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Sensitivity of heterogeneity priors in meta-analysis

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Bayesian approaches to incorporating historical information in clinical trials

Joint work (in progress!) with Isaac Gravestock and Leonhard Held

STAT-Net/COMBACTE

ND4BB COMBACTE

Supported by IMI/EU and EFPIA

innovative medicines initiative

Synthesis of historical evidence

- Power-prior approach:

  Chen et al. (2006), Neuenschwander et al. (2009)

- Meta-analytical approach:

  Neuenschwander et al. (2010), Schmidli et al. (2014)

Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia

All-Cause Mortality with Linezolid/Aztreonam:

Rubinstein et al. (2001): $36/203 = 18\%$

$y_1 = \log(\text{odds}_1) = -1.534$, $\sigma_1 = \text{SE}(\log(\text{odds}_1)) = 0.184$

Wunderink et al. (2003): $64/321 = 20\%$

$y_2 = \log(\text{odds}_2) = -1.390$, $\sigma_2 = \text{SE}(\log(\text{odds}_2)) = 0.140$

Meta-Analysis

Normal-normal hierarchical model for $i = 1, \ldots, I$:

Sampling model: $Y_i \mid \theta_i \sim \mathrm{N}(\theta_i, \sigma_i^2)$

Parameter model: $\theta_i \sim \mathrm{N}(\mu, \tau^2)$

Priors for hyperparameters:

$\mu \sim$ flat distribution

$\tau \sim \pi_{a_0}$ scaled distribution

Scaled distribution

$\tau \sim \pi_{a_0} = a_0 X$

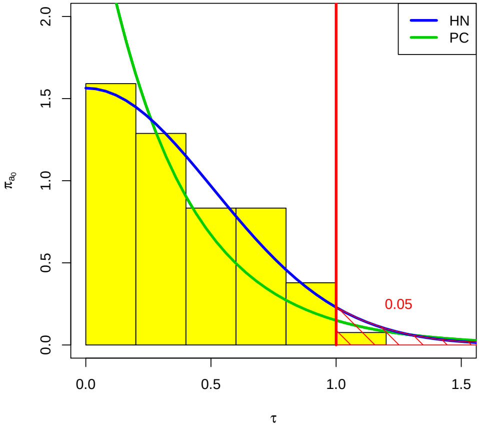
Neuenschwander et al. (2010), half-normal (HN) prior:

$X \sim |\mathrm{N}(0, 1)|$

Simpson et al. (2014), penalised complexity (PC) prior:

$X \sim \mathrm{Exp}(1)$

$\Rightarrow 1/\tau^2 \sim$ Type-2 Gumbel


HN
PC
0.05
2.0
1.5
1.0
0.5
0.0
0.0
0.5
1.0
1.5
π_{a_0}
τ

Sensitivity

How sensitive is the output to the input

$$\pi_{a_0}(\tau|\mathbf{y}) \propto f(\mathbf{y}|\tau)\pi_{a_0}(\tau)$$

with a fixed base prior parameter specification a_0

for Bayesian hierarchical models?

Epsilon-local sensitivity

Roos, Martins, Held and Rue (2015):

- A formal approach
- Applicable to complex hierarchical models
- Invariant to any one-to-one transformation
- Reacts correctly to an increased number of observations

Epsilon-local sensitivity measure

Roos, Martins, Held and Rue (2015):

Discrepancy measure: Hellinger distance

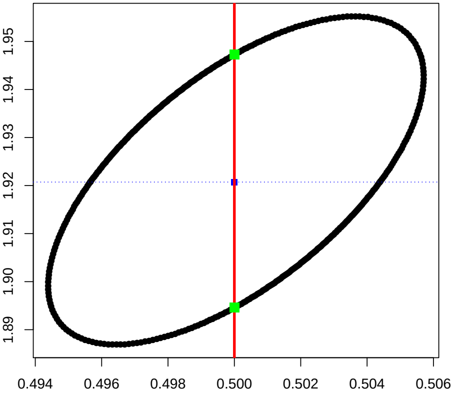
$$H(\pi_a(\tau), \pi_{a_0}(\tau)) = \sqrt{1 - \int \sqrt{\pi_a(\tau)\pi_{a_0}(\tau)} d\tau}$$

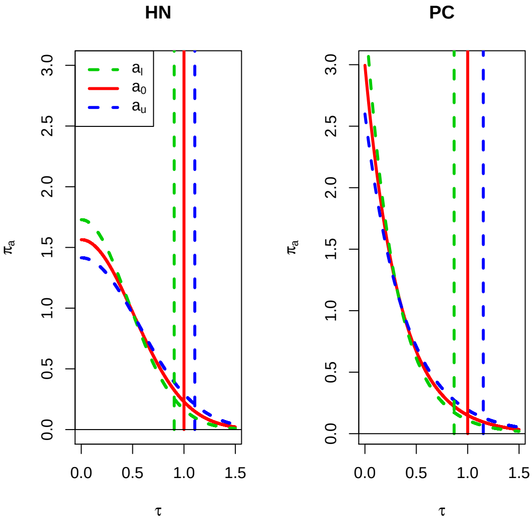
Epsilon-grid:

