{-1}(FPF) = \frac{\mu_n - X}{\sigma_n} \quad (11.16)$$



❖ **Then we have,**

$$\Phi^{-1}(TPF) = \frac{\mu_d - X}{\sigma_d} = \frac{\mu_d - \mu_n + \mu_n - X}{\sigma_d} = \frac{\mu_d - \mu_n}{\sigma_d} + \frac{\mu_n - X}{\sigma_d}$$

$$= \frac{\mu_d - \mu_n}{\sigma_d} + \frac{\sigma_n}{\sigma_d} \times \left(\frac{\mu_n - X}{\sigma_n}\right) = \frac{\mu_d - \mu_n}{\sigma_d} + \frac{\sigma_n}{\sigma_d} \times \Phi^{-1}(FPF)$$

Let,

$$a = \frac{\mu_d - \mu_n}{\sigma_d} \qquad b = \frac{\sigma_n}{\sigma_d}$$

Then:

$$\Phi^{-1}(TPF) = \left(\frac{\mu_d - \mu_n}{\sigma_d}\right) + \left(\frac{\sigma_n}{\sigma_d}\right) \times \Phi^{-1}(FPF)$$

$$= a + b \times \Phi^{-1}(FPF)$$

Finally:

$$TPF = \Phi\left[a + b \times \Phi^{-1}(FPF)\right] \qquad (11.17)$$

❖ **This is TPF vs. FPF, a binormal ROC curve.**

(e) How to determine *a* and *b:*

- From equation (11.17):

$$TPF = \Phi[a + b \times \Phi^{-1}(FPF)] \qquad (11.17)$$

- Recall the example of **Handout 11.5**, several pairs of FPF and TPF values can be determined through clinical measurements, at corresponding threshold locations. Take any two pairs of them, we have:

  - Threshold 1 (FPF_1, TPF_1) are known:

$$TPF_1 = \Phi[a + b \times \Phi^{-1}(FPF_1)]$$

$$\Rightarrow a + b \times \Phi^{-1}(FPF_1) = \Phi^{-1}(TPF_1) \qquad (11.18)$$

  - Threshold 2 (FPF_2, TPF_2) are known:

$$TPF_2 = \Phi(a + b \times \Phi^{-1}(FPF_2))$$

$$\Rightarrow a + b \times \Phi^{-1}(FPF_2) = \Phi^{-1}(TPF_2) \qquad (11.19)$$

❖ From equation (11.18) and (11.19),

$$\begin{cases} a + b \times \Phi^{-1}(FPF_1) = \Phi^{-1}(TPF_1) & (11.18) \\ a + b \times \Phi^{-1}(FPF_2) = \Phi^{-1}(TPF_2) & (11.19) \end{cases}$$

Again, $\mathbf{FPF_1}$, $\mathbf{TPF_1}$, $\mathbf{FPF_2}$ and $\mathbf{TPF_2}$ are with known values.

❖ Then we can calculate ***a*** and ***b***.

11.7 Generate ROC Curves

(1) An Example

Recall the example in Handout 11.5

- Assuming: there are a total of 200 cases, among them, 100 benign cases (no lesion) and 100 malignant cases (lesion present), an observation study resulted the following

	Sensitivity (TPF)	**Specificity (TNF)**	**FPF=1-TNF**
Point (1,1)	100/100	0/100	100/100
Threshold 1	(10+5+50+20)/100=85/100	55/100	1-55/100=45/100
Threshold 2	(5+50+20)/100=75/100	(55+15)/100=70/100	1-70/100=30/100
Threshold 3	(50+20)/100 = 70/100	(55+15+10)/100=80/100	1-80/100=20/100
Threshold 4	20/100	(55+15+10+12)=92/100	1-92/100=8/100
Point (0,0)	0/100	100/100	0/100

(2) Calculating *a* and *b*:

❖ **We use two pairs of FPF and TPF values as:**

Threshold 1 (FPF_1=0.45, TPF_1=0.85), we get:

❖ **FPF_1:** =NORMSINV(0.45)=-0.125661

$$\Phi^{-1}(FPF_1) = \Phi^{-1}(0.45) \approx -0.126$$

❖ **TPF_1:** =NORMSINV(0.85)=1.03643

$$\Phi^{-1}(TPF_1) = \Phi^{-1}(0.85) \approx 1.036$$

Threshold 2 (FPF_2=0.30, TPF_2=0.75)

