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Statistical Science

BAYLOR
UNIVERSITY

Inference and sample size determination for clinical trial with rare events and potential misclassification

Bayesian SSD

- Does not require fixed values for unknown parameters
- Uses prior distributions as weight functions to average over sample space.
- Several criterion for both interval estimation and hypothesis testing as well as moment based.

Sampling and Fitting Priors

- Wang and Gelfand (2002) advocate sampling priors (also called design priors) for data simulation and fitting priors (also called analysis priors) for posterior distribution.
- Sampling priors should be more informative than fitting priors.

Terminology

- Suppose quantity of interest is τ
- ***d*** denotes data from experiment
- Posterior density is denoted $\pi(\tau \mid \boldsymbol{d})$
- Marginal density is denoted $m(\boldsymbol{d})$
  - Marginal used as weighting function in samples size determination is based on sampling priors

Sample size determination for interval estimation

- Average Coverage Criterion (ACC)
- Finds sample that for a given width yields (1 – α)100% coverage on average

$$\int_{d}\left[\int_{\hat{\tau}-l/2}^{\hat{\tau}+l/2}\pi(\tau\,|\,\boldsymbol{d})d\tau\right]m(\boldsymbol{d})\geq 1-\alpha$$

Sample size determination, cont.

- Average Length Criterion (ALC)
- Finds the sample size that for a given coverage yields a specified width on average.

$$\int_{d} l'(\boldsymbol{d}) m(\boldsymbol{d}) \leq l$$

Sample size determination criteria for hypothesis testing

- For the one sided hypothesis, $\tau > 0$
- Find sample size, n such that

$$E_{\boldsymbol{d}}\left[P(\tau > 0 \mid \boldsymbol{d}) > 1-\alpha\right] = 1-\beta$$

- For the hypothesis $\tau < 0$,

$$E_{\boldsymbol{d}}\left[P(\tau < 0 \mid \boldsymbol{d}) > 1-\alpha\right] = 1-\beta$$

Computation

- Markov Chain Monte Carlo (MCMC) and Monte Carlo (MC) methods predominantly used to approximate posterior densities.
- Computationally burdensome for sample size determination problems (recall summation required for criteria).

Model

- Let T_i denote the outcome of the test where $T_i = 0$ denotes a negative result and $T_i = 1$ denotes a positive result for population i, $i = 1, 2$.
- Let D_i denote the true status of the result.
- Let $\Pr(D_i = 1) = p_i$ and $\Pr(T_i = 1) = \pi_i$, where $\pi_i = p_i S + (1 - p_i)(1 - C)$.

Model

- For n total subjects, let n_{1i} be the number of positive results for sample i.
- Over parameterized model (4 parameters, 2 degrees of freedom)
- Prior distributions

$p_i \sim \text{beta}(\alpha_i, \beta_i)$ $i = 1, 2,$

$S \sim \text{beta}(\delta, \varepsilon),$

$C \sim \text{beta}(\gamma, \kappa)$

BETA PRIORS

$$\mathbf{b}(\mathbf{p} \mid \alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} \mathbf{p}^{\alpha - 1} (1 - \mathbf{p})^{\beta - 1}$$

Data for one test

Sample 1		Sample 2
n11		n12
p1*S+(1-p1)*(1-C)		p1*S+(1-p1)*(1-C)
n01 = n-n11		n02 = n-n12
p1*(1-S)+C*(1-p1)		p1*(1-S)+C*(1-p1)

Data for two tests

	Sample 1	
n111		n101
p1*S1*S2+(1-p1)*(1-C1)*(1-C2)		p1*S1*(1-S2)+(1-p1)*(1-C1)*C2
n011		n001
p1*(1-S1)*S2+(1-p1)*C1*(1-C2)		p1*(1-S1)*(1-S2)+(1-p1)*C1*C2
	Sample 2	
n112		n102
p1*S1*S2+(1-p1)*(1-C1)*(1-C2)		p1*S1*(1-S2)+(1-p1)*(1-C1)*C2
n012		n002
p1*(1-S1)*S2+(1-p1)*C1*(1-C2)		p1*(1-S1)*(1-S2)+(1-p1)*C1*C2

