

Bayesian Methods for Diagnostic Screening



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Outline

- “Impossible” to estimate test accuracy with only a single test, when no gold standard test exists and without extra information
- With two tests and two or more populations and under some “reasonable” assumptions, there is a way
- Examples of testing for *Neospora salmonis* in rainbow trout and *Toxoplasma gondii*
- Conditional independence versus dependence
- References-WinBugs Code



One Test:

T_1^+ Denotes positive outcome on Test 1

T_1^- Denotes negative outcome on Test 1

$$Se = \Pr(T_1^+|I), \quad Sp = \Pr(T_1^-|\text{no } I)$$

$$\text{Prevalence} = \Pr(I); \quad I = \text{Infection}$$

$X/n =$ Apparent Prevalence of Infection

is an estimate of

$$\Pr(T_1^+) = Se * \text{Prev} + (1-Sp) * (1-\text{Prev})$$



Problem

- How to estimate Se and Sp when you don't know who is I and who is not
- Can't be done with a single sample based on a single test, without extra information.
- Solution: Model developed by Hui and Walter (1981) using two tests and two or more populations. *Will return to this.*



One Test Example

- Microscopic Examination (ME) for testing for *Nucleospora salmonis* in trout
- 30 trout sampled in high prevalence population
- $X/n = 3/30 = 0.10$ is the apparent prev
- It is believed that $Sp = 1$ (approx)
- So, $E(X/n) = \text{prev} * Se$ (approx)



Example continued

- So, a natural estimate of Se is the apparent prevalence divided by a reasonable guess for the prevalence, if such a guess is available
- If the prevalence is believed to be 0.9, the estimated Se is 0.11, while if it is 0.1, the estimated Se is 1.0
- If the prevalence is less than 0.1, the “natural” estimate is greater than 1, which violates probability law



Example continued

- Thus, scientific information can play important role in estimating test accuracy, if it is available
- This information can result in poor estimates if the scientific information is poor



Two Ways to Proceed

- “Pretend” **two** of the three parameters are **known** precisely and solve for the remaining parameter using formula

$$x/n = \text{prev} * \text{Se} + (1 - \text{prev}) * (1 - \text{Sp})$$

And do Max Likelihood

- Model uncertainty about all parameters with probability that reflects scientific uncertainty in each of the unknown quantities eg. **Bayesian approach**



Bayesian Test Evaluation

- All uncertainty is modeled as probability; probability laws obeyed
- Approach allows **latent** (unobserved) data to be incorporated in the model e.g. **true infection status**
- Can **easily** obtain inferences for **any** parameter of interest eg. PVP, PVN etc



Advantages of Bayesian models

- Allow incorporation of (prior) scientific information
- No need for large sample sizes
- True probability intervals and statements
- Can be used to easily handle very complicated models
- Can be used for evaluation of correlated tests



Potential Disadvantages

- Inferences depend on particular scientific input, which may be incorrectly specified
- Real prior distributions can be difficult to obtain in complicated models
- Sensitivity analysis is necessary



Bayesian Inference

- Ingredients are the likelihood function
· $\text{Likelihood} = P(\text{data}|\text{parameters}),$
- and a “prior” probability model for the parameters, $P(\text{parameters})$
- Bayes theorem gives a prescription for posterior inference
- $P(\text{parameters}|\text{data}) = \frac{\text{Likelihood} * \text{prior}}{\text{constant}}$



Binomial Proportion Example

- Let X be the number of infected individuals in a sample of size n
- Let q be the proportion of infected individuals in the population sampled
- Suppose the value of q is completely unknown and that all values are deemed a priori “equally plausible”



Binomial Proportion Example

- Then $X \sim \text{Bin}(n, q)$
- $p(x|q) = \text{Lik} = \text{const}^* q^x (1-q)^{n-x}$
- We take $p(q) = 1$ for $0 < q < 1$
- Then $p(q|x) = \text{const}^* q^x (1-q)^{n-x}$

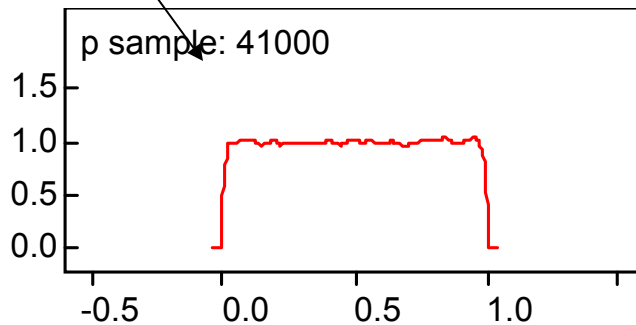


Beta Distribution

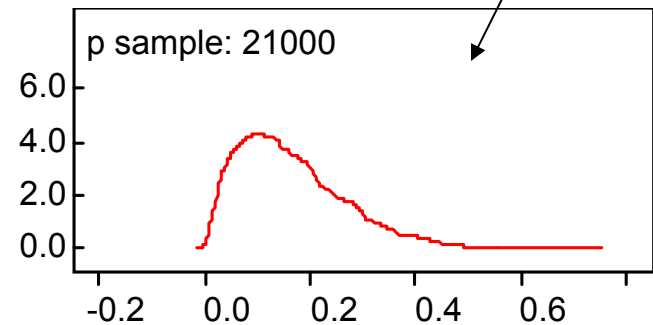
- $q \sim \text{Beta}(a, b)$ if $p(q) = \text{const} * q^{a-1} (1-q)^{b-1}$
- Pictures on next slide
- Posterior on prev slide is $\text{Beta}(x+1, n-x+1)$
- If $x = 1, n = 10$, posterior is $\text{Beta}(2, 10)$
- If $x = 10, n = 100$, posterior is $\text{Beta}(11, 91)$
- Mode of posterior is x/n [$1/10$ in both cases]
- $\text{Beta}(1, 1)$ is also called $\text{Uniform}[0, 1]$

Binomial Proportion Example

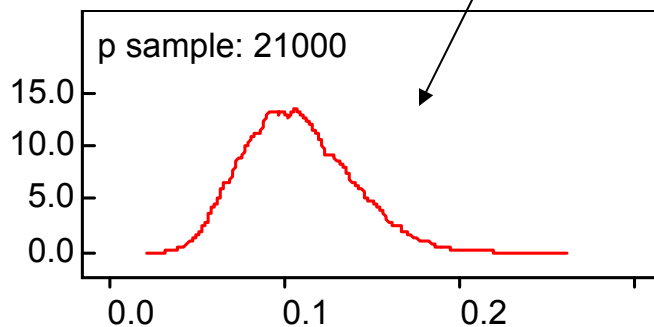
Prior for q



Posterior for q with $n=10$, $x=1$



Posterior for q with $n=100$, $x=10$



Here, $X \sim \text{Bin}(n, q)$

Prior information about q
Is reflected by a distribution
That gives equal uncertainty
To all values of q .



