HARMONY

Novel tools for test evaluation and disease prevalence estimation

Home • About • News • Structure • Training Material • Calls • Slack

Your Search...

COST ACTION CA18208

Novel tools for test evaluation and disease prevalence estimation

Know More

BLCMs for diagnostic methods measured on a continuous scale

Berlin, Germany 12 – 14 September 2022

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Eleftherios Meletis

Test Result		Total
Positive	Negative	
23	77	100

Individual - ID	Test result	Test result
1	Positive	1
2	Negative	0
3	Negative	0
4	Positive	1
…		
100	Positive	1

Individual - ID	Continuous result
1	2.1
2	1.8
3	1.5
4	2.5
…	
100	3

If Continuous result ≥ 2

↓

Test result = Positive (1),

else

Test result = Negative (0)

Test result	Test result
Positive	1
Negative	0
Negative	0
Positive	1
…	
Positive	1

▶️ **But dichotomizing results in loss of valuable information.**

▶️ **All positive results are equal, no matter how near or far they are from the cutoff.**

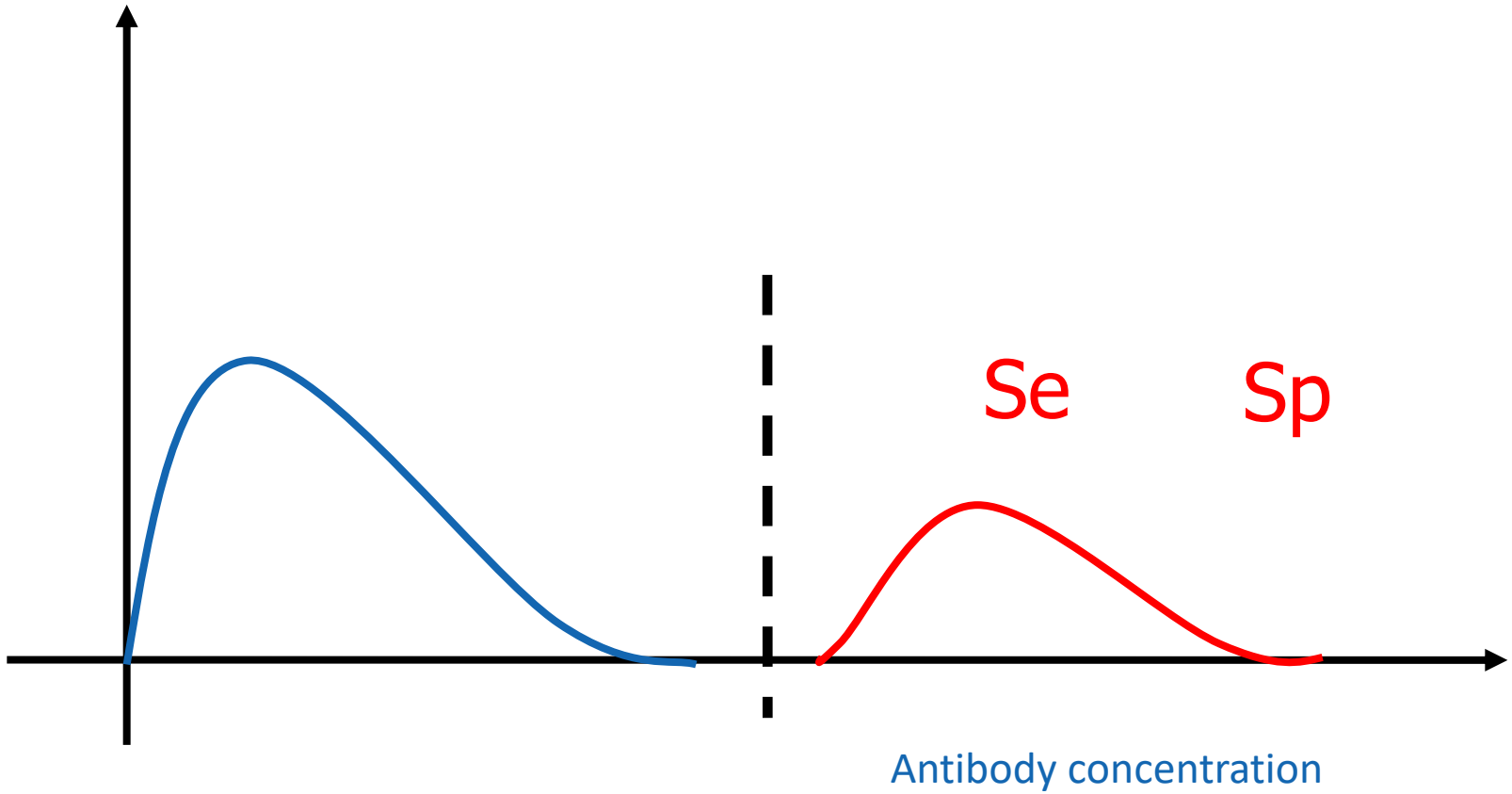
Presentation outline

Receiver Operating Characteristic curve (ROC) analysis

ROC Analysis with BLCMs

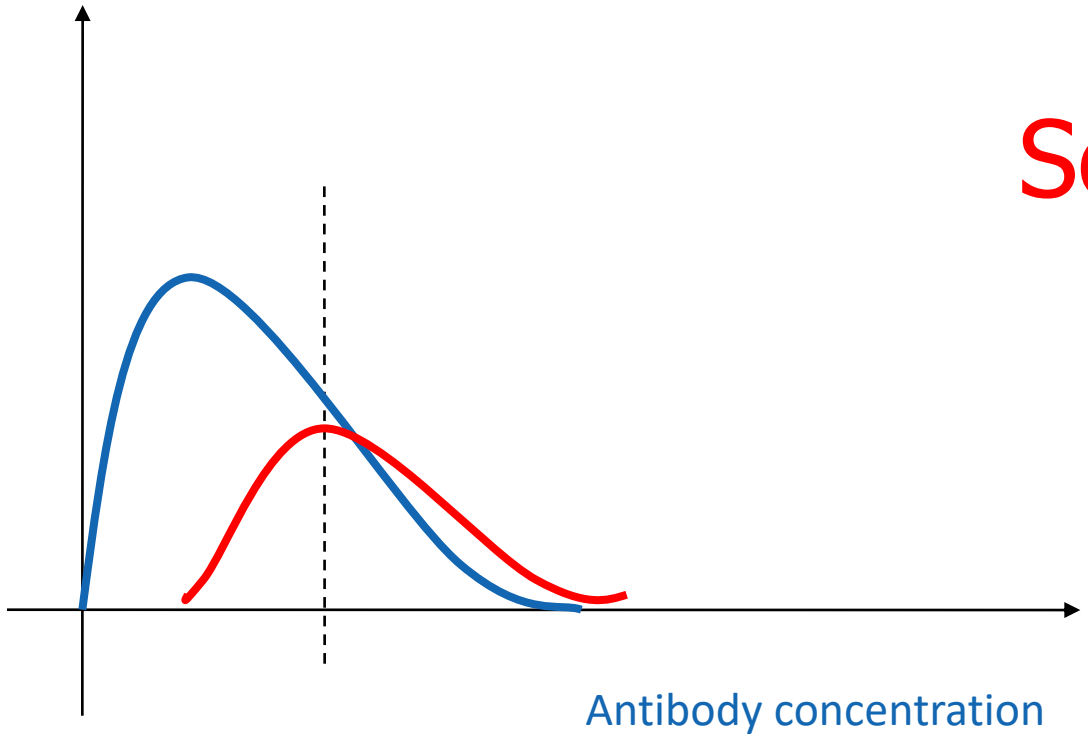
Se, Sp estimation for methods measured on a continuous scale