❖ **FPF_2** =NORMSINV(0.30)=-0.524401

$$\Phi^{-1}(FPF_2) = \Phi^{-1}(0.30) \approx -0.524$$

❖ **TPF_2** =NORMSINV(0.75)=0.67449

$$\Phi^{-1}(TPF_2) = \Phi^{-1}(0.75) \approx 0.675$$

$$\Phi^{-1}(FPF_1) = -0.126 \qquad \Phi^{-1}(TPF_1) = 1.036$$

$$\Phi^{-1}(FPF_2) = -0.524 \qquad \Phi^{-1}(TPF_2) = 0.675$$

❖ From equation (11.18) & (11.19):

$$\begin{cases} a + b \times (-0.126) = 1.036 \\ a + b \times (-0.524) = 0.675 \end{cases}$$

$$\begin{cases} a = \dfrac{0.675 \times (-0.126) - 1.036 \times (-0.524)}{-0.126 - (-0.524)} = 1.15 \\ b = \dfrac{1.036 - 0.675}{-0.126 - (-0.524)} = 0.91 \end{cases}$$

a= 1.15, b=0.91

(3) ROCFIT Method

- ROCFIT developed by Metz et al. at the University of Chicago is a widely used computer software package for generating "smooth" ROC curves.
- ROCFIT uses a procedure of maximum-likelihood estimation (MLE) to fit both continuously-distributed (e.g., from 0 to 100) or ordinal/discrete category (e.g., five or six scale confidence-ratings) data to ROC curves.
- MLE is a statistical method of estimating population parameters from a sample.
- For more details about MLE, please refer to "W. Mendenhall and T. Sincich, <<Statistics for Engineering and the Sciences>>, Pearson, 5th edition, 2006".

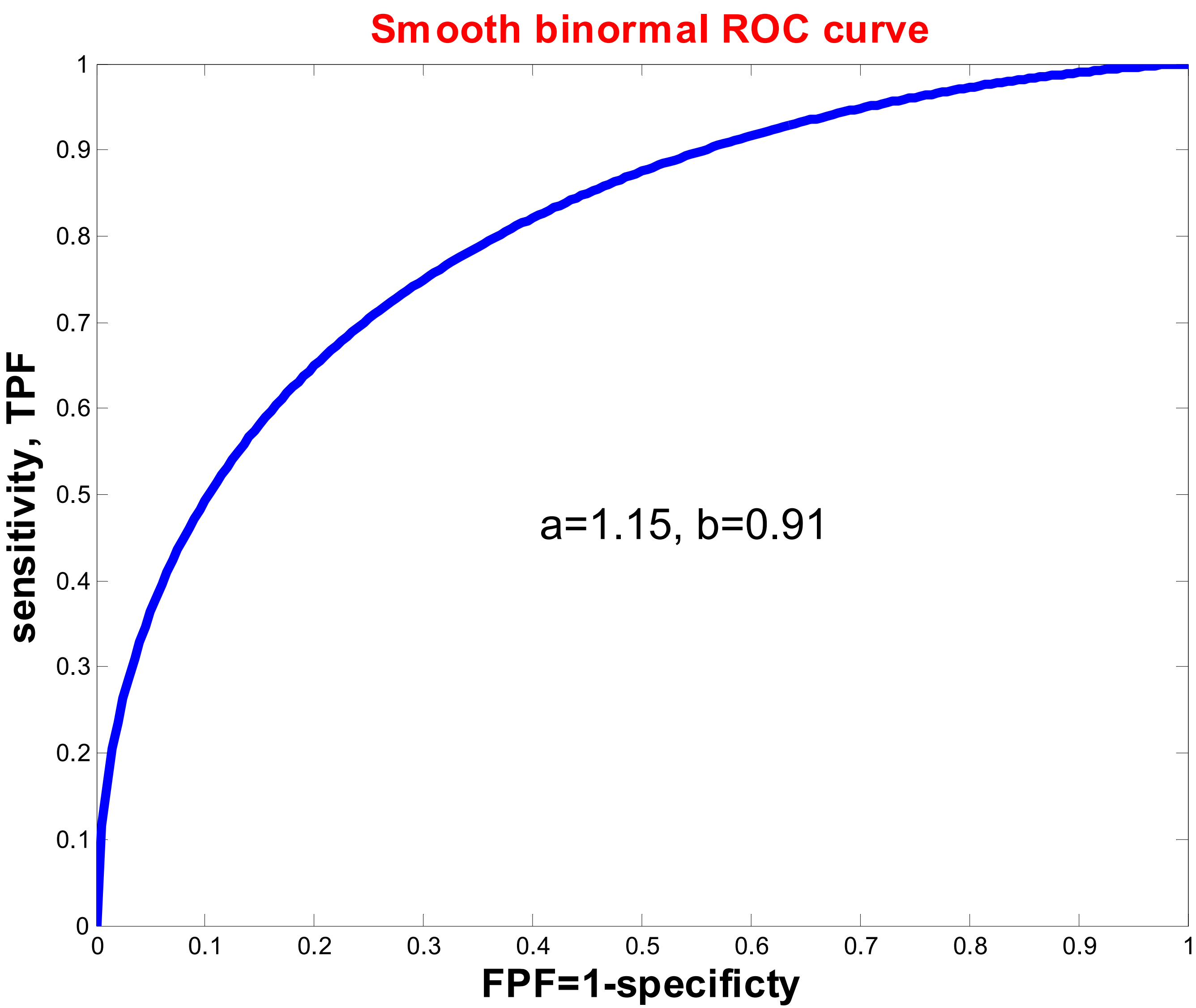
(4) A Matlab Code for Plotting Smooth ROC Curves

