KU Leuven Summer School
Segment 3A
Misclassification

Paul Gustafson

September 15, 2022

A **case-control** study of association between herpes simplex virus and cervical cancer

Women with invasive cervical cancer ($Y = 1$) versus healthy controls ($Y = 0$).

Explanatory variable is presence of HSV ($X = 1$) versus not ($X = 0$).

But, a lab test to definitively determine X for a study participant is very expensive.

A lab test ('western blot') that is less definitive is much cheaper. Let X^* be the result of this test.

The data

```
dim(dta)
```

```
## [1] 2044    3
```

Have (X^*, Y) for all patients:

```
table(dta[,"y"],dta[,"xstr"], dnn=c("y","xstr"))
```

```
##    xstr
## y     0   1
##   0 750 562
##   1 336 396
```

But distinguish the unvalidated and validated sub-samples

```
unv <- is.na(dta[,"x"])
vld <- !unv

c(sum(unv),sum(vld))
```

```
## [1] 1929  115
```

Unvalidated

```
table(dta[unv,"y"],dta[unv,"xstr"], dnn=c("y","xstr"))
```

```
##    xstr
## y     0   1
##   0 701 535
##   1 318 375
```

Validated

```
table(dta[vld,"x"],dta[vld,"xstr"],dta[vld,"y"],
      dnn=c("x","xstr","y"))
```

```
## , , y = 0
##
##    xstr
## x    0  1
##   0 33 11
##   1 16 16
##
## , , y = 1
##
##    xstr
## x    0  1
##   0 13  3
##   1  5 18
```

Pause, what inference might we draw if we go the simple/naive route

Say the validation exercise had not been carried out, and we weren't aware that western-blot lab assay was error-prone.

```
summary(glm(y~xstr, family=binomial, data=dta))$coef
```

```
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -0.803     0.0656  -12.23 2.11e-34
## xstr            0.453     0.0928    4.88 1.06e-06
```

Technical note: could have determined point-estimate and SE direct from 2 by 2 table. Logistic regression is overkill here.

Or another extreme: Only willing to work with X, treat all X^* measures as worthless

```
summary(glm(y~x, family=binomial, subset=vld, data=dta))$coef
```

```
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -1.012      0.292   -3.47  0.00053
## x              0.681      0.400    1.70  0.08845
```

The Bayesian, latent variable approach

Let's build a generative model:

$$f(\gamma_0, \gamma_1, Sn, Sp) \prod_{i=1}^{n} f(y_i)\ f(x_i|y_i, \gamma_0, \gamma_1)\ f(x_i^*|x_i, y_i, Sn, Sp)$$

Pause: Missing at Random assumption here? Interpretation?

Code-up the generative model

```
genmod.string <- "model{

  ### prior distribution
  gamma.0 ~ dunif(0,1)
  gamma.1 ~ dunif(0,1)
  sens ~ dunif(0.5, 1)
  spec ~ dunif(0.5, 1)

  trgt <- logit(gamma.1)-logit(gamma.0)

  ### statistical model
  for (i in 1:n) {
    x[i] ~ dbern(pr.x[i])
    pr.x[i] <- (1-y[i])*gamma.0 + y[i]*gamma.1

    xstr[i] ~ dbern(pr.xstr[i])
    pr.xstr[i] <- (1-x[i])*(1-spec) + x[i]*sens
  }
}"
```

Turn the crank

```
### generative model, data go in
mod <- jags.model(textConnection(genmod.string),
  data=list(x=dta$x, y=dta$y, xstr=dta$xstr,
    n=dim(dta)[1]),
  n.chains=3)

update(mod, 2000)  ### burn-in

###  MC output comes out
opt.JAGS <- coda.samples(mod, n.iter=10000, thin=1,
  variable.names=c("gamma.0","gamma.1","sens","spec","trgt"))
```

Our answer

```
MCMCsummary(opt.JAGS)
```

```
##            mean     sd  2.5%   50% 97.5% Rhat n.eff
## gamma.0 0.418 0.0459 0.326 0.418 0.506    1   743
## gamma.1 0.653 0.0503 0.554 0.652 0.752    1  1106
## sens    0.675 0.0388 0.600 0.674 0.752    1  1038
## spec    0.740 0.0419 0.658 0.739 0.821    1   810
## trgt    0.975 0.2414 0.539 0.958 1.487    1  1501
```

Computationally frustrating (ess / wall-time) - Collapse?

E.g., for the unvalidated controls:

Code this up

```
genmod.clps.string <- "model{
  ### prior distribution
  gamma.0 ~ dunif(0,1)
  gamma.1 ~ dunif(0,1)
  sens ~ dunif(0.5, 1)
  spec ~ dunif(0.5, 1)

  s.0 ~ dbin(gamma.0, nv.0)
  t.00 ~ dbin(1-spec, nv.0-s.0)
  t.01 ~ dbin(sens, s.0)

  s.1 ~ dbin(gamma.1, nv.1)
  t.10 ~ dbin(1-spec, nv.1-s.1)
  t.11 ~ dbin(sens, s.1)

  du.0 ~ dbinom(pr.0, nu.0)
  pr.0 <- (1-gamma.0)*(1-spec) + gamma.0*sens

  u.1 ~ dbinom(pr.1, nu.1)
  pr.1 <- (1-gamma.1)*(1-spec) + gamma.1*sens
```