$$G_{a_0} = \{a : H(\pi_a(\tau), \pi_{a_0}(\tau)) = \epsilon\}$$

$$= \{a_l, a_u\}$$

for a small, fixed ϵ


1.89
1.90
1.91
1.92
1.93
1.94
1.95
0.494
0.496
0.498
0.500
0.502
0.504
0.506


HN
PC
a_l
a_0
a_u
π_a
τ
0.0
0.5
1.0
1.5
2.0
2.5
3.0

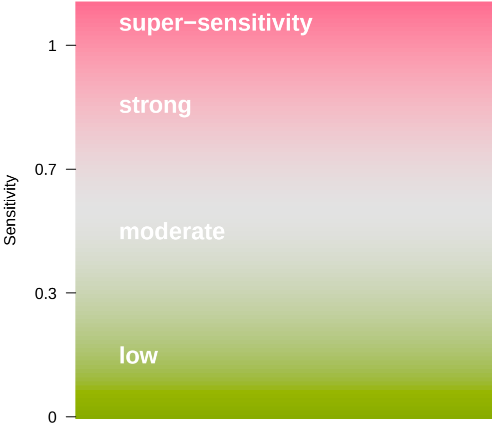
Epsilon-local sensitivity measure (continued)

Roos, Martins, Held and Rue (2015):

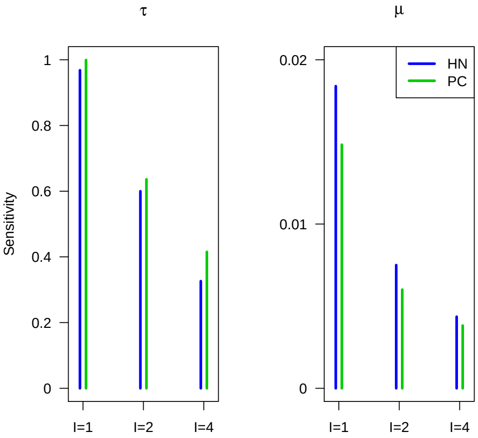
Worst-case sensitivity:

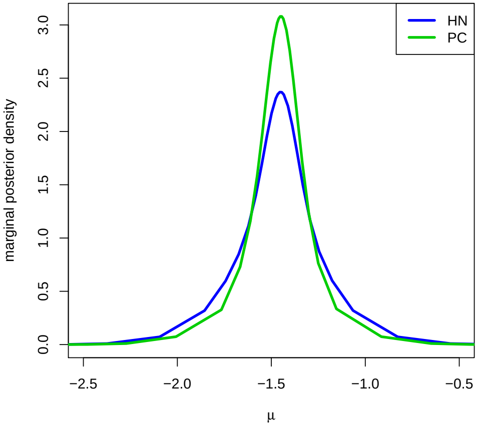
$$S_{a_0} = \max\{\mathrm{H}(\pi_{a_l}(\tau|\mathbf{y}), \pi_{a_0}(\tau|\mathbf{y}))/\epsilon, \mathrm{H}(\pi_{a_u}(\tau|\mathbf{y}), \pi_{a_0}(\tau|\mathbf{y}))/\epsilon\}$$

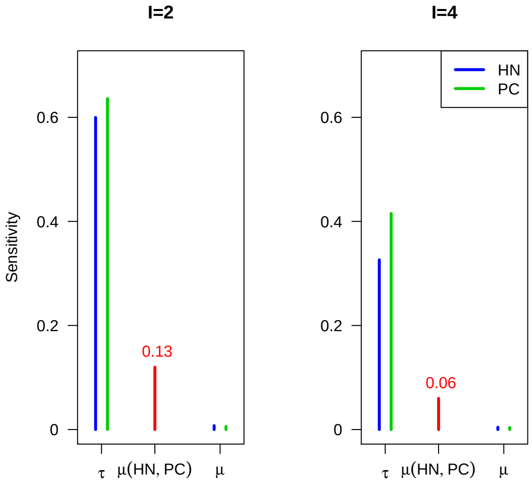
Marginal posterior densities: `R-INLA` (Rue et al. (2009))


super−sensitivity
strong
moderate
low
Sensitivity
1
0.7
0.3
0

Results




HN
PC
marginal posterior density
0.0
0.5
1.0
1.5
2.0
2.5
3.0
−2.5
−2.0
−1.5
−1.0
−0.5
μ


I=2
I=4
Sensitivity
0.6
0.4
0.2
0
0.13
0.06
HN
PC
τ
μ(HN, PC)
μ

Discussion

Pros:

- Sensitivity analysis can guide priorities in eliciting priors
- Scaled prior distributions lead to easy epsilon-grids
- Epsilon-local sensitivity can compare different prior assumptions given the data at hand
- Co-parameter sensitivity can be quantified

Further work needed:

- Extend the sensitivity approach to distributions defined by MCMC samples

Thank you for your attention!

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