- ❖ The following Matlab code is developed based on the algorithm used in ROCFIT:

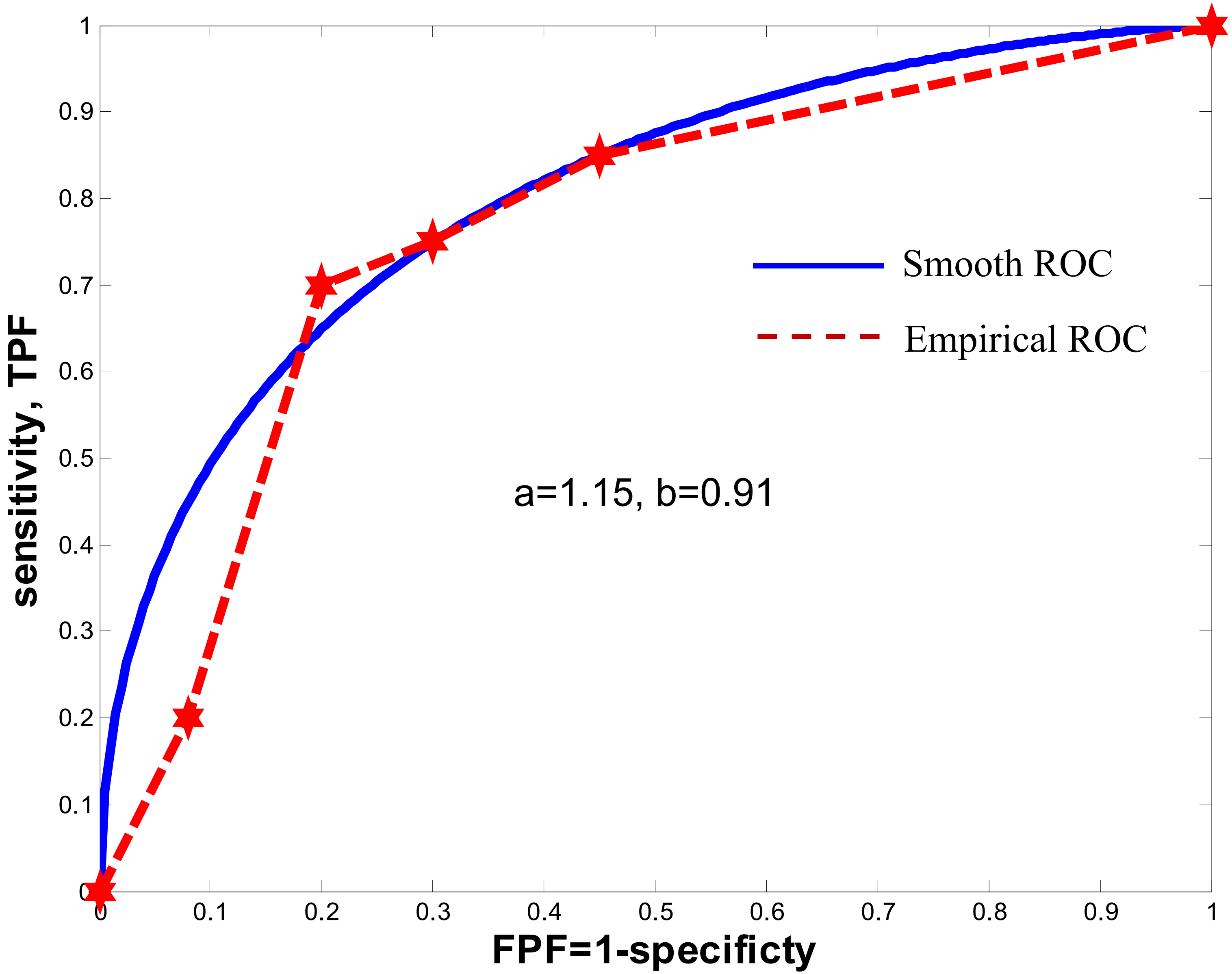
MATLAB Code

```
%1. For given two parameters a=1.15 and b=0.91
% 2.clear up the workspace and define FPF and TPF value;
clear;clc;close all;
aa=1.15; bb=0.91;
kk=1/200; % 0.005 interval;
xx=[0:kk:1]; % Setting up the FPF Value;
yy= normcdf(norminv(xx)*bb+aa); % Calculating TPF value;
% 3. plot the ROC curve
figure;
plot(xx,yy, 'LineWidth', 4);
title('Smooth binormal ROC curve','FontSize',16,'FontWeight','bold','Color','r');
xlabel('FPF=1-specificty','FontSize',16,'FontWeight','bold')
ylabel('sensitivity, TPF','FontSize',16,'FontWeight','bold');
```