Basic approach

- Prior probability distributions for
 - Test **Sensitivity** & **Specificity** &
 - **Prevalence**
- Data (test results: $(++, +-, -+, --)$
in 2 populations)
- Posterior probability distributions for all unknowns



Prior Distributions

- Scientific information about sensitivity, specificity and prevalence is modeled with **beta distributions** based on data and/or expert opinion
- Expert opinion (inputs)
 - Elicit most plausible value
 - Elicit Value that expert is 95% sure that the value exceeds (or is less than)
 - Translate these into a particular Beta distn

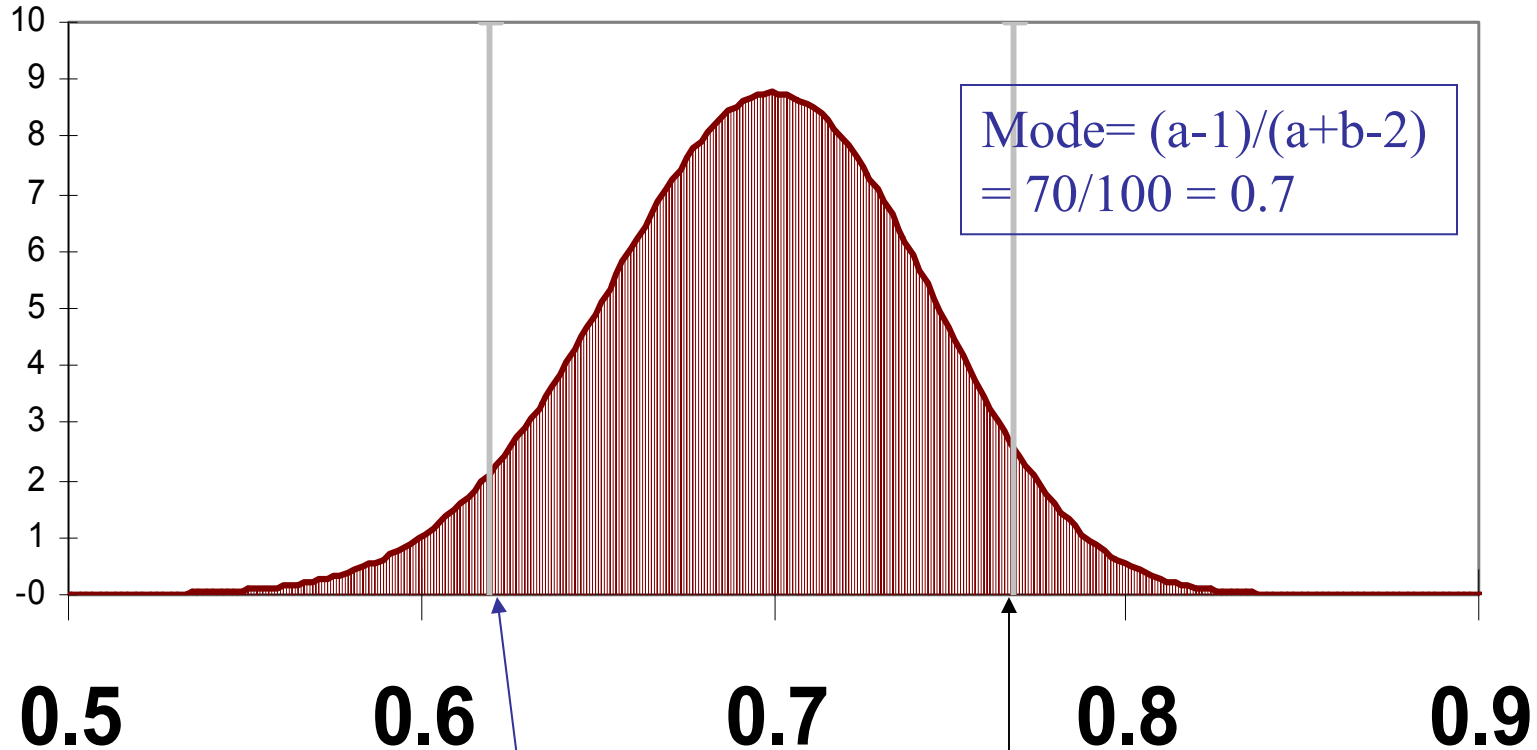


Example: Previous Data

- Validation study that found 70 test-positive out of 100 infected individuals
- Beg. of time: Uniform Prior on Prev
- Posterior is then Beta(71,31)
- Use this as prior for new experiment provided the validation study population and new population are \sim same

$$P(\text{prev}) = \text{const} * \text{prev}^{70} (1 - \text{prev})^{30}$$

Sensitivity: beta (71, 31)

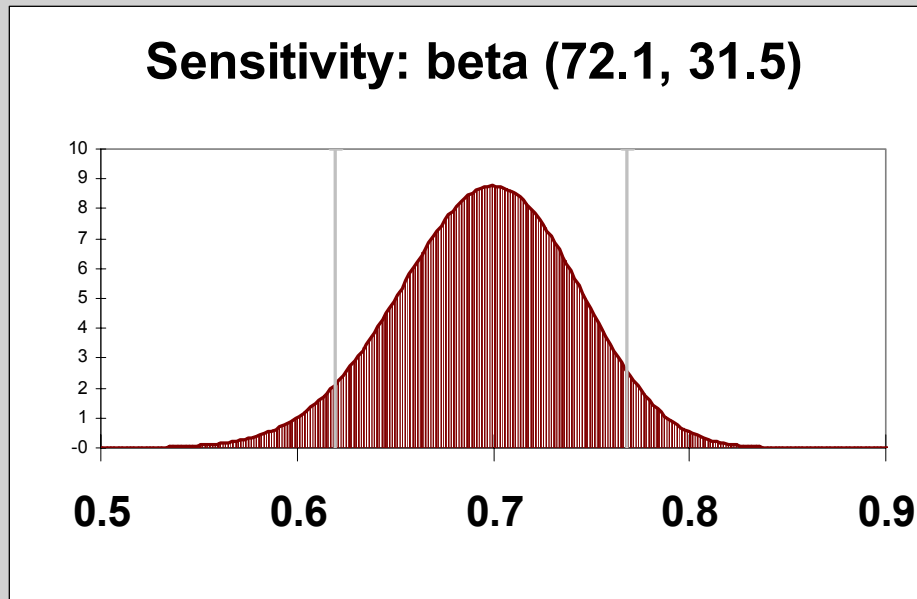


95% area above 0.62

95% area below 0.78

Expert Opinion

- Best guesses for sensitivity were
 - Most plausible value (mode) = 0.70
 - 95% sure it is above 0.62
 - Use program to find (a, b)