What type of test (Se,Sp) does this figure describe?

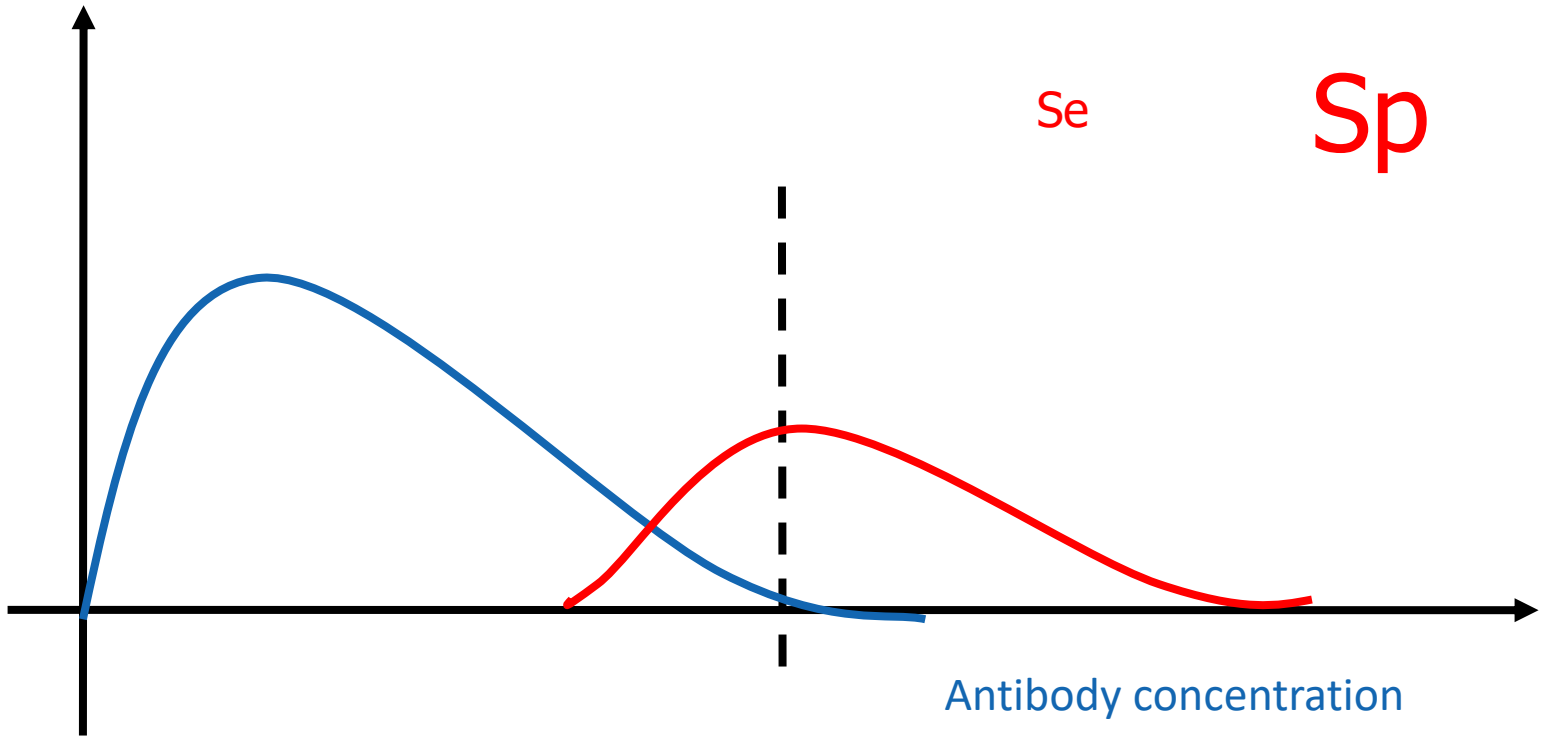


Eleftherios Meleti

On the other hand this figure describes a test with poor discriminatory ability, right?



The following figure describes the most usual setting



Basic definition

$Se = Pr(T^+ | D^+)$ and $FNR^* = Pr(T^- | D^+)$

$Sp = Pr(T^- | D^-)$ and $FPR^{**} = Pr(T^+ | D^-)$

In the "binary" world

$Se = Pr(T = 1 | D^+)$

$Sp = Pr(T = 0 | D^-)$

But using the continuous test output, Se and Sp are defined as

$Se = Pr(\text{Con. Result} \geq \text{Cut-off} \mid D^+) = 1 - Pr(\text{Con. Result} < \text{Cut-off} \mid D^+) = FNR$