❖ ROC curves by the Matlab

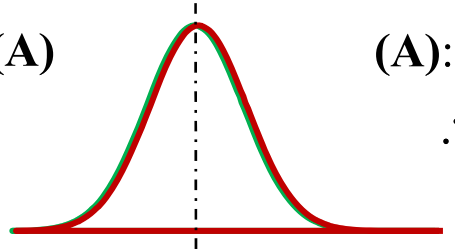


❖ Smooth and empirical ROC curves



11.8. More Discussion: Binormal Distributions & ROC Curves

(A)



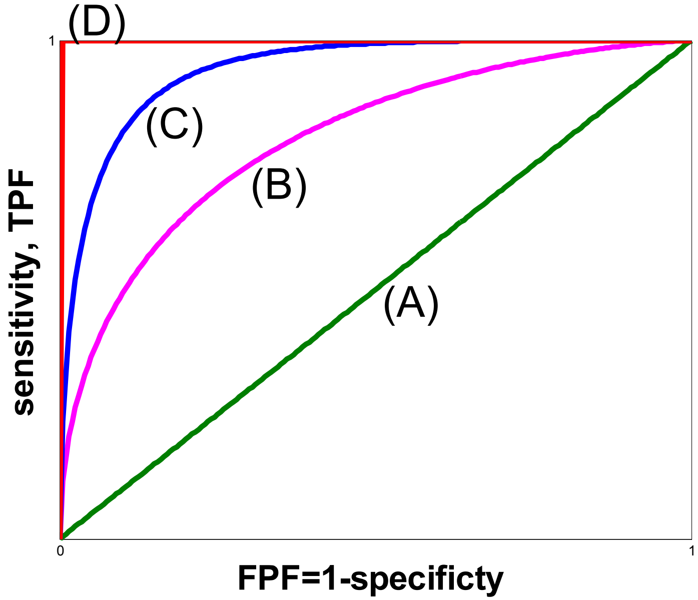
(A): $\mu_n = \mu_d$, $\sigma_n = \sigma_d$