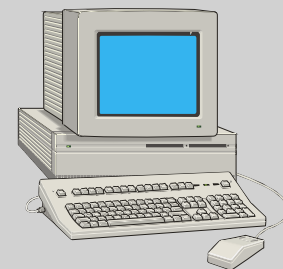


Selection of priors

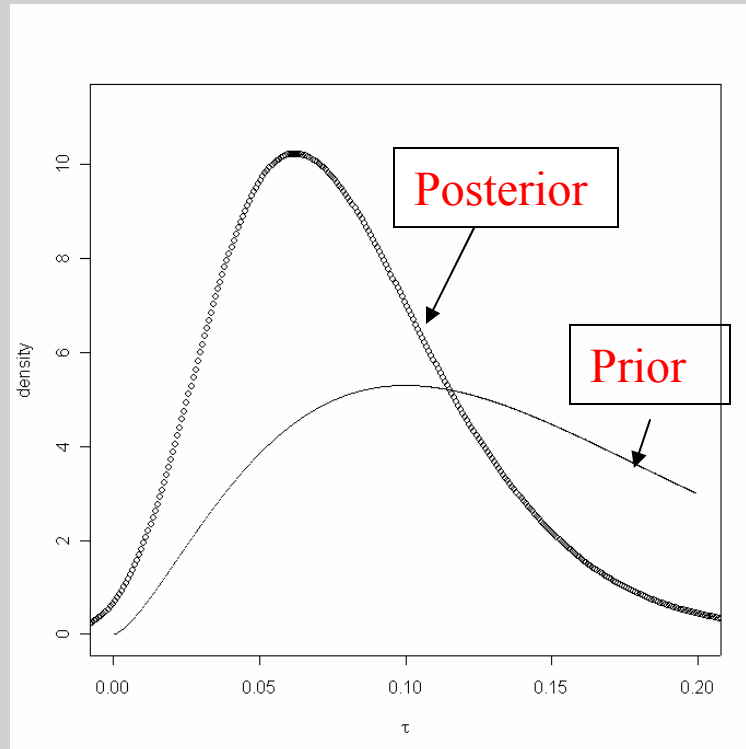
- Important that prior “correctly” centered and has “sufficient” spread
- If the model is “identified”, can use non-informative “flat priors” i.e. Beta (1,1) or relatively diffuse priors with minimal weight
- Should always do a sensitivity analysis – evaluation of different priors.

Bayesian Inference

- Implemented using Gibbs sampling, an iterative **Markov-chain Monte Carlo** simulation method
- Write code in S-plus, Matlab, **WinBUGS** etc.
- Generates Sample from the joint posterior
- Results presented as a smoothed histogram and percentiles



Prior and Posterior Densities



False-negative proportion ($1 - \text{sensitivity}$)

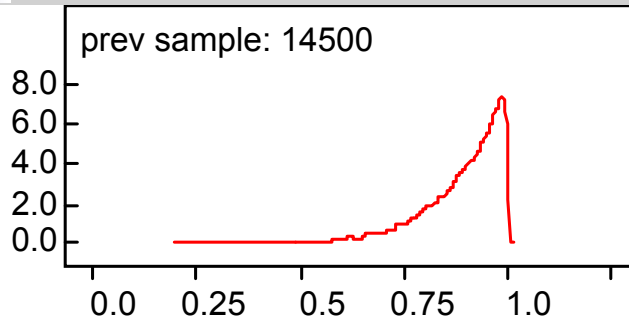


Microscopic Examination Ex.

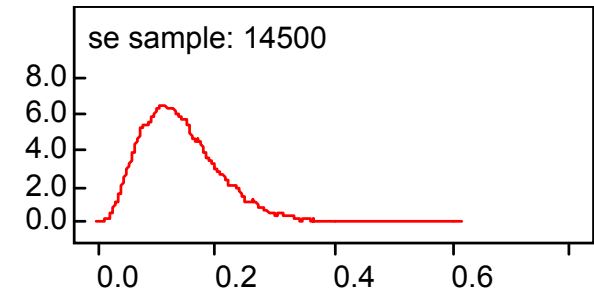
- Recall $X = 3$, $n = 30$, S_e is unknown, $S_p = 1$
- We consider $\text{prev} \sim \text{Beta}(9, 1)$ and $\text{prev} \sim \text{Beta}(900, 10)$
- With $X = 300$, $n = 3000$
- And then let $\text{prev} \sim \text{Beta}(1, 9)$ and $\text{prev} \sim \text{Beta}(1000, 9000)$

Microscopic Examination Example

Prev ~
Beta(9,1)

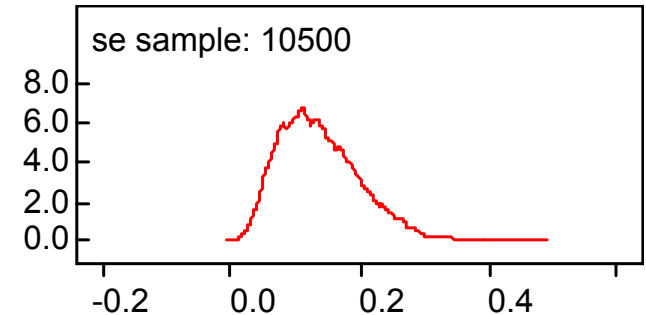
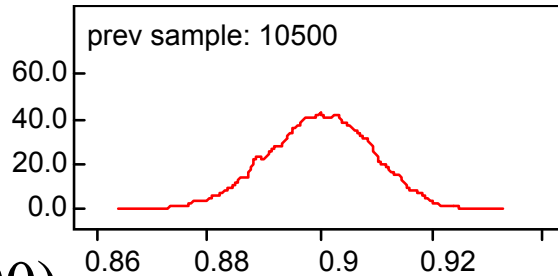


0.303



strong prior on prev; reg data

Prev ~
Beta(900,100)



Prevalence

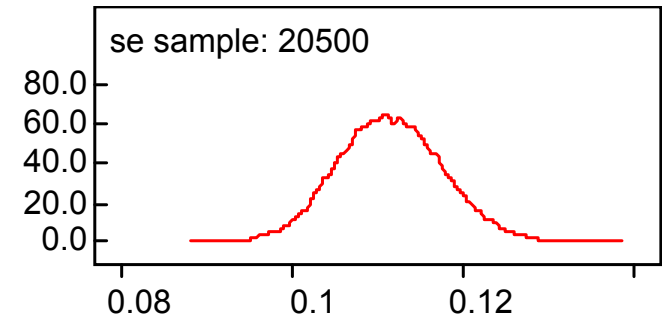
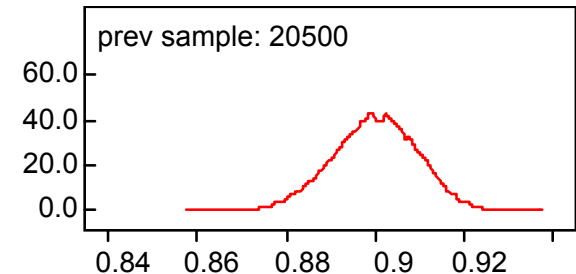
Sensitivity

Posteriors for Prev and Se

- $X=300, n=3000$
- $\text{Prev} \sim \text{Beta}(900, 100)$
- $\text{Se} \sim \text{Beta}(1, 1)$
- $\text{Sp} = 1$