Algorithm for simulation based approach

- Select range of sample sizes
- For each sample size, for $i = 1$ to Q
  - Generate parameter values from prior distributions
  - Generate data
  - Approximate posterior using Gibbs sampler
  - Compute interval length, probability quantity exceeds 0
- Compute average coverage, width, power
- Repeat for all selected sample sizes
- Fit curve

Example

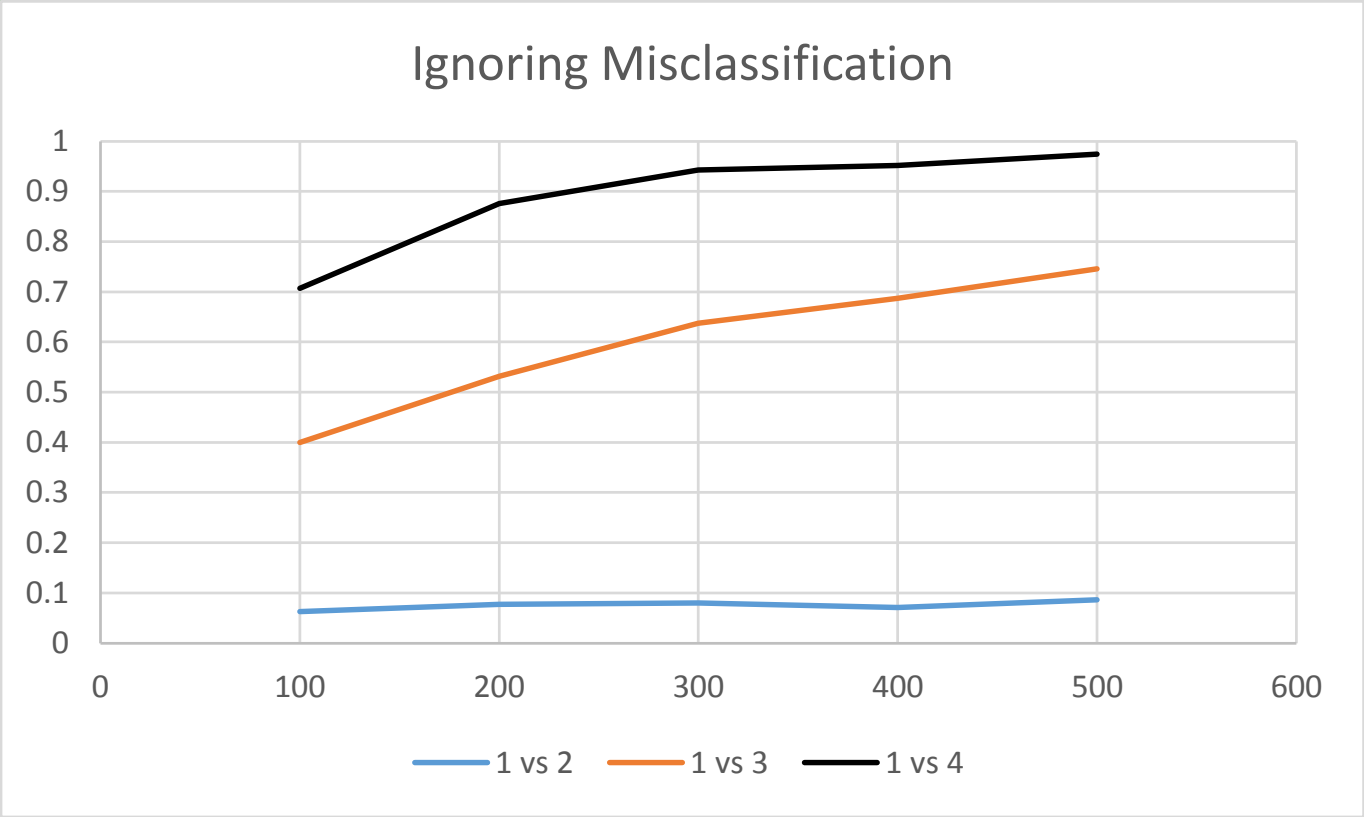
- We consider the case of 4 proportions and one diagnostic test.

