

BLCMs for continuous tests

CA18208 HARMONY Zurich Training School -

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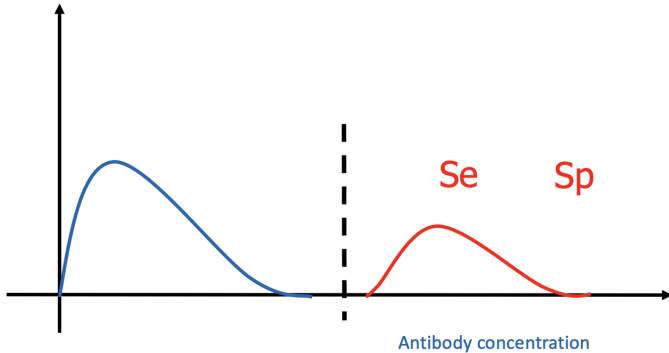
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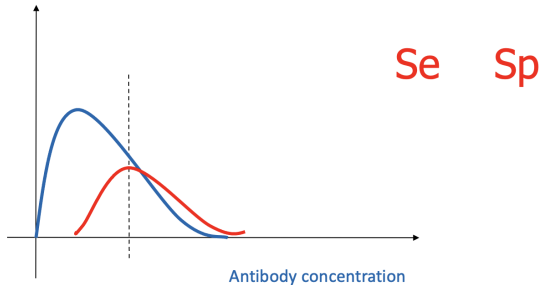
Presentation Outline

- ▶ Didactic Teaching
 - ▶ Receiver Operating Characteristic curve (ROC) analysis
 - ▶ ROC Analysis with BLCMs
- ▶ Practical Session
 - ▶ Hands-on example

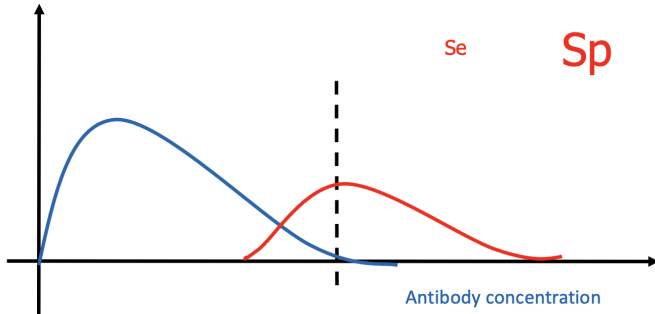
What type of test (Se,Sp) does this picture describe?



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

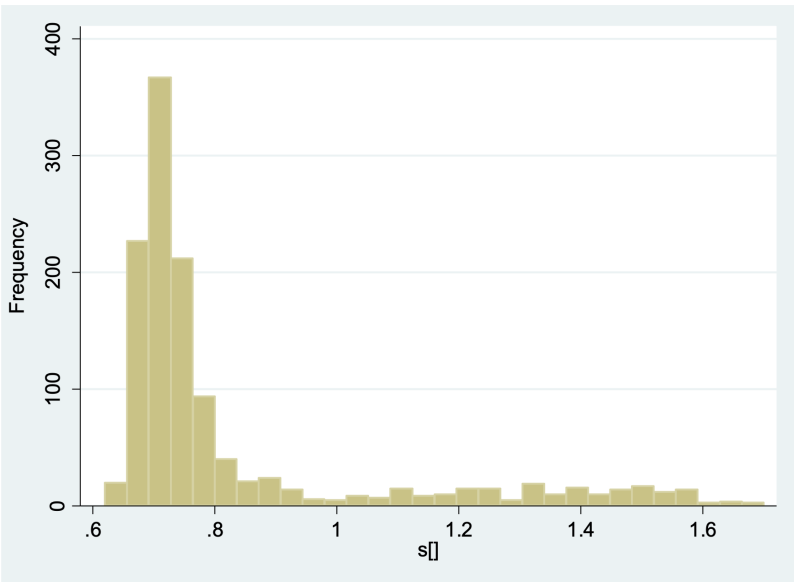


The following picture describes the most usual setting.