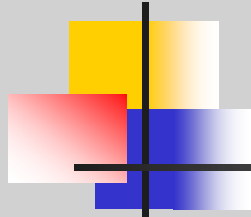
Prevalence

1000 times the data

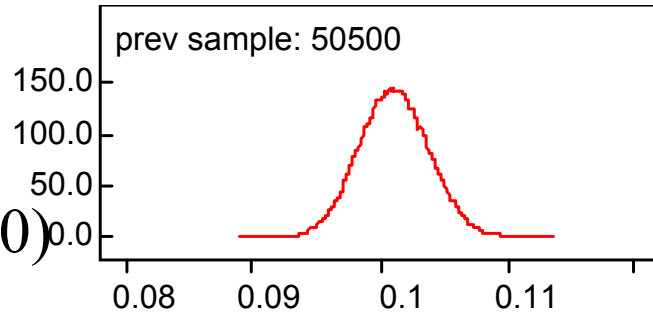


Sensitivity

Change the Prior on Prev

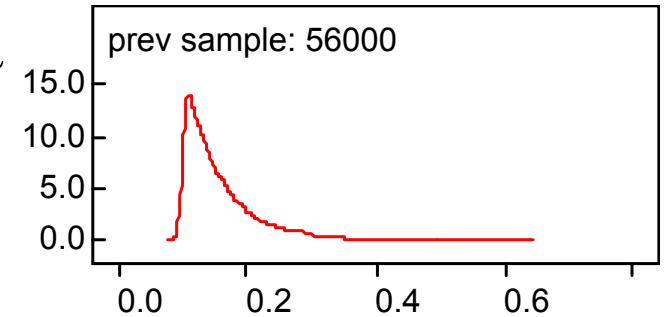


Prevalence

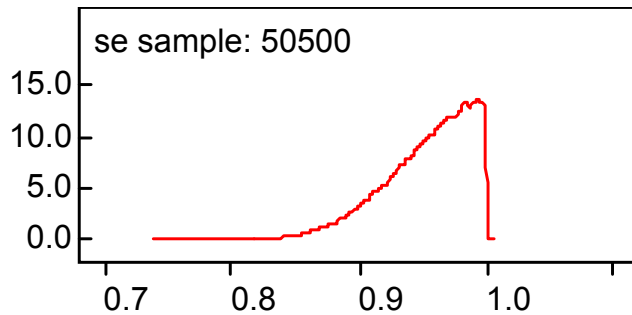


Prev ~
Beta
(1000,9000)

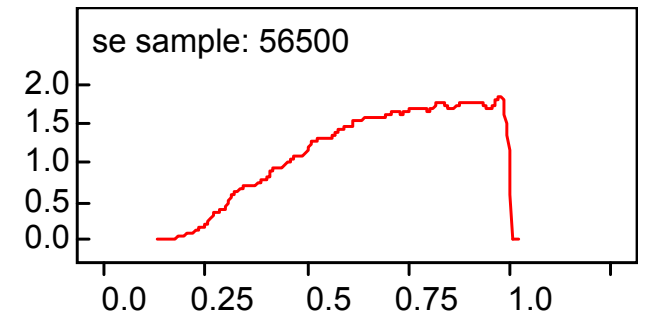
Prevalence



Prev ~
Beta
(1,9)



Sensitivity



Sensitivity



Two Tests, Two Populations

- Here we consider the Hui-Walter (1980) model.
- We assume two samples of data are collected from distinct populations
- Two screening tests are applied separately to each data set and results presented in two, two by two tables
- There are 6 parameters and 6 dof



Hui-Walter Assumptions

- **Conditional Independence** of diagnostic tests, namely, the sensitivity of test one, when applied to test 2 positive (negative) results, is the same as the sensitivity of test 1 e.g.

$$\Pr(T_1+ | T_2+, I) = Se_1$$

$$\Pr(T_1- | T_2+, \text{not } I) = Sp_1 \text{ etc.}$$

- **Prevalences** are **Distinct**
- The sensitivities and specificities of the two tests are the same across popns

Testing for *Nucleospora salmonis*

	T_1^+	T_1^-
T_2^+	0	0
T_2^-	3	129

	T_1^+	T_1^-
T_2^+	3	0
T_2^-	24	3



- Two Samplings of Trout
- Test 1: PCR and
- Test 2: Microscopic Examination (ME)



Validity of Assumptions

- **Microscopy** relies on visual inspection of the parasite; **PCR** is DNA based, so **Conditional Independence** was considered to be **reasonable** since biologic basis for the tests is different.
- Sp should be the same from one population to the next
- **Prevalences** in samples are **distinct**
- Se may vary from low prev. popn to high prev popn due to differences in staging of disease



Maximum Likelihood Estimates

$$\text{Prev}_1 = 0.0,$$

$$\text{Prev}_1 = 0.9$$

$$\text{Se}_{\text{ME}} = 0.11, \text{Se}_{\text{PCR}} = 1.0 \quad \text{Sp}_{\text{ME}} = 1.0, \text{Sp}_{\text{PCR}} = 0.98$$

- Standard errors are difficult for these data because of the zeros.
- ML inferences (Confidence Intervals) rely on large samples, which is questionable for these data.

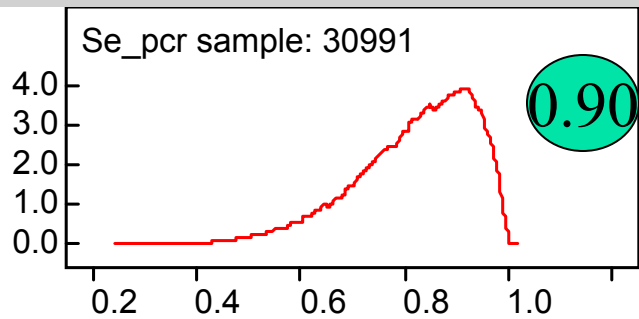


Bayesian Methods

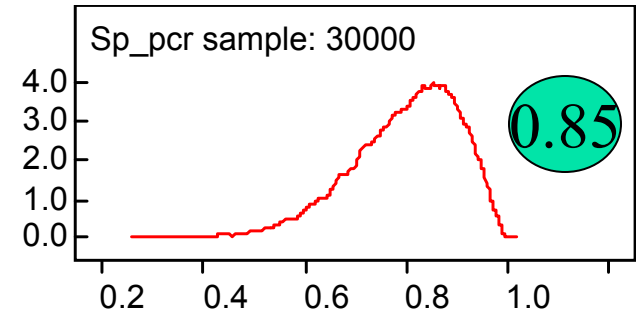
- Elicit expert opinion about two Se's, and two Sp's and two Prevalences, independently of the data, and model this with probability
- Use independent Beta distributions cf. Joseph et al (1995), Johnson et al (1991, 2001), Enoe* et al (2000)

Expert Opinion as Probability

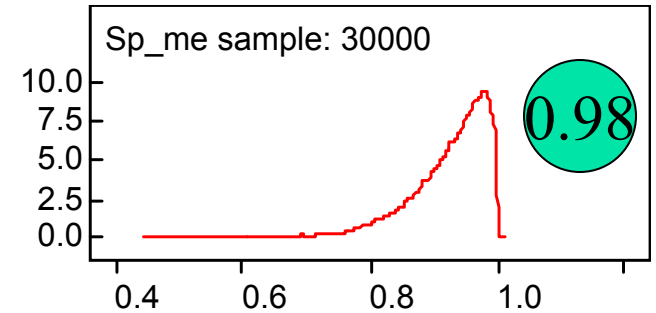
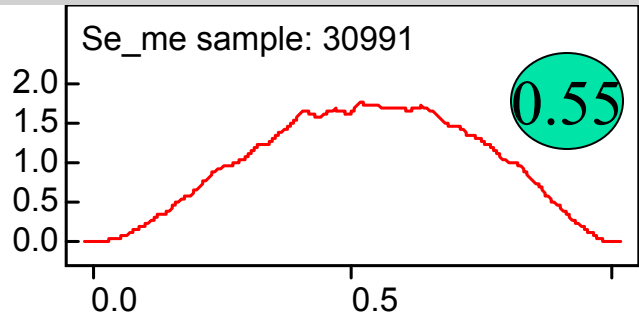
PCR