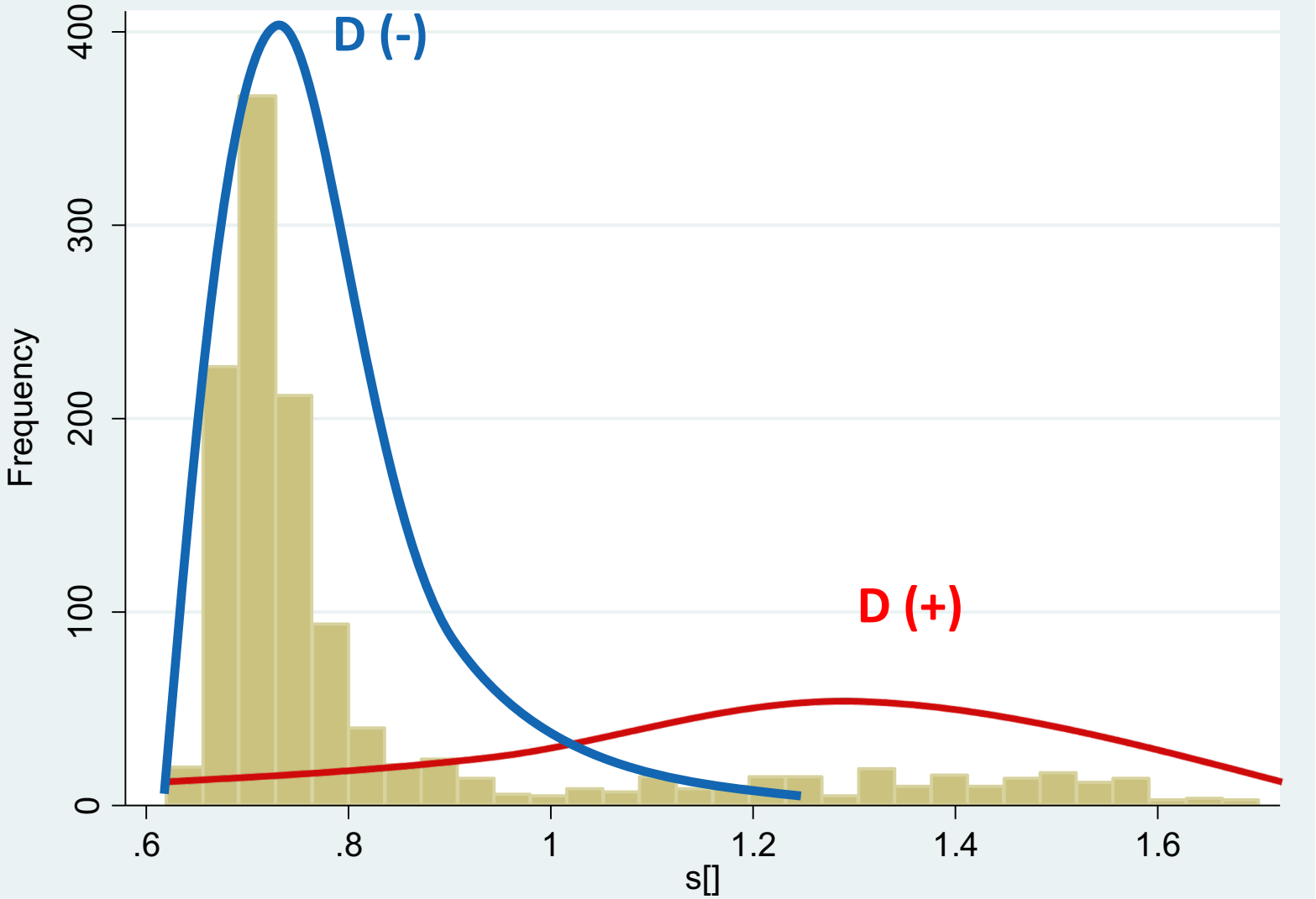
$Sp = Pr(\text{Con. Result} < \text{Cut-off} \mid D^-) = 1 - Pr(\text{Con. Result} > \text{Cut-off} \mid D^+) = FPR$