$$p_1 \sim beta(.5, 99.5) \qquad p_2 \sim beta(.5, 99.5)$$

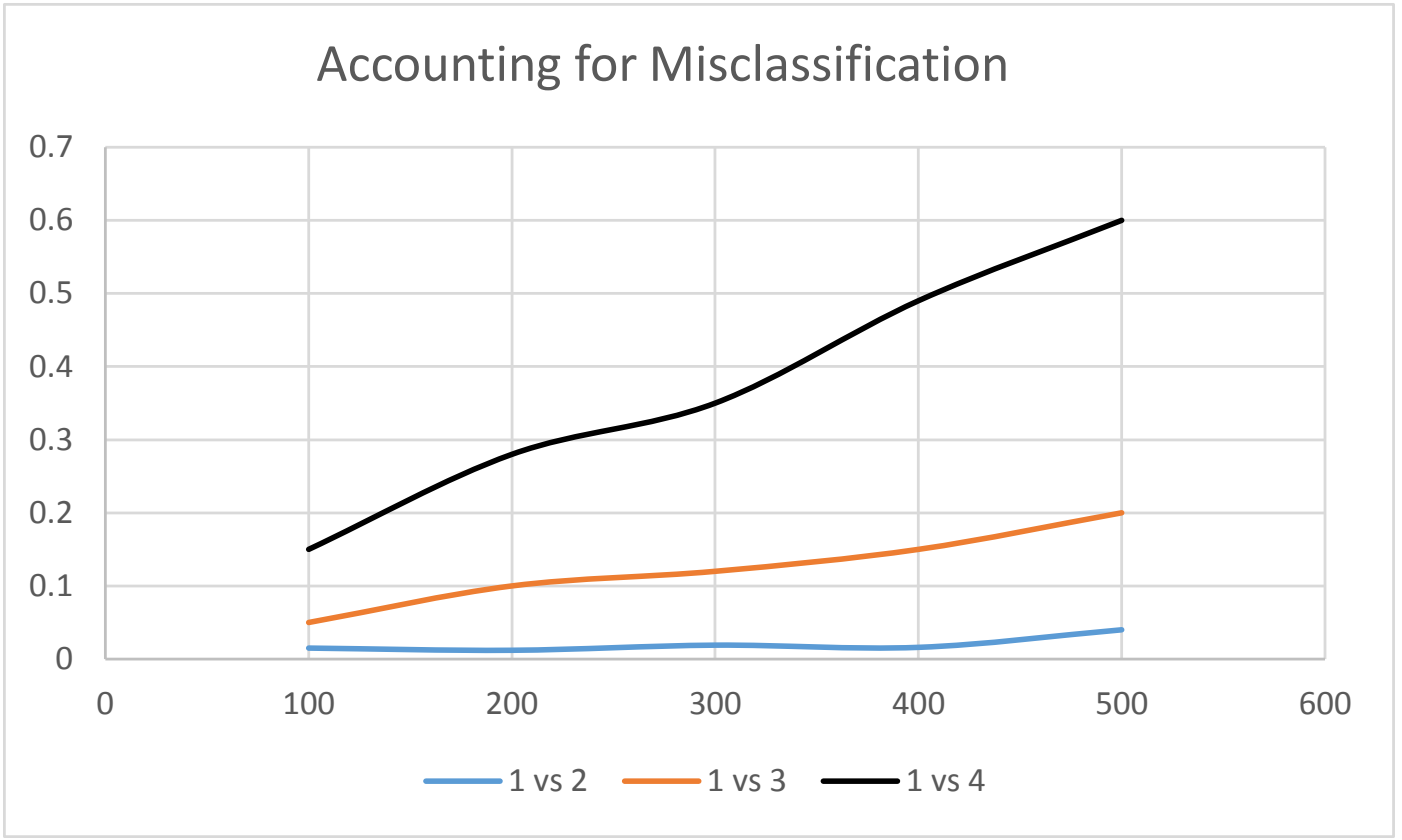
$$p_3 \sim beta(6, 94) \qquad p_4 \sim beta(12, 88)$$