Specificity



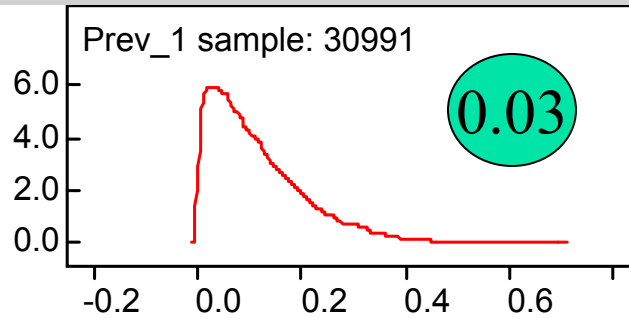
ME



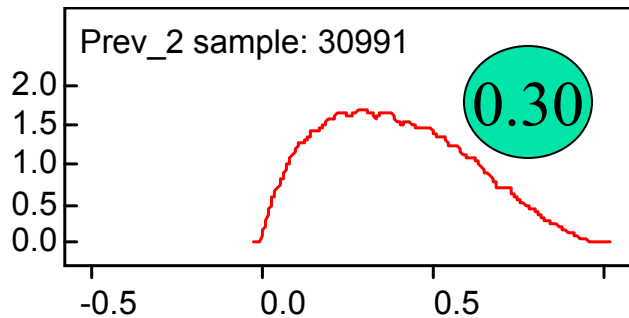
Prior Estimates

Expert Opinion about Prevalences

Prev 1



Prev 2



- First population expected to have low prevalence and second is thought to be infected but with lots of uncertainty



Bayesian Inferences

Parameter	Est	sd	2.5%	97.5%
Prev_1	0.012	0.013	0.0008	0.047
Prev_2	0.861	0.066	0.704	0.960
Se_me	0.166	0.065	0.066	0.318
Se_pcr	0.938	0.047	0.815	0.992
Sp_me	0.993	0.007	0.972	0.9996
Sp_pcr	0.968	0.016	0.928	0.991

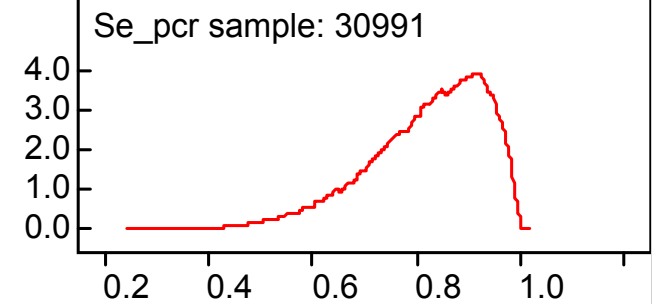
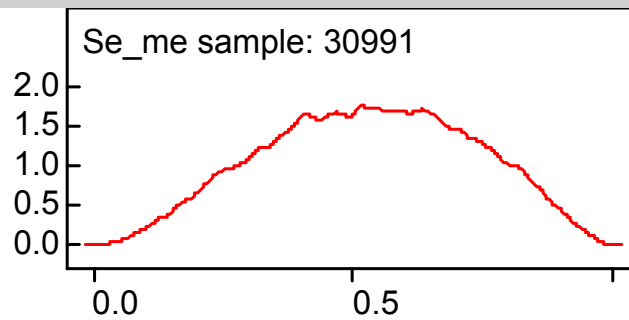
Bottom line no-gold standard inferences
accounting for all uncertainty in imprecisely
known quantities

Prior vs Posterior for Se

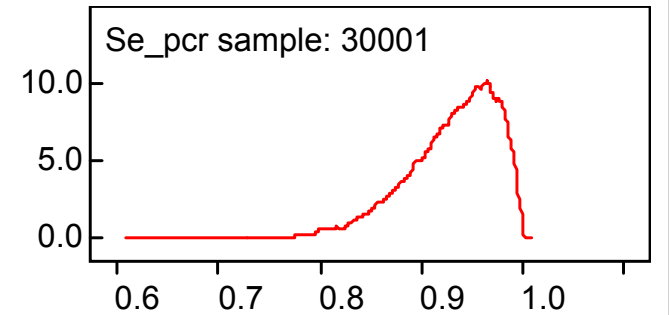
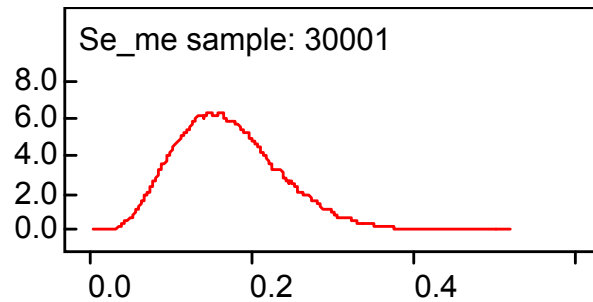
ME

PCR

Prior
Inference



Posterior
Inference

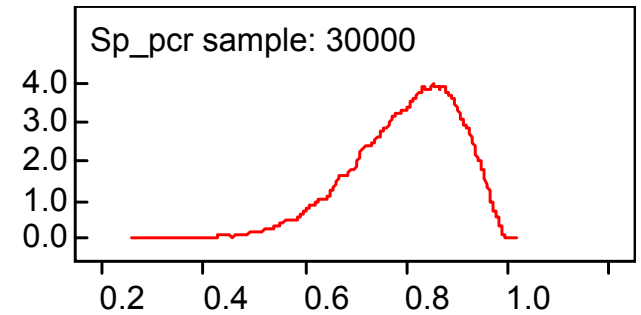
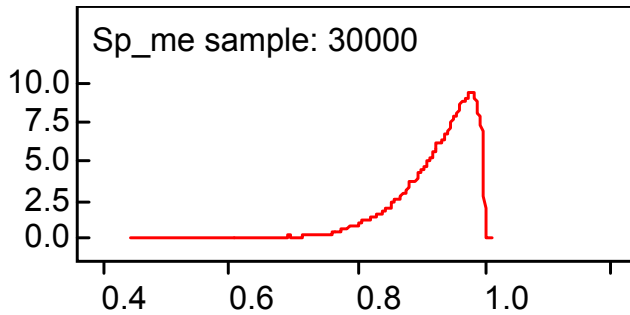


Prior vs Posterior for Sp

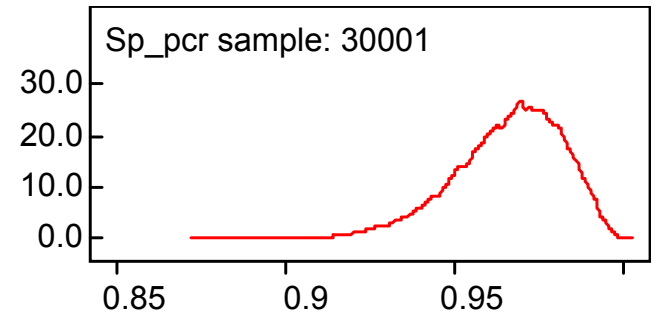
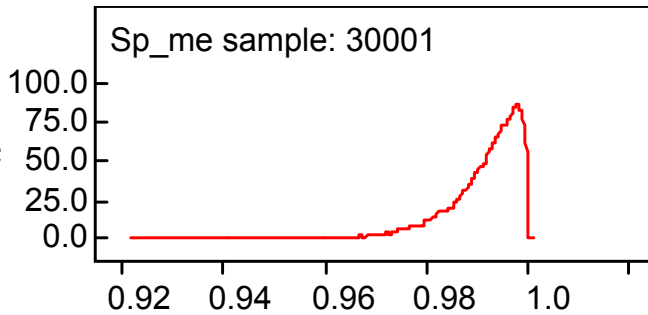
ME