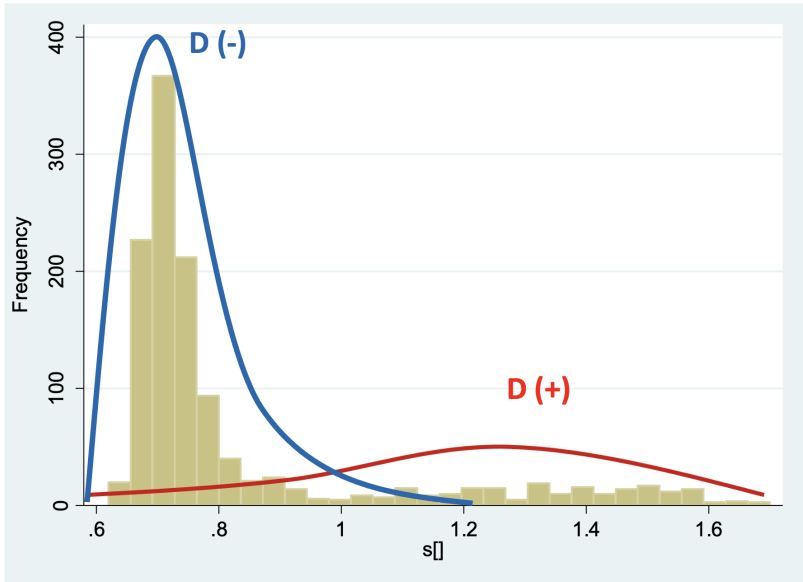
Let's start building our hands-on example.

In the next slide we'll see a histogram of the values of a continuous test result (e.g. ELISA measuring antibodies), on the logarithmic scale.



Antibody concentration

Assuming the infectious status of each individual known we can plot/add the distributions of the diseased and healthy.

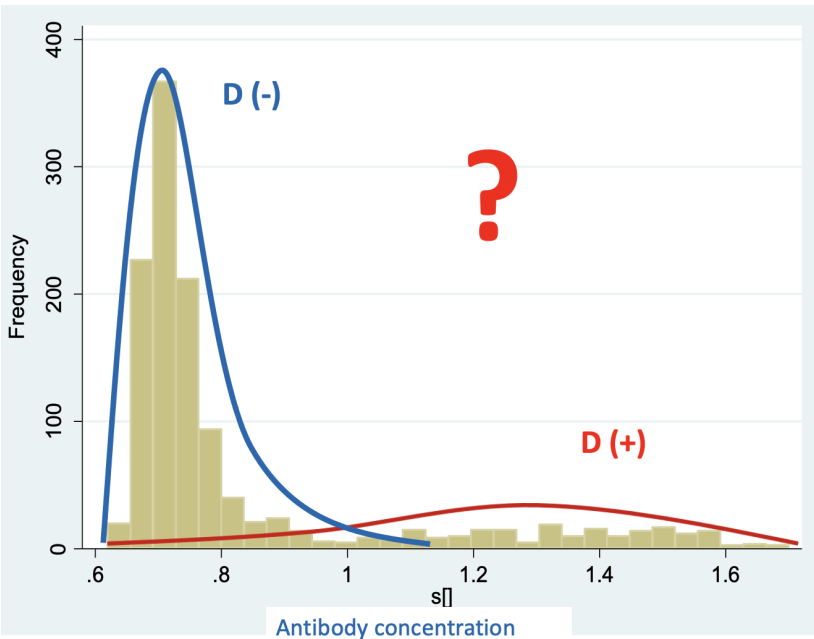


Antibody concentration

ROC Analysis with BLCMs

Point 1

- ▶ 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.



Point 2

- ▶ Most studies dichotomize the continuous test output based on a pre-selected cut-off value and apply the BLCMs we discussed yesterday.
- ▶ But this results in loss of valuable information.
 - ▶ All positive results are equal, no matter how near or far they are from the cutoff.

Model Specification - Mixture Normal Model

- ▶ The data are best described by a mixture of two normal distributions:
 - ▶ D (-) individuals with mean (μ_1) and variance ($1/\tau_1$)
 - ▶ D (+) individuals with mean (μ_2) and variance ($1/\tau_2$)
 - ▶ $1/\tau = \text{Precision}$
- ▶ The disease status for each individual is indicated by a latent variable.
- ▶ For identifiability we assume: $\mu_1 < \mu_2$
 - ▶ Diseased individuals are expected to have higher value of the continuous marker

Mixture Normal Model explained

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

Data - Initial Values

```
summary(S)
```

```
##      Min. 1st Qu.  Median    Mean 3rd Qu.    Max.  
## -3.100 -2.900 -2.700 -2.414 -2.430  0.840
```

Define initial values:

```
lambda <- list(chain1=c(-3, 0), chain2=c(-2,-2))  
gamma  <- list(chain1=c(10, 0.1), chain2=c(30, 5))
```