$\therefore a = 0 \qquad b = 1$

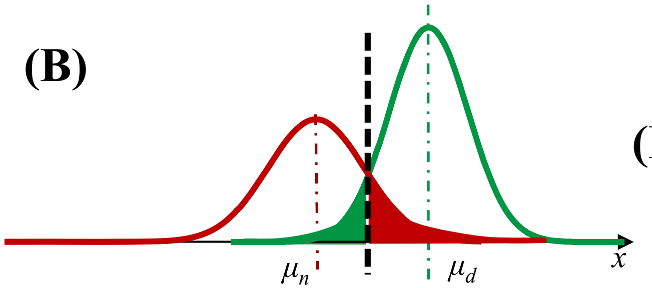
$TPF \equiv FPF$

Non-diseased cases $N(\mu_n, \sigma_n^2)$

Diseased cases $N(\mu_d, \sigma_d^2)$



(B)

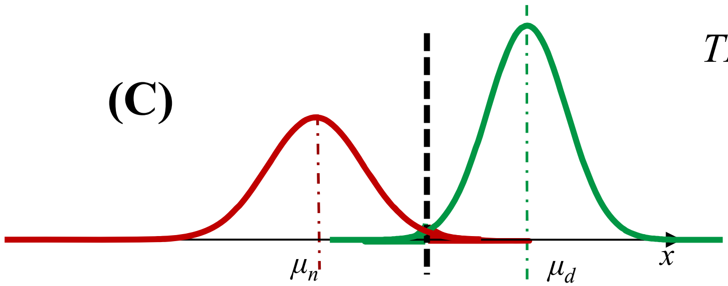


(B) & (C):

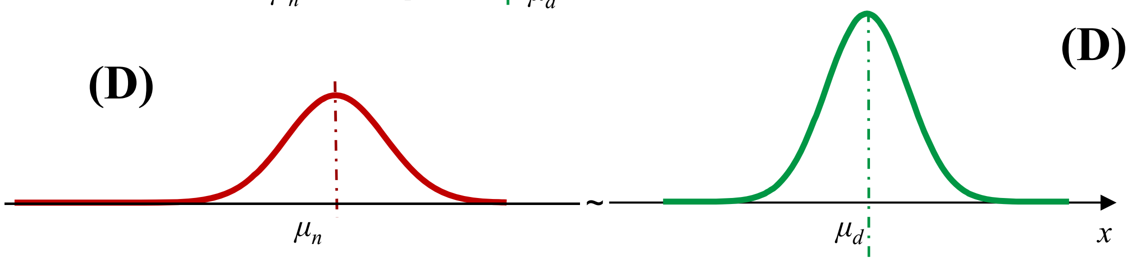
$$a = \frac{\mu_d - \mu_n}{\sigma_d} \qquad b = \frac{\sigma_n}{\sigma_d}$$

$$TPF = \Phi[a + b \times \Phi^{-1}(FPF)]$$

(C)



(D)



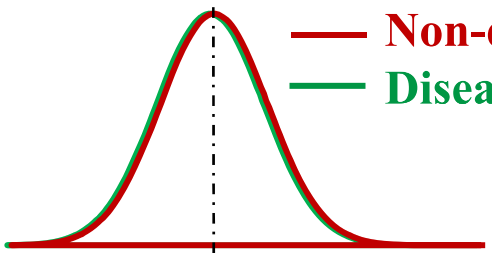
(D): μ_d - $\mu_n = \infty \quad \therefore a = \infty$

$$\begin{cases} TPF \equiv 1 & \text{when } FPF \neq 0 \\ TPF \in [0,1] & \text{when } FPF = 0 \end{cases}$$

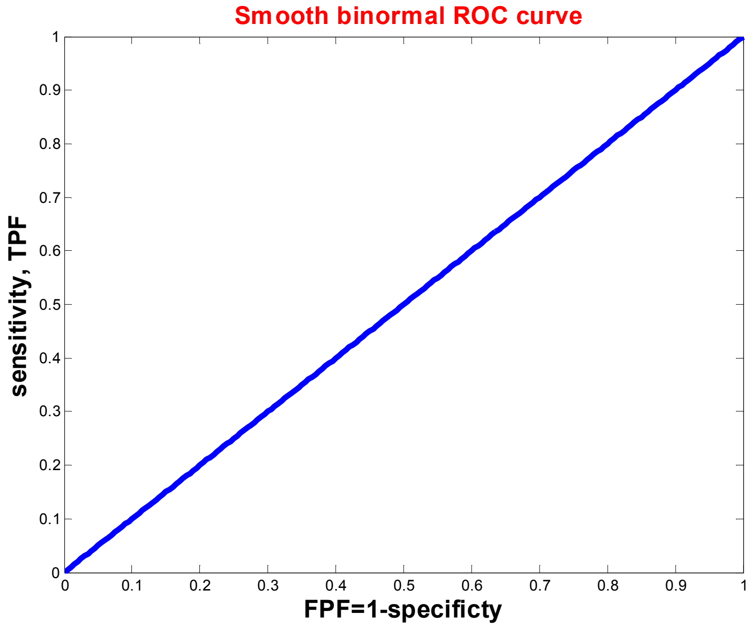
Figure: Pure guessing is the diagonal marked as **A**; the ROC curves marked as **C** shows a better performances than **B**; a perfect ROC curve rides the left and top edges, marked as **D**.