PCR

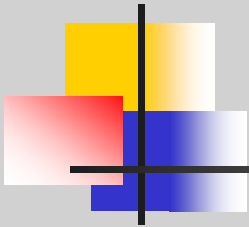
Prior
Inference



Posterior
Inference



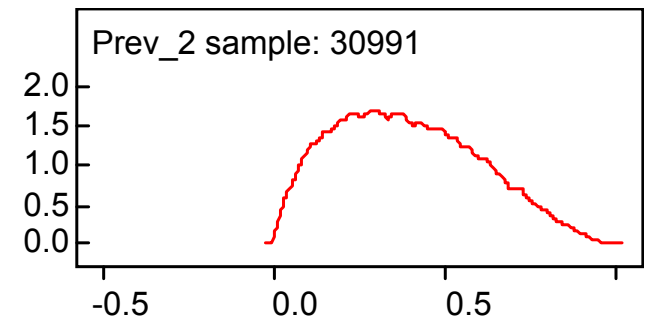
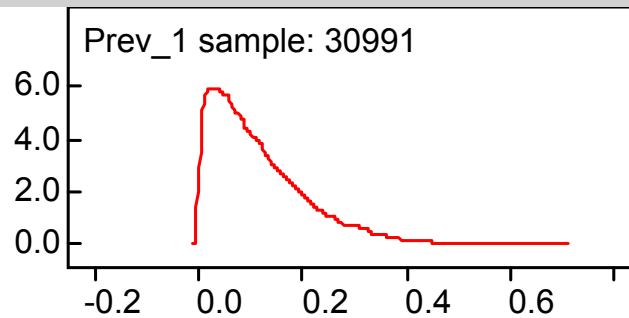
Prior vs Posterior Prevalence



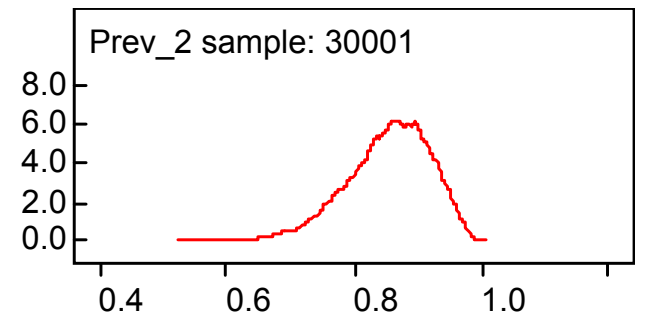
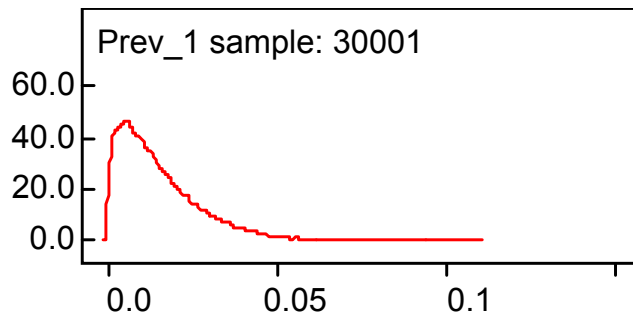
Prevalence 1

Prevalence 2

Prior
Inference



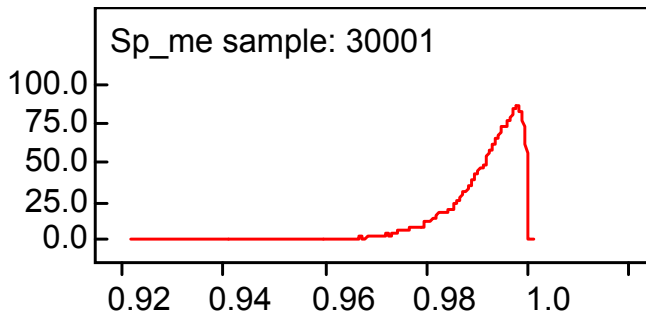
Posterior
Inference



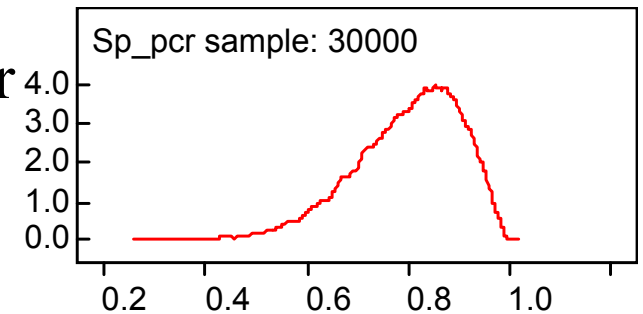
Larger Sample Size (x 4)

Bayesian Inferences

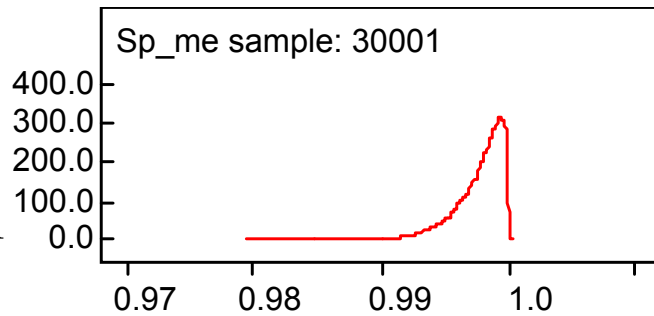
Actual
Data



Prior
Inf.

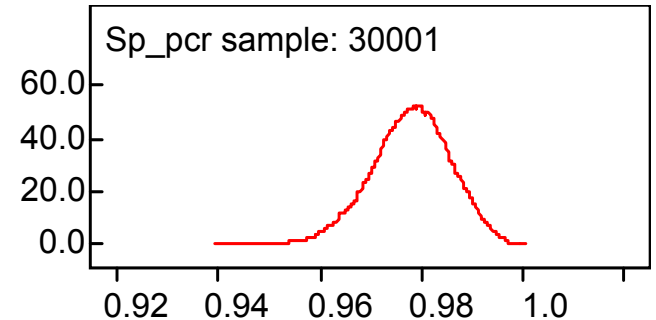


Four
Times
Actual
Data



Sp_ME

Four
Times



Sp_PCR



Conclusions for Data Analysis

- With two tests that have distinct biologic bases and with two (or more) samples from distinct populations, it is possible to estimate the accuracy of both tests e.g. [pull the rabbit out of the hat](#)
- Larger sample sizes result in more accurate inferences e.g. smaller standard deviations.
- If the biologic bases for the tests are similar or same, more complicated methods are available. They require very good information on either the prevalences of the two groups or on the sensitivity and specificity of one of the tests e.g. to within plus or minus 0.05 on each ([Georgiadis et al., 2003](#))



What About ML Estimation?