*FNR: False Negative rate
**FPR: False Positive rate

Receiver Operating Characteristic curve (ROC) analysis

Let’s go through an example to see how we can construct the ROC curve

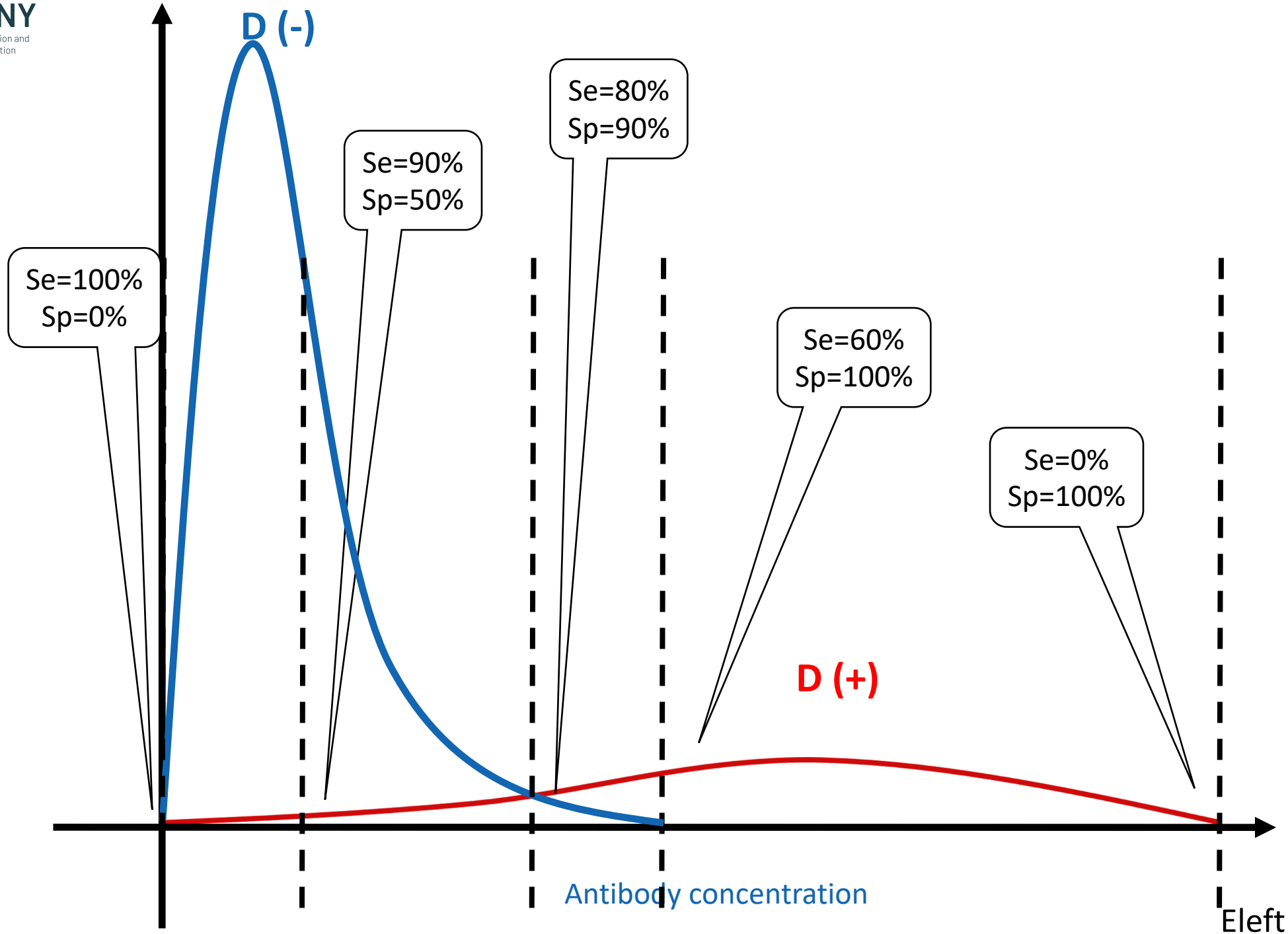
Eleftherios Meletis



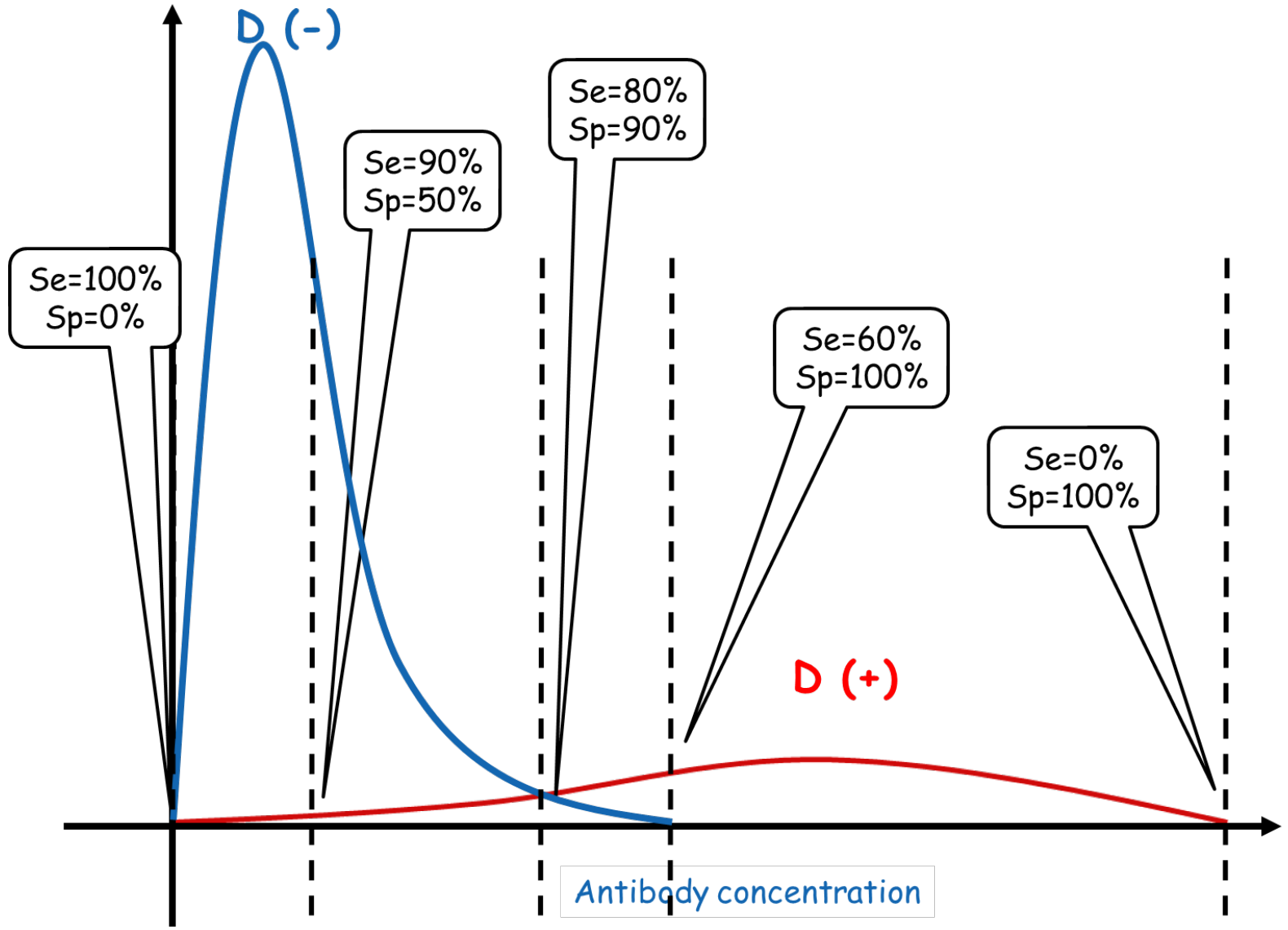
Antibody concentration

Individual - ID	Continuous result	Disease Status
1	2.1	Infected
2	1.8	Healthy
3	1.5	Healthy
4	2.5	Infected
…		
100	3	Infected