Exercise-1:
Please prove that the binormal distributions showing by the following figure results a ROC curve of pure guessing.

Proof:



Non-diseased cases $N(\mu_n, \sigma_n^2)$
Diseased cases $N(\mu_d, \sigma_d^2)$



Here: $\mu_n = \mu_d$, $\sigma_n = \sigma_d$

$$a = \frac{\mu_d - \mu_n}{\sigma_d} = 0 \qquad b = \frac{\sigma_n}{\sigma_d} = 1$$

❖ From equation (11.17):

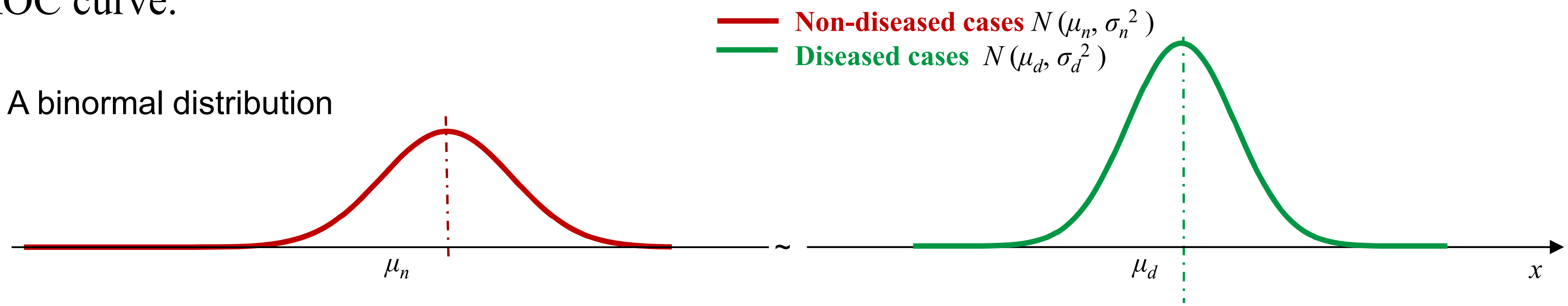
$$TPF = \Phi[a + b \times \Phi^{-1}(FPF)] = \Phi[0 + 1 \times \Phi^{-1}(FPF)]$$

$$= \Phi[\Phi^{-1}(FPF)] = FPF$$

$$\therefore TPF \equiv FPF$$

Exercise-2:

Please prove that the binormal distribution showing by the following figure results a perfect ROC curve.



Proof:

Here: $\mu_d - \mu_n = \infty$

$$\therefore a = \frac{\mu_d - \mu_n}{\sigma_d} = \infty \qquad b = \frac{\sigma_n}{\sigma_d}$$

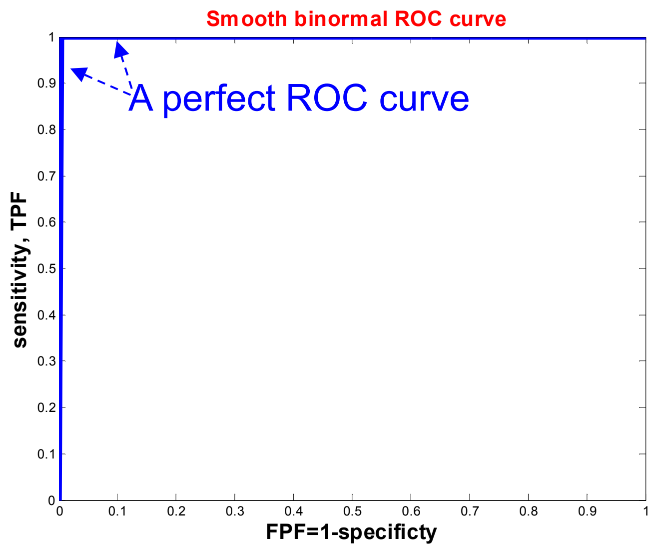
❖ From equation (11.17):