- Lots of software exists for lots of problems
- Does not require input of scientific information beyond selection of probability model for the data
- In large sample problems without too many parameters, estimates are consistent, efficient and asymptotically unbiased that is they are “good”



Disadvantages

- In order to get CI's for complicated functions of the parameters, must use the Delta Method, which is very complicated and highly non-user friendly
- You often don't know if the sample size is large enough for the large sample theory basis for ML estimation to be appropriate



Disadvantages Cont.

- The likelihood may be multimodal or its mode may be on the boundary of the parameter space so that the MLE may not even exist and or convergence may be difficult (*esp. if zeros in cells*)
- For problems that *lack identifiability*, it is impossible to do ML unless “guesses” are used for unknown parameters. But then it’s difficult to measure added uncertainty about those guesses



MLE's for Fish Example (EM)

$$\text{Prev}_1 = 0.0,$$

$$\text{Se}_{\text{ME}} = 0.11,$$

$$\text{Sp}_{\text{ME}} = 1.0,$$

$$\text{Prev}_2 = 0.9$$

$$\text{Se}_{\text{PCR}} = 1.0,$$

$$\text{Sp}_{\text{PCR}} = 0.98$$

- Standard errors are difficult because of the zeros.
- Sample sizes are not large so large sample normal theory is questionable for these data.



Comparison of NR and EM

(NR with 0.185 added to each cell):

	<u>Newton-Raphson</u>	<u>EM</u>
Se (PCR)	0.9999	1.0
Sp (PCR)	0.9987	0.977
Se (Micro)	0.1107	0.1114
Sp (Micro)	1.0	1.0
Prev (T1)	0.0254	0.0000
Prev (T2)	1.0	0.8977

NR would not converge without adding a constant to each cell



More Conclusions

- Bayesian method seems preferable to maximum likelihood unless there are very large samples.
- Computer code/software is available for both Bayesian and ML inferences at the website

www.epi.ucdavis.edu/diagnostictests/



Correlated Tests

- Tests that measure same biologic response

- Serum antibodies
- Bacterial isolation
- Skin antigen tests

are likely to be correlated

- Solution: needs Bayesian approach because 2 additional correlation parameters (i.e. 8 parameters > 6 d.f.)
- Adding more populations, resulting in 9 parameters and 9 “dof” doesn’t work



Bayesian approach

- Incorporates knowledge about the sensitivity and specificity of **the established test** using prior knowledge
- Allows inferences about the characteristics of the 2 tests adjusted for correlation ie.. it fixes the correlation problem!
- Provides estimates of the test correlations



Example: toxoplasmosis

- Data from evaluation of serologic tests for *T.gondii* in 1000 naturally-infected sows, Dubey et al. (1995) AJVR 56: 1030-1036
- **"Gold standard"?:** mouse and cat bioassay using heart muscle
- Test results: MAT titer $\geq 1:20$ considered positive, negative otherwise



Toxoplasmosis in pigs

Observed data

		Batch 1		Batch 2	
		ELISA		ELISA	
		+	-	+	-
MAT	+	67	25	97	33
	-	41	329	36	371
		463		536	



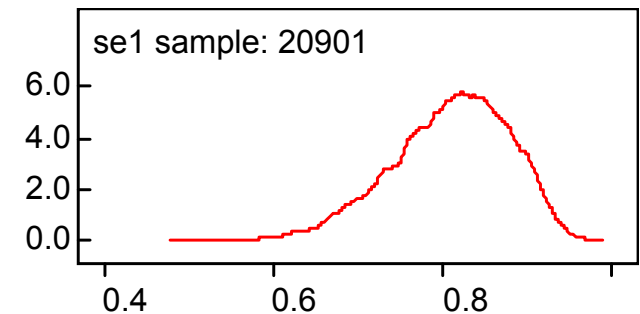
T. Gondii serologic tests

- Need to provide prior estimates for one of the tests (usually the existing test -- i.e. MAT)
- Move to replace MAT with ELISA because ELISA can be automated, yields results more rapidly and is amenable to use in mass screening of pigs

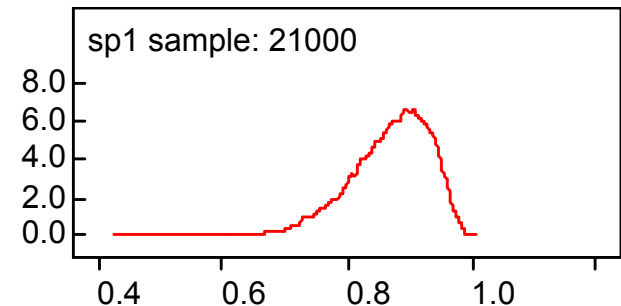
Prior for Se and Sp for the MAT

- Mode for Se = 0.82 and 5th percentile = 0.68
- Mode for Sp = 0.9 and 95th percentile = 0.75
- Modes for prev1 and prev2 are 0.07 and 0.20; very diffuse

Se



Sp





Comparison of 3 models

- **No correlation**

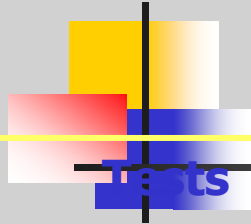
 - Maximum Likelihood

 - Bayesian

- **Correlation**

 - Bayesian

Results



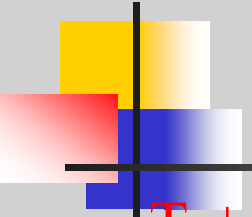
Tests	True values	Max. likelihood (no corr)	Bayes (no corr)	Bayes (corr)
MAT – Se	0.83	0.999 (0.99, 1)	0.83 (0.7, 0.93)	0.81 (0.63, 0.92)
- Sp	0.90	0.972 (0.97, 0.98)	0.94 (0.90, 0.99)	0.90 (0.77, 0.94)
ELISA - Se	0.73	0.81 (0.79, 0.83)	0.91 (0.78, 1)	0.72 (0.63, 0.92)
- Sp	0.86	0.90 (0.899, 0.903)	0.94 (0.90, 0.99)	0.86 (0.77, 0.94)



Alternative Situation

- Suppose there is a third test, conditionally independent of the two tests of interest and for which there is good prior information about the third test
- The third test may be an “almost” gold standard
- Then a data set can be split into two parts according to T_3+ or T_3- status

Toxoplasmosis Data Revisited:



T_3^+	T_1^+	T_1^-
T_2^+	73	17
T_2^-	4	14

T_3^-	T_1^+	T_1^-
T_2^+	91	41
T_2^-	73	687

- Test 1: ELISA and
- Test 2: MAT
- Test 3: Mouse Bioassay has $Sp_3=1$ and should be cond indep of ELISA and MAT



Example Cont

- From the Mouse+Cat (“perfect” test data), we know that Cat+ occurred for 108 animals out of 170 CM+ animals
- The “Cat” test is regarded as virtually 100% specific
- So a pretty good guess for the Mouse Se is $108/170 = .63$
- We proceed to analyze the data with relatively non-informative priors for everything else