$$S \sim beta(98, 2) \qquad C \sim beta(60, 40)$$

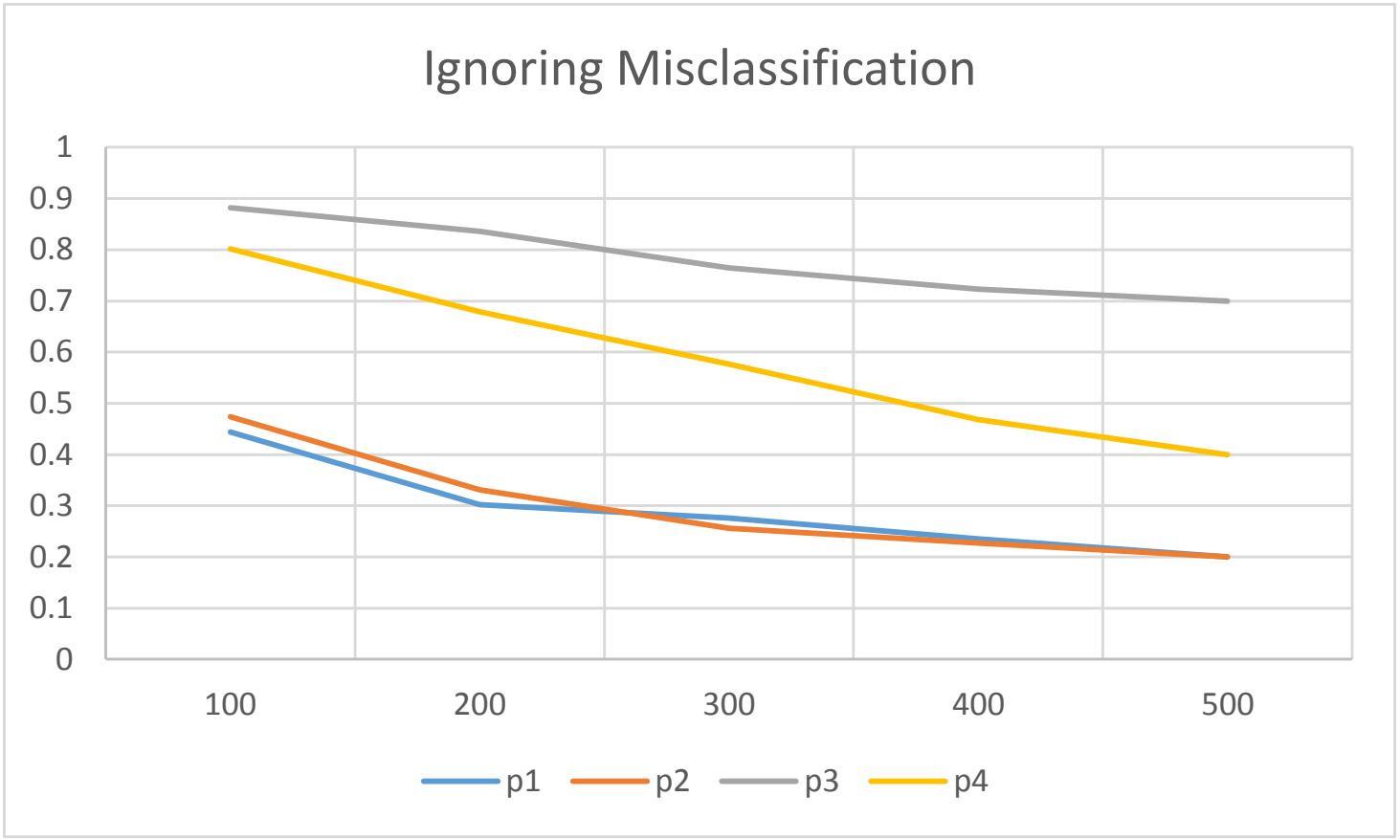
Power


Ignoring Misclassification
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
600
1 vs 2
1 vs 3
1 vs 4

