Borrowing information at the planning stage

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On behalf of Asterix, and especially UMC Utrecht and Hannover Medical School teams

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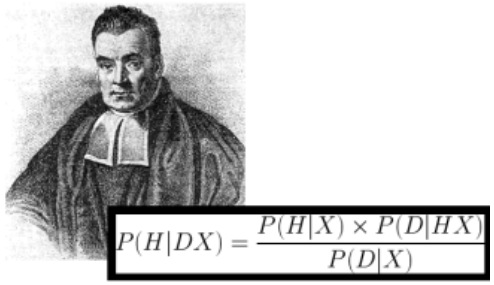
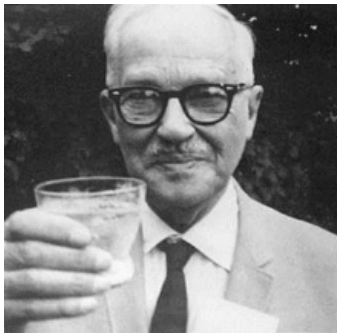
“Controversies in the field of mathematical statistics seem largely to have arisen because statisticians have been unable to agree upon how theory is to provide, in terms of probability statements, the numerical measures most helpful to those who have to draw conclusions from observational data.”

E.S. PEARSON (1955)





Clinical research in rare diseases

Average 761 (median 538) patients in orphan drug trials.

Average 3,549 (median 1588) in non-orphan drug trials.

- For many new drugs more than 1 clinical trial performed.
- More often than not trials of reasonable size.

Special attention:

- Sparse settings with small trials or (and) less efficient endpoints.
- In light of potential *heterogeneity* (disease course, standard of care, etc.) – especially in rare diseases.

Meta-analysis in sparse settings

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- Given the nature of rare diseases and their treatment, the possibility of heterogeneity between trials cannot be ignored.

- It is also not easily tackled, as is clear from other research and presentations today.

- Can we do something sufficiently robust at the planning stage of a new trial?

Borrowing infomation at the planning stage

- Assume data from (small) trial D_0 is available (e.g. Ph II).
- The second trial D_1 is being planned (e.g Ph III).
- Can inference be improved by:
  - Prospectively including the results of D_0 in the analysis of D_1.
  - Downweighting results of D_0 with increasing heterogeneity between the two studies.
  - Whilst controlling the type 1 error properties.
- *Hybrid Bayesian-Frequentist approach*

Borrowing infomation at the planning stage

Several (bayesian) methods and modeling approaches exist that could be used.

Not always added value (Galwey, Stats in Medicine Dec 2016)

We developed* approach based on:

- *Power priors (prior data conflict calibrated).*
- Using prior information on *treatment effect*
- Allowing full pre-specification, whilst taking observed heterogeneity into account.
- Can be extended in other directions (e.g. sample size re-assessment).

* PhD Thesis, Stavros Nikolakopoulos

Calibrated power prior