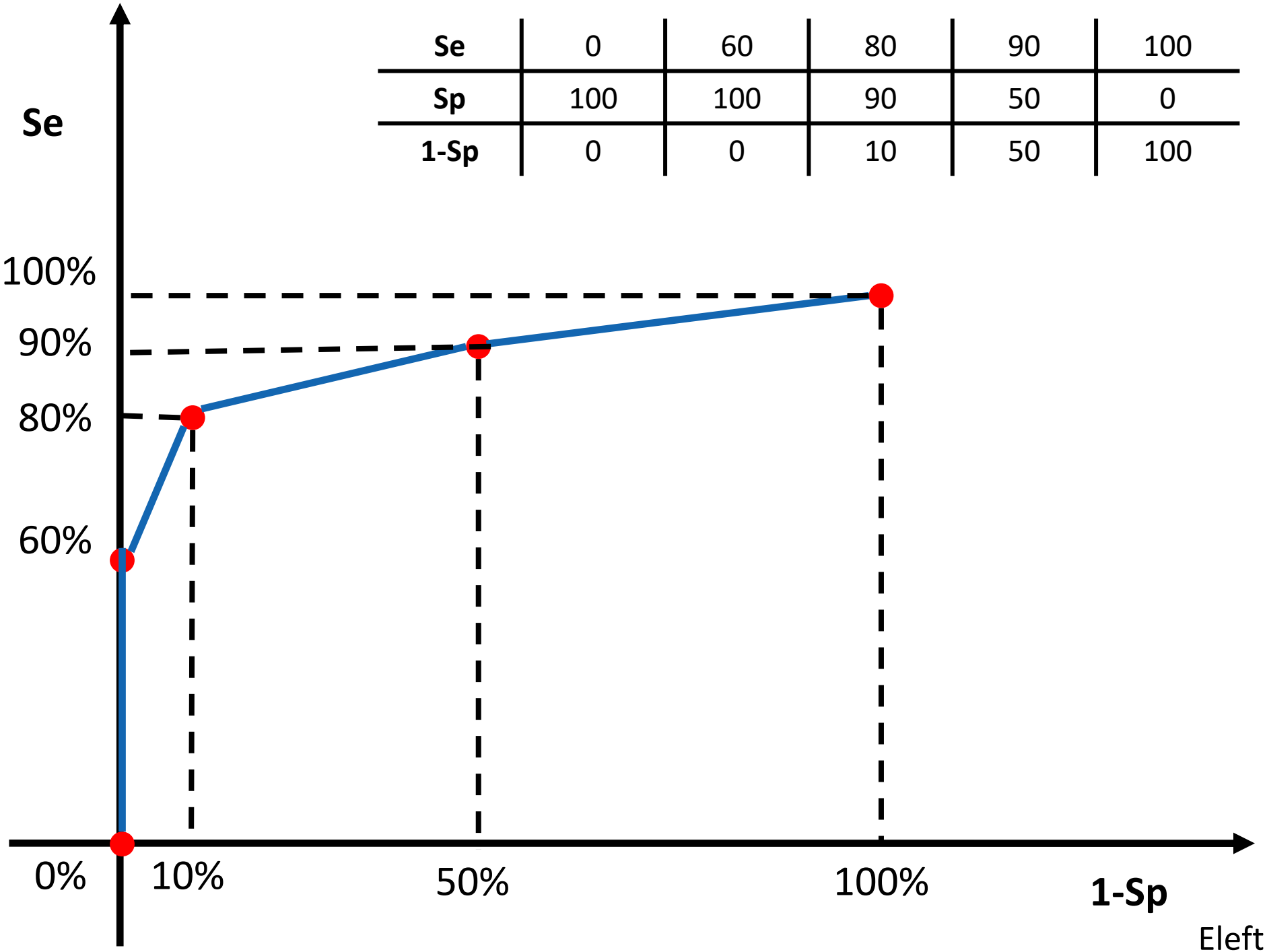
Eleftherios Meletis


D (-)
Se=100%
Sp=0%
Se=90%
Sp=50%
Se=80%
Sp=90%
Se=60%
Sp=100%
Se=0%
Sp=100%
D (+)
Antibody concentration

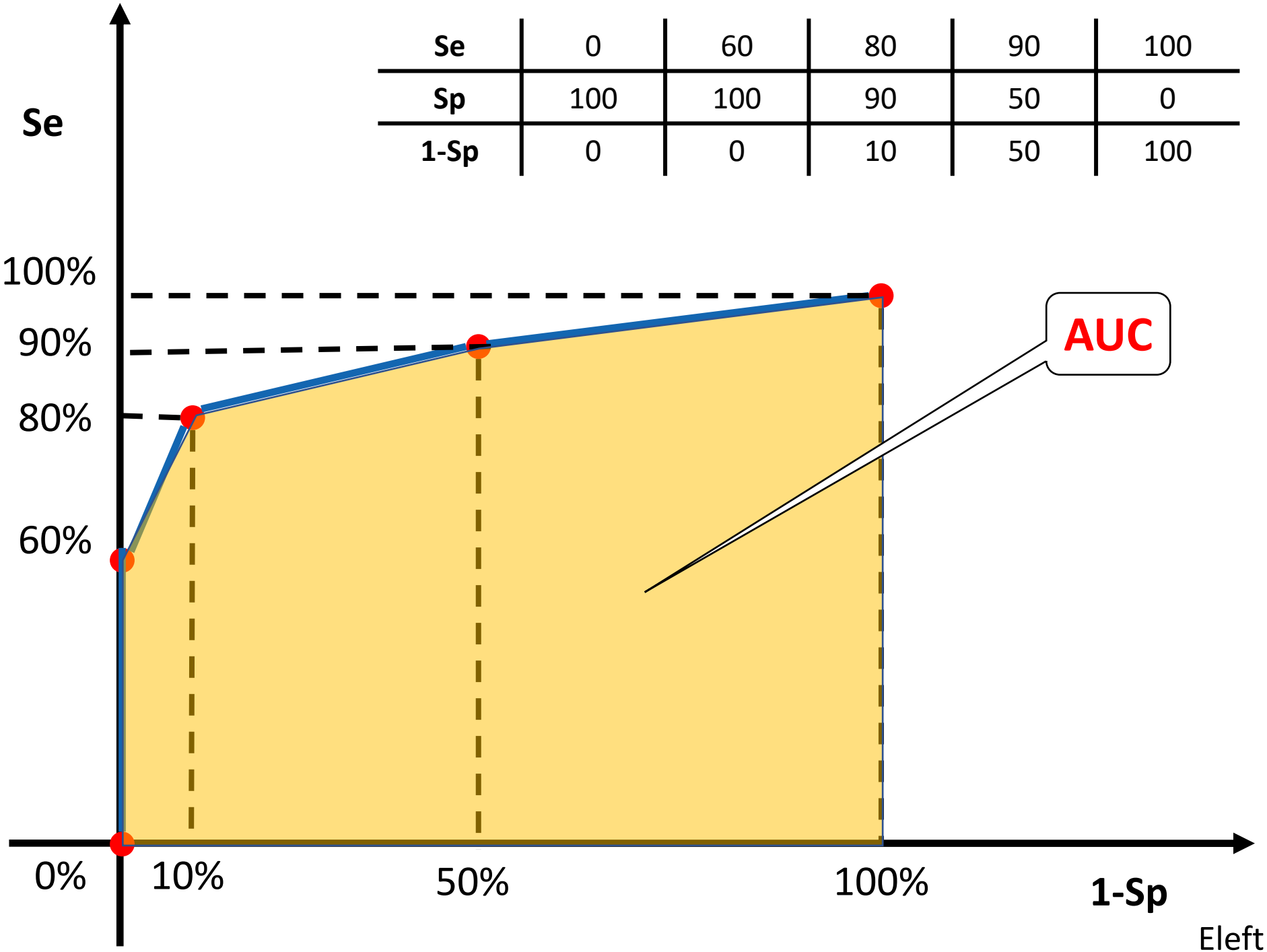
Se	0	60	80	90	100
Sp	100	100	90	50	0
1-Sp	0	0	10	50	100