Turn the crank

```
### generative model, data go in
mod.clps <- jags.model(textConnection(genmod.clps.string),
  data=list(u.0=535, nu.0=535+701,
            u.1=375, nu.1=375+318,
            s.0=16+16, nv.0=16+16+33+11,
            t.00=11,t.01=16,
            s.1=5+18, nv.1=5+18+13+3,
            t.10=3, t.11=18),
  n.chains=3)

update(mod, 2000) ### burn-in

###  MC output comes out
opt.clps.JAGS <- coda.samples(mod.clps, n.iter=10000, thin=1,
  variable.names=c("gamma.0","gamma.1","sens","spec","trgt"))
```

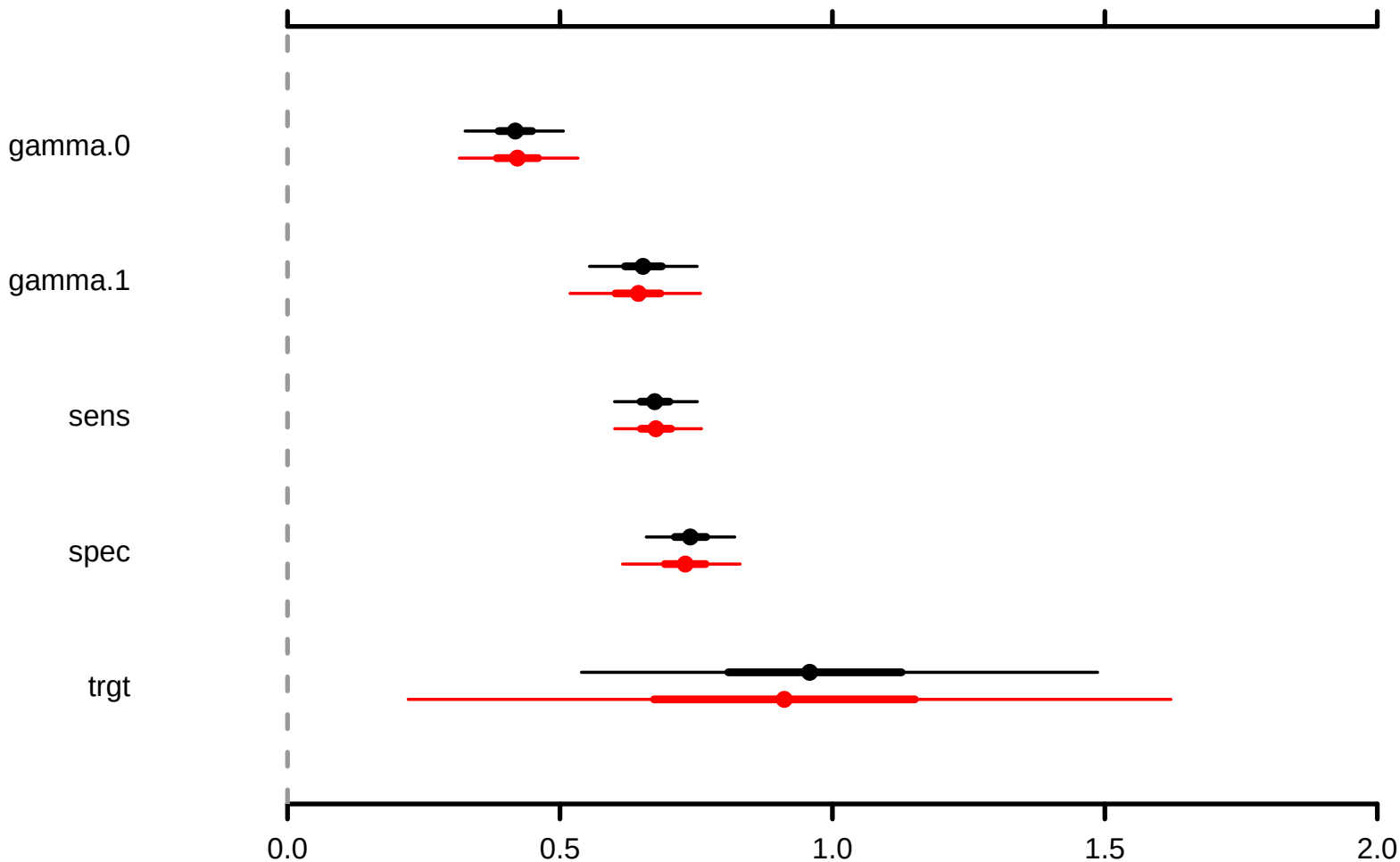
Get an answer

```
MCMCsummary(opt.clps.JAGS)
```

```
##            mean     sd  2.5%   50% 97.5% Rhat n.eff
## gamma.0 0.422 0.0559 0.315 0.422 0.533    1 20595
## gamma.1 0.642 0.0613 0.518 0.644 0.758    1  6008
## sens    0.677 0.0409 0.600 0.676 0.760    1  5812
## spec    0.729 0.0553 0.615 0.730 0.831    1  7086
## trgt    0.913 0.3566 0.221 0.912 1.621    1  8538
```

Sanity check: Two computational approaches going after **the** posterior distribution

```
MCMCplot(opt.JAGS, opt.clps.JAGS)
```



Putting the inference in context

Have estimated the log oddd-ratio describing the (X, Y) association to be 0.91 (posterior mean), with an uncertainty estimate 0.36 (posterior SD).

- Contrast to complete-case analysis?

- Contrast to pretending X^* is the gold-standard?

Many things that could be followed up on here

- Generality of idea: How to make the best use of (X^*, Y) data when the relationship between X and Y is of interest.
- Computation: Tradeoff in collapsing.
- Assumptions to be considered: we have invoked $(X^* \perp Y|X)$.
- Study design: If you were given a budget, how would you trade-off total number of patients versus number validated?