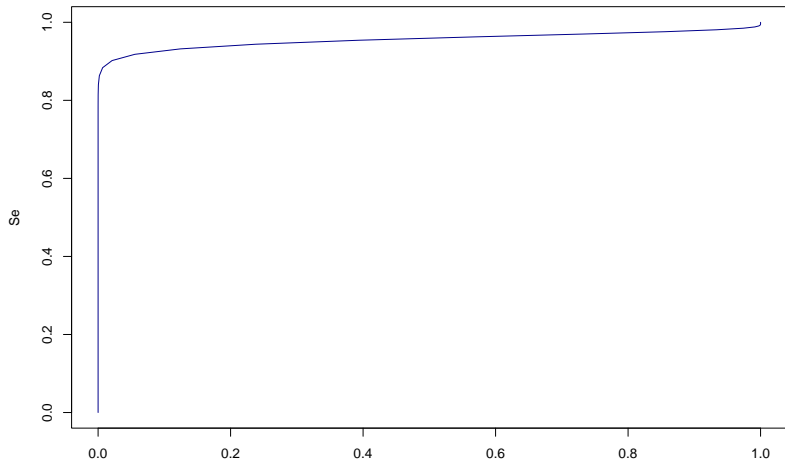
```
results <- run.jags('cont_test.txt', n.chains = 2)
```

```
#plot(results, vars=c('AUC', 'P', 'lambda', 'gamma', 'sigma'))
```

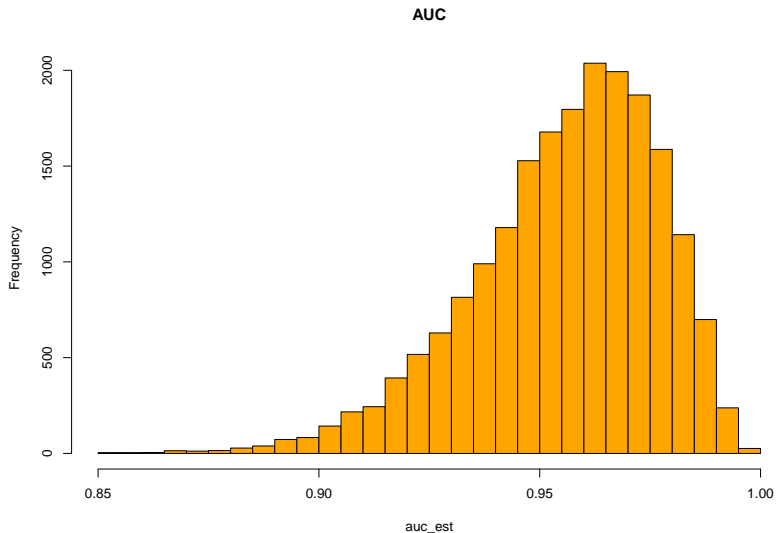
```
results_summary <- add.summary(results, vars=c('AUC', 'P', 'lambda', 'gamma', 'P', 'lambda', 'gamma', 'sigma'))
```



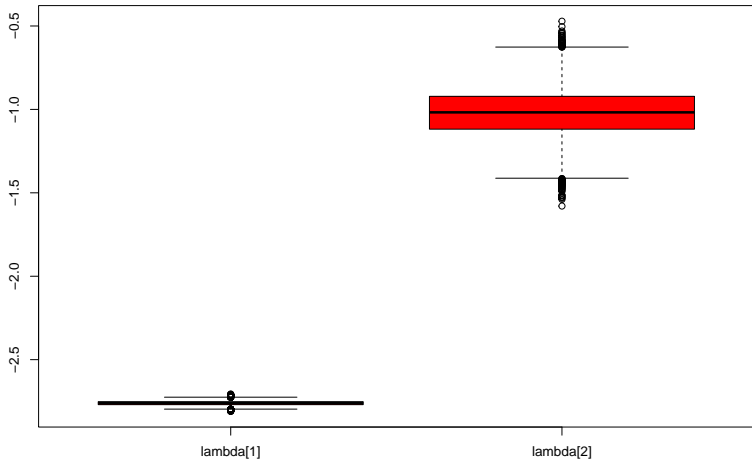
```
se_est <- combine.mcmc(results, vars='se')
sp_est <- combine.mcmc(results, vars='sp')
ses_mu <- apply(se_est, 2, mean)
sps_mu <- apply(sp_est, 2, mean)
par(mfrow=c(1,1))
plot((1-sps_mu), ses_mu, type="l", col="darkblue", xlab = "1-Sp", ylab = "Se")
```



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



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



Conclusion - Remarks

- ▶ Normality assumption?
- ▶ Distance between the $D(-)$ and $D(+)$ distributions
- ▶ Label switching
- ▶ More complicated settings
 - ▶ Correlated tests
 - ▶ Multiple populations
 - ▶ More than 2 infectious stages
 - ▶ etc. . .

Exercises

- ▶ Run the model and produce the same output.
- ▶ Try to run the model under different prior specification for λ
- ▶ What happens if you remove $T(\lambda[1],)$? Does the model converge?
- ▶ Try and find the cut-off value that maximizes Youden's index?

Another approach

```
# Another option in JAGS is to use dnormmix:  
# S[i] ~ dnormmix(mu[1:2], tau[1:2], P[1:2])  
# This is more efficient than explicitly simulating the latent class  
#modules# mix  
#factories# mix::TemperedMix sampler off  
##### /Alternative
```