Se	0	60	80	90	100
Sp	100	100	90	50	0
1-Sp	0	0	10	50	100



Se	0	60	80	90	100
Sp	100	100	90	50	0
1-Sp	0	0	10	50	100



Area Under the Curve

Measures the overall discriminatory power of the test

Low: $0.5 < AUC \leq 0.7$

Medium: $0.7 < AUC \leq 0.9$

High: $0.9 < AUC < 1$

Perfect: 1

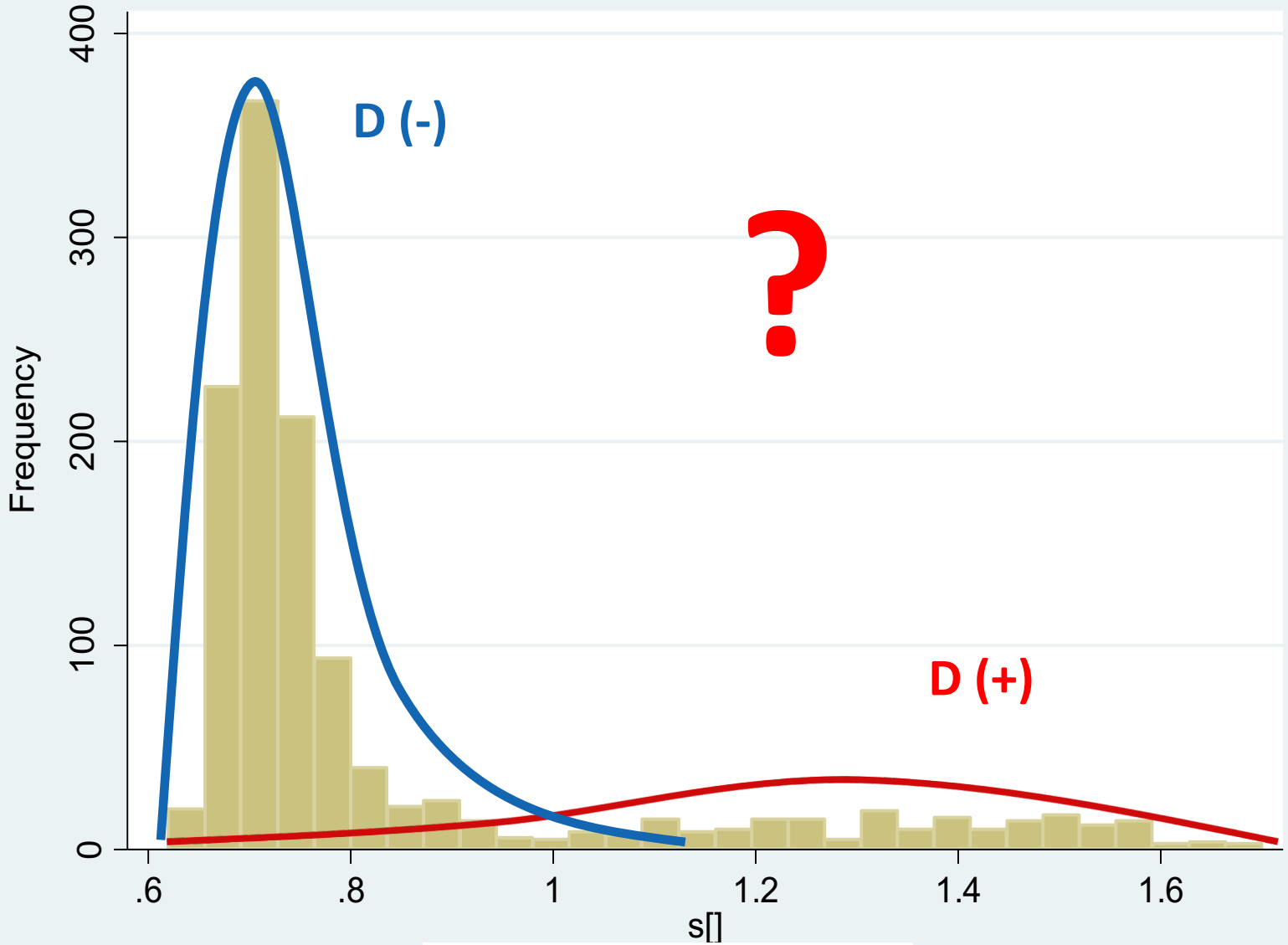
Selection of cut-off points:

- Informed decision

The cut-off closer to the upper left corner minimizes the overall false classifications (positive and negative) and maximizes the AUC

In the absence of a gold standard the true disease status of each individual is unknown.

The available information we have is the continuous test output from each individual.



Antibody concentration

Individual - ID	Continuous result	Disease Status
1	2.1	?
2	1.8	?
3	1.5	?
4	2.5	?
…		
100	3	?

Eleftherios Meletis

Mixture normal model

The data are best described by a mixture of two normal distributions.

The distribution of the:

D (-) individuals with mean (mu1) and variance (1/tau1)

D (+) individuals with mean (mu2) and variance (1/tau2)

mu1 < mu2 → Diseased individuals are expected to have higher value of the continuous marker

BUGS model

Like any other BUGS model we need to define the likelihood part and the prior part

Likelihood Part

```
model {
  for (i in 1:481) {
      #S[i] diagnostic test value for ith individual

      S[i] ~ dnorm(mu[i],tau[i])

      #Value of mu & tau depending on the group (diseased
or disease-free)

      mu[i] <- lambda[T[i]]

      tau[i] <- gamma[T[i]]

      #dcat <- categorical #D(-) if T[i]=1, D(+) if T[i]=2

      T[i] ~ dcat(P[])
  }
    P[1:2] ~ ddirch(alpha[])
```

Prior Part

```
# lambda[1]- gamma[1] mean-precision of non-disease
group
lambda[1] ~ dnorm(0,0.001)
lambda[2] ~ dnorm(0,0.001)T(lambda[1],)
gamma[1] ~ dgamma(0.001,0.001)
gamma[2] ~ dgamma(0.001,0.001)

# variance = 1/precision(tau)
sigma[1] <- 1/gamma[1]
sigma[2] <- 1/gamma[2]
```