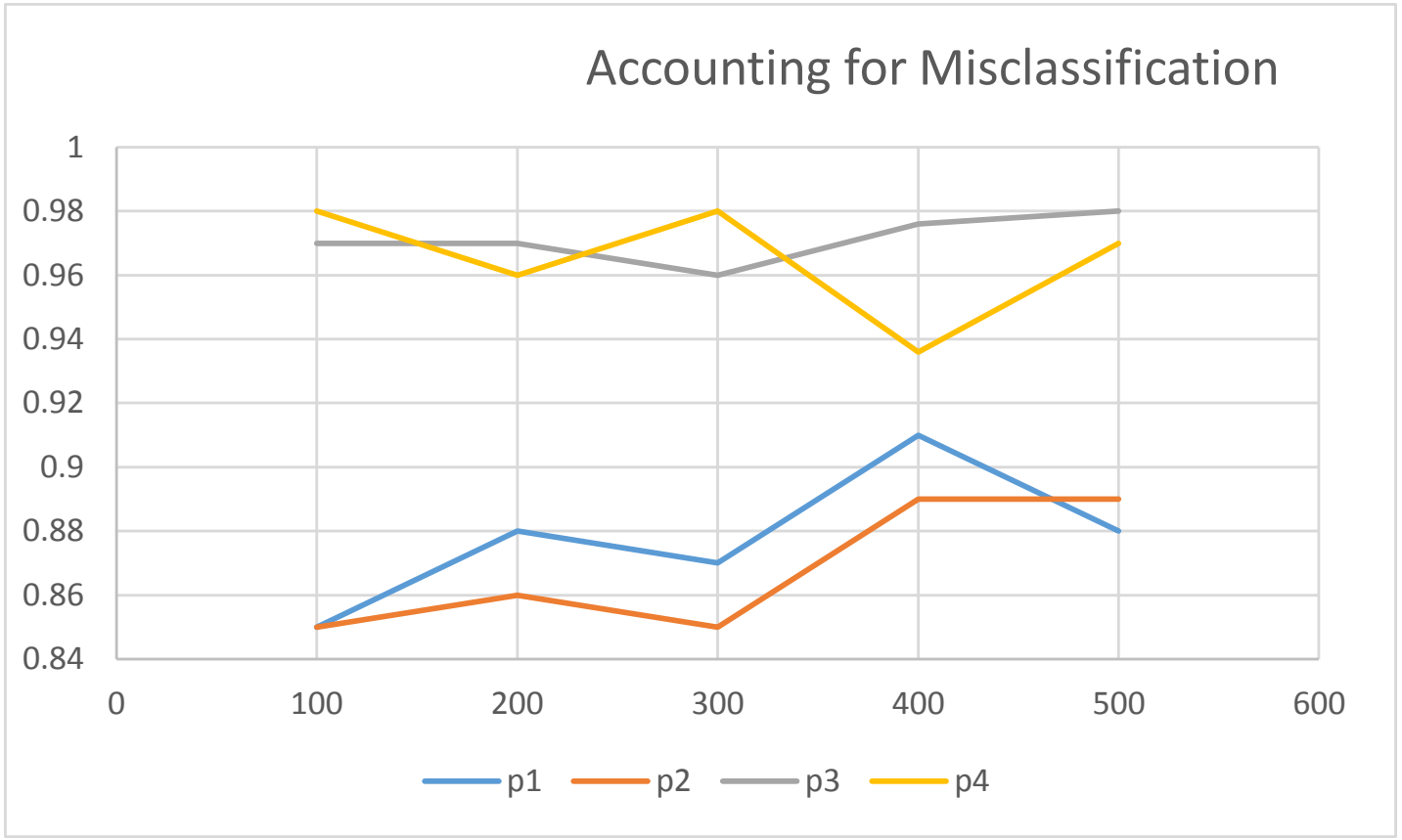
Power


Accounting for Misclassification
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
600
1 vs 2
1 vs 3
1 vs 4

Coverage


Ignoring Misclassification
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
100
200
300
400
500
p1
p2
p3
p4

Coverage


Accounting for Misclassification
1
0.98
0.96
0.94
0.92
0.9
0.88
0.86
0.84
0
100
200
300
400
500
600
p1
p2
p3
p4

Conclusions

- For low response probabilities and a single diagnostic test, does not appear that accounting for misclassification improves power
- Accounting for misclassification greatly improves bias and coverage

Questions?

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