Posterior Inferences

mouse with 63% sensitivity and .995 spec

node	est	sd	2.5%	97.5%	``True''
pi	0.166	0.0187	0.132	0.205	0.171
se[1]	0.856	0.0345	0.786	0.919	0.827
se[2]	0.733	0.0445	0.643	0.817	0.727
se[3]	0.630	0.0367	0.556	0.700	-----
sp[1]	0.905	0.0165	0.873	0.937	0.901
sp[2]	0.856	0.0165	0.824	0.888	0.858
sp[3]	0.994	0.0022	0.989	0.998	-----



Posterior Inferences

Mouse with **63% sensitivity** and **100% spec**
node est sd "True"

pi 0.174 0.0187 0.171

se[1] 0.828 0.0320 0.827

se[2] 0.709 0.0400 0.727

sp[1] 0.905 0.0166 0.901

sp[2] 0.857 0.0165 0.858



The Prior

- $se[1] \sim \text{Beta}(24.09, 5.73)$
- $sp[1] \sim \text{Beta}(23.05, 3.45)$
- $se[3] \sim \text{Beta}(108, 62)$
- Everything else (6 other parameters) was given a uniform[0,1] distribution



End of Example

- Down weighting (by a factor of 5) the prior on Test 1 characteristics had virtually no effect on the inferences
- Shifting to uniform priors on everything except the sensitivity for Mouse had little effect as well
- So knowing the specificity well and having a good guess for the sensitivity of Mouse gets excellent inferences here



Conclusions

- Can easily handle more than two conditionally independent tests. Model will be identifiable with two or more populations
- Multiple correlated tests can be handled, but require care since not all dependence models will be identifiable
- WinBugs makes models very simple to implement



What I didn't talk about

- You may be sampling finite populations and thus the Binomial/Multinomial model assumptions may fail
- Su, Gardner and Johnson (2003) have addressed the “Hypergeometric” nature of this problem and have extended the HW model to finite population sampling and to accommodate correlated tests



Joint and Sequential Testing

- With **joint** testing, say **+** if **either** test indicates **+**, or if **both** tests indicate **+**
- Sequential version 1 would indicate **+** if the first test was **+** or if the first was **-** and the second was **+**
- Sequential version 2 would indicate **-** if the first test was **-** and **+** only if both were **+**



More that was “missed”

- You may sample multiple populations and test individuals from each sub-population. With two tests, and a “large” number of populations, it is possible to consistently estimate sensitivity and specificity of both tests, (**no-gold standard necessary**) and the distribution of prevalences in the population (Hanson, Johnson and Gardner, 2003)



more

- Sample size calculations for determining a single population is “free from disease” based on imperfect screening tests (Johnson, Su and Gardner, 2003)
- Extensions to multiple sub-populations regarded as a super-population is underway
- ROC curve estimation without a gold standard is considered in Fosgate et al (2003) and is currently being further investigated



The “Future”

- Instead of dichotomizing test outcome results, we are developing models and methods for determining “disease status” based on the actual numerical test outcomes, when no gold standard exists. This amounts to calculating the probability that an individual is “diseased” given their test outcomes and given any other relevant diagnostic information. (Thurmond et al, 2002; Su et al, 2003)



References

- Hui and Walter ([Estimating the error rates of diagnostic tests](#), Biometrics, 1980)
- Enoe, Georgiadis and Johnson ([Estimation of sensitivity and specificity of diagnostic tests and disease prevalence when the true disease state is unknown](#), Prev. Med., 2000)
- Georgiadis, Johnson, Gardner and Singh ([Correlation-Adjusted estimation of sensitivity and specificity](#), Applied Statistics, 2003)



More References

- Joseph, Gyorkos and Coupal (Bayesian estimation of disease prevalence and parameters for diagnostic tests in the absence of a gold standard, Am. J. Epi., 1995)
- Johnson, Gastwirth and Pearson (Screening without a gold standard: The Hui-Walter paradigm revisited, Am. J. Epi., 2001)
- Georgiadis, Gardner and Hedrick (Field evaluation of Se and Sp of a PCR for detection of *N. salmonis* in rainbow trout, J. Aquatic Animal Health, 1998)



More References

- Singer, Boyce, Gardner et.al. (Evaluation of bluetongue virus diagnostic tests in free-ranging bighorn sheep, *Prev. Vet. Med.*, 1998)
- Su, Johnson, Gardner (Diagnostic test accuracy and prevalence inferences based on joint and sequential testing with finite population sampling; Submitted to *Biometrics*)
- Johnson, Su and Gardner (Sample size calculations for surveys to substantiate disease freedom; *Biometrics*, in revision)



Refs

- McInturff, Johnson, Gardner and Cowling (Modeling risk when binary outcomes are subject to error; *St. Med.*, in revision)
- Thurmond, Johnson, Munoz, Su, Hietala (Probability diagnostic assignment for serologic measures, with application to *Neospora caninum* infection, *Am. J. Vet. Res.*, 2002)
- Fosgate, et al. (Comparison of Rrucellosis Serologic Tests without a Gold Standard in Cattle and Water Buggalo (*Bubalus bubalis*) of Trinidad, *Am J Vet Res*, 2002)



Refs

- Fosgate, et al. (Receiver-operating characteristic (ROC) curves for detection of Brucella infection using a competitive enzyme-linked immunosorbent assay in cattle and water buffalo, *Am J Vet Res*, 2003)

WinBugs Version 1.3, (1.4) Spiegelhalter, Thomas and Best. Cambridge University.

- <http://www.mrc-bsu.cam.ac.uk/bugs>



WinBugs HW Computer Code

```
model;{Se_me ~dbeta(2.82,2.49)
  Se_pcr ~dbeta(8.29,1.81)
  Sp_me ~dbeta(15.7,1.3)
  Sp_pcr ~ dbeta(10.69,2.71)
  Prev_1 ~ dbeta(1.27,9.65)
  Prev_2 ~dbeta(1.73,2.71)
x1[1:N, 1:N] ~ dmulti(p1[1:N, 1:N],m1)
  for(j in 1:N){
    for(k in 1:N){
      p1[j,k] <- Prev_1*(j-1+Se_me*(3 - 2*j))*( k-1 + Se_pcr*(3-2*k )) + (1-Prev_1)*(2 - j +
  Sp_me*( 2*j - 3 ) )*(2 - k + Sp_pcr*( 2*k - 3 ) ) }}
x2[1:N, 1:N] ~ dmulti(p2[1:N, 1:N],m2)
  for(j in 1:N){
    for(k in 1:N){
      p2[j,k] <- Prev_2*(j-1+Se_me*(3 - 2*j))*( k-1 + Se_pcr*(3-2*k )) + (1-Prev_2)*(2 - j +
  Sp_me*( 2*j - 3 ) )*(2 - k + Sp_pcr*( 2*k - 3 ) ) }}
}

list(m1=132,x1= structure(.Data = c(0,0,3,129),.Dim = c(2,2)),m2=30,x2= structure(.Data = c(3,0,24,3),.Dim =
c(2,2)),N=2)

list(Sp_me =.5,Sp_pcr=.5,Se_me=.5,Se_pcr=.5,Prev_1=.5,Prev_2=.5)
```