BUGS model continued

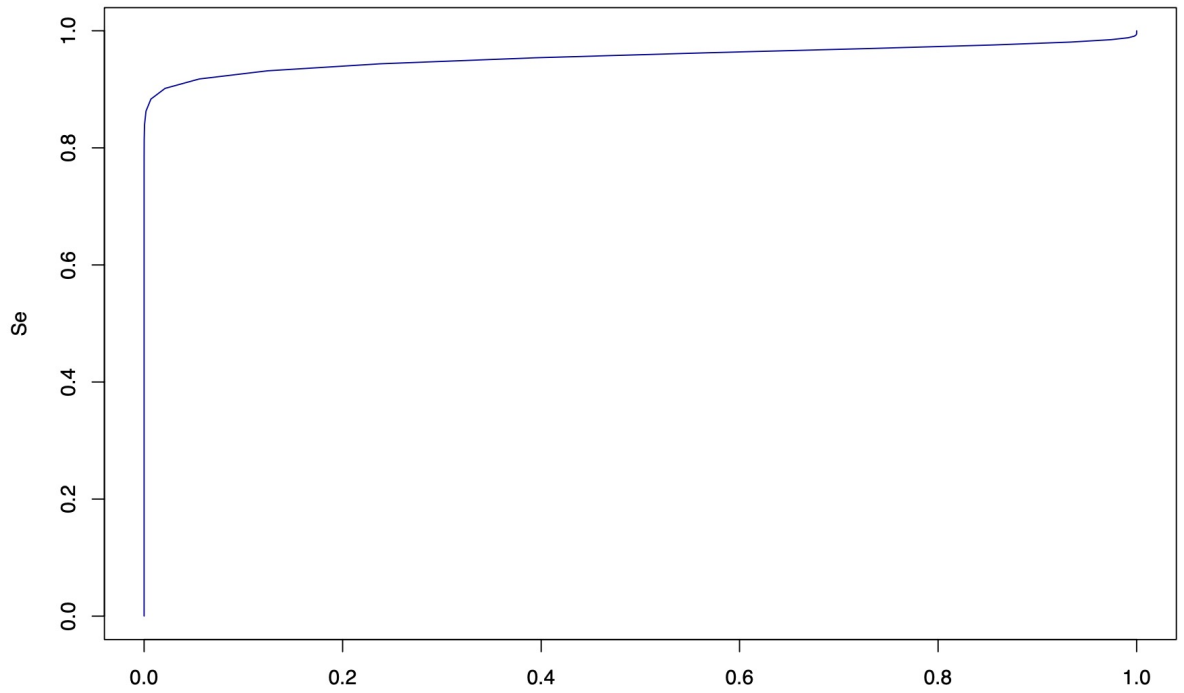
```
# AUC
        AUC <- phi(-(lambda[1]-lambda[2])/sqrt(sigma[2]+sigma[1]))

        # ROC curve
        for(i in 1:111) {
          c1[i] <-  ((-8.1+0.1*i)-lambda[2])/sqrt(sigma[2]) # grid is from -3 to 8
          se[i] <- 1-phi(c1[i])
          c2[i] <-  ((-8.1+0.1*i)-lambda[1])/sqrt(sigma[1])
          sp[i] <- phi(c2[i])

          Y[i] <- se[i] + sp[i] - 1
        }
        #data# alpha, S
        #inits# lambda, gamma
        #monitor# AUC, se, sp, P, lambda, gamma, sigma
}
```

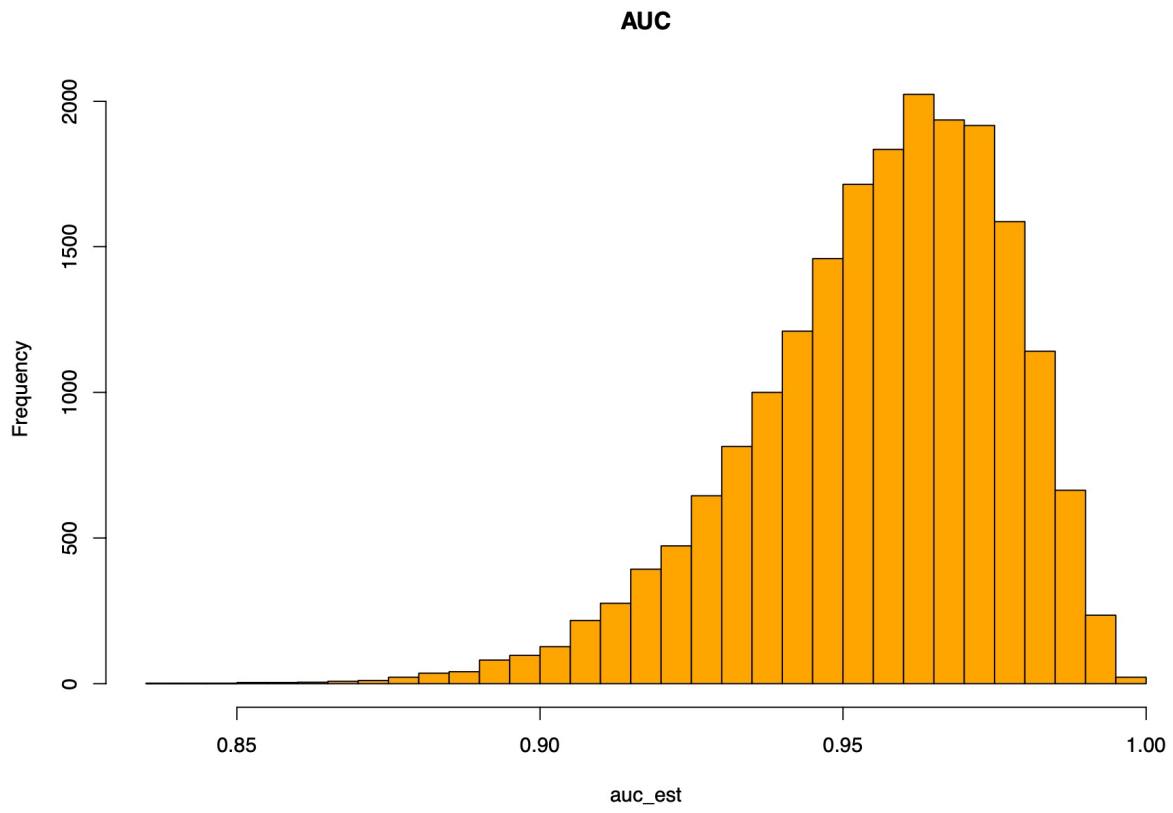
Results

```
se_est <- combine.mcmc(results, vars='se')
sp_est <- combine.mcmc(results, vars='sp')
ses_mu <- apply(se_est, 2, mean)
sps_mu <- apply(sp_est, 2, mean)
par(mfrow=c(1,1))
plot((1-sps_mu), ses_mu, type="l", col="darkblue", xlab = "1-Sp", ylab = "Se")
```