When $FPF \neq 0$, $\quad TPF = \Phi[a + b \times \Phi^{-1}(FPF)] = \Phi[\infty] = 1$

When $FPF = 0$, $\quad \Phi^{-1}(FPF) = \Phi^{-1}(0) = -\infty$

$$a = \infty \Rightarrow TPF \in [0,1]$$

$$\therefore \begin{cases} TPF \equiv 1 & \text{when } FPF \neq 0 \\ TPF \in [0,1] & \text{when } FPF = 0 \end{cases}$$



11.9 How to Evaluate Performance by ROC Curves?

- Recall early discussions in Handout 11.4, the area under the ROC curve (AUC) is commonly used as a measure to compare the overall performance of a diagnostic tests.
- A larger AUC indicates a better performance.
- AUC can be calculated with parameters ***a*** and ***b***:

$$AUC = \Phi\left(\frac{a}{\sqrt{1+b^2}}\right) \qquad (11.20)$$

An example: a=1.15 and b=0.91, we have:

$$AUC = \Phi\left(\frac{a}{\sqrt{1+b^2}}\right) = \Phi\left(\frac{1.15}{\sqrt{1+0.91^2}}\right) = \Phi(0.85) = 0.8023$$

- More details about the above AUC formula, please refer to McClish DK, "Analyzing a portion of the ROC curve", Medical. Decision Making, Vol.9, 190-198, 1989

11.10 Summary:

- **ROC** analysis was developed and applied in statistical decision theory and signal detection theory.
- Conventional **ROC** analysis based on binormal distribution model as introduced in this lecture is a very useful tool to evaluate the performance of diagnostic tests and/or medical imaging systems
- Overall, an **ROC** curve displays the trade-offs between sensitivity and specificity of a diagnostic test.
- Extensions of conventional ROC methodology such as Location ROC (LROC), Free-Response ROC (FROC), Alternative Free-Response ROC (AFROC) have also been developed for various applications/testing conditions.

Reference Reading:

1. **Charles E. Metz, “Basic Principles of ROC Analysis”, *Seminars in Nuclear Medicine*, Vol. VIII, No. 4, 1978**
2. Charles E. Metz and Helen B. Kronman, “Statistical Significance Tests for Binormal ROC Curves”, Journal of Mathematical Psychology Vol. 22, 218-243, 1980
3. Metz CE, Herman BA, Shen JH, “Maximum likelihood estimation of receiver operating characteristic (ROC) curves from continuously-distributed data”, Statistics In Medicine (17): 1033-1053, 1998
4. Report 79: “Receiver Operating Characteristic Analysis in Medical Imaging”, Journal of the ICRU, Vol.8 (1), 2008
5. W. Mendenhall and T. Sincich, “Statistics for Engineering and the Sciences”, Pearson, 5th edition, 2006

Homework #10-B:

1. An observer study for comparing the performance of two medical imaging systems has resulted the following data:

For system A

	Sensitivity (TPF)	Specificity (TNF)
Threshold 1	85/100	55/100
Threshold 2	75/100	70/100

For system B

	Sensitivity (TPF)	Specificity (TNF)
Threshold 1	88/100	53/100
Threshold 2	78/100	74/100

(1) Please calculate **a** and **b** values, and plot ROC curves for both of the systems by using Matlab.

(2) Please calculate the area under the ROC curve (**AUC**) for both of the systems.

(3) Which system is better?

2. The **cumulative distribution function (CDF)**, Φ(X), of the standard normal distribution can be computed as:

$$CDF = \Phi(X) = \int_{-\infty}^{X} \frac{1}{\sqrt{2\pi}} \times e^{-x^2/2} \times dx$$

Please prove that the symmetry property of Φ(X): i.e. for a real number ***X***, we have

$$\Phi(-X) = 1 - \Phi(X)$$