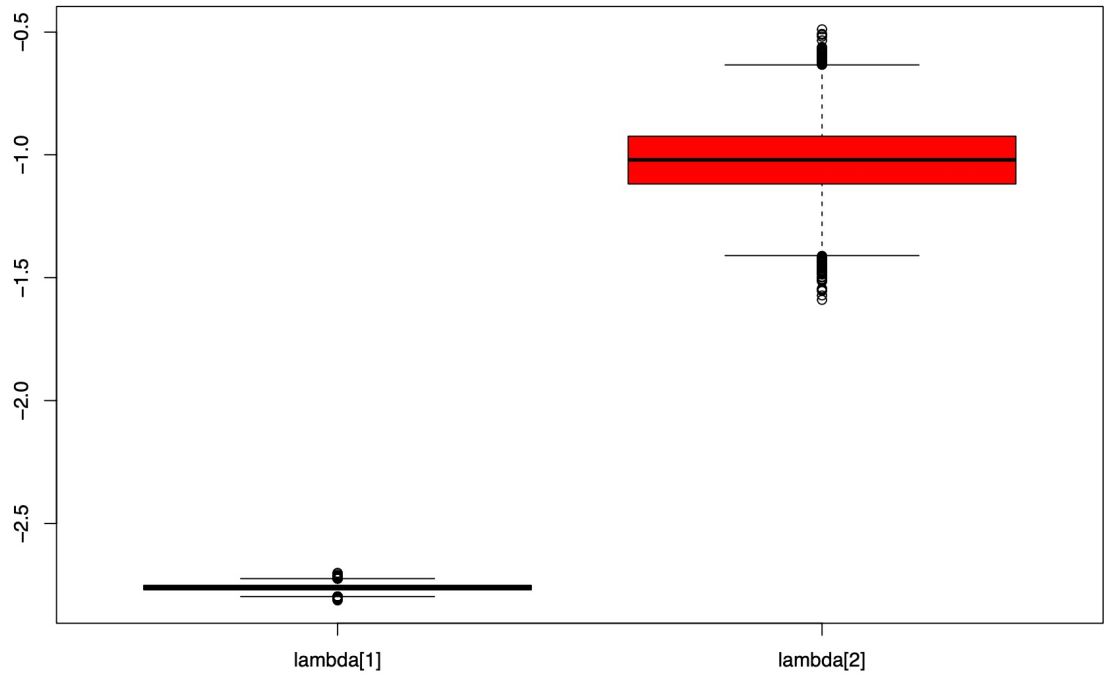
Results

```
auc_est <- combine.mcmc(results, vars='AUC')
hist(auc_est, breaks=50, col="orange", main="AUC")
```



Results

```
lambda_est <- combine.mcmc(results, vars='lambda')
boxplot(as.matrix(lambda_est), col="red")
```



Discussion

Fixed cut-off – Think again

YouTube video: https://www.youtube.com/watch?v=1gQ-lLKl5CQ&ab_channel=PolychronisKostoulas

Discussion

Most of the studies referenced before are published between 2005 – 2010

Keeping continuous diagnostic data continuous: Application of Bayesian latent class models

Yang, D. A., Xiao, X., Jiang, P., Pfeiffer, D. U., & Laven, R. A., PVM April 2022

Conclusions - Remarks

Normality assumption? – What happens when tests results do not have a Gaussian distribution?

Distance between the D(-) and D(+) distributions

Label switching (m1 < m2) – What happens for tests for RT-PCR?

More complicated settings

Diagnostic tests with a limit of detection (upper/ lower) + More than two infectious stages (Jafarzadeh, et al., 2010)

Semi-parametric + Non-parametric ROC analysis, in the absence of a gold standard (Erkanli et al., 2006)

Correlated diagnostic tests (Choi et al., 2006)

Incorporating covariate information (Jones et al., 2009, Branscum et al., 2015)

Evaluation of a continuous + dichotomous test applied together (Joseph, Olsen et al., 2022)

Coffee break

Diagnostic tests with a limit of detection - (Jafarzadeh, et al., 2010)

- Diagnostic tests like qPCR, RT-PCR have a lower limit of detection of the target analyte
- Test scores are known to lie only in certain range of values $d1 \leq S \leq d2$

Individual - ID	Continuous result (PCR cycles)
1	25
2	38
3	NA / -

More than two infectious stages - (Jafarzadeh, et al., 2010)

Heavily infected
Infected
Healthy

Semi-parametric ROC analysis (Erkanli et al., 2006)

- Results of the test/biomarker do not follow a Gaussian/normal distribution
- ”Stick-breaking algorithm”

Correlated diagnostic tests (Choi et al., 2006)

- Adjusting for conditional dependence between tests

Conditional independence

$P(T\,1+, T\,2+|D+) = P(T\,1+|D+) \times P(T\,2+|D+)]$

Conditional dependence

$P(T\,1+, T\,2+|D+) \neq P(T\,1+|D+) \times P(T\,2+|D+)$

Seen from a biological perspective, conditional dependency
between two diagnostic tests could occur if both tests are based on the same biological principle.

Evaluation of a continuous + dichotomous test applied together (Olsen et al., 2022)

2 dichotomous + 1 continuous test in 7 populations settings

Summary

Selection of cut-off points is critical

Availability of Bayesian methods to model the continuous test output

References

Yang, D. A., Xiao, X., Jiang, P., Pfeiffer, D. U., & Laven, R. A. (2022). Keeping continuous diagnostic data continuous: Application of Bayesian latent class models in veterinary research. Preventive Veterinary Medicine, 201, 105596.

Jafarzadeh, S. R., Johnson, W. O., Utts, J. M., & Gardner, I. A. (2010). Bayesian estimation of the receiver operating characteristic curve for a diagnostic test with a limit of detection in the absence of a gold standard. Statistics in medicine, 29(20), 2090-2106.

Erkanli, A., Sung, M., Jane Costello, E., & Angold, A. (2006). Bayesian semi-parametric ROC analysis. Statistics in medicine, 25(22), 3905-3928.

Choi, Y. K., Johnson, W. O., Collins, M. T., & Gardner, I. A. (2006). Bayesian inferences for receiver operating characteristic curves in the absence of a gold standard. Journal of agricultural, biological, and environmental statistics, 11(2), 210-229.

Branscum, A. J., Johnson, W. O., Hanson, T. E., & Baron, A. T. (2015). Flexible regression models for ROC and risk analysis, with or without a gold standard. Statistics in medicine, 34(30), 3997-4015.

Olsen, A., Nielsen, H. V., Alban, L., Houe, H., Jensen, T. B., & Denwood, M. (2022). Determination of an optimal ELISA cut-off for the diagnosis of Toxoplasma gondii infection in pigs using Bayesian latent class modelling of data from multiple diagnostic tests. Preventive Veterinary Medicine, 201, 105606.

Jones, G., Johnson, W. O., & Vink, W. D. (2009). Evaluating a continuous biomarker for infection by using observed disease status with covariate effects on disease. Journal of the Royal Statistical Society: Series C (Applied Statistics), 58(5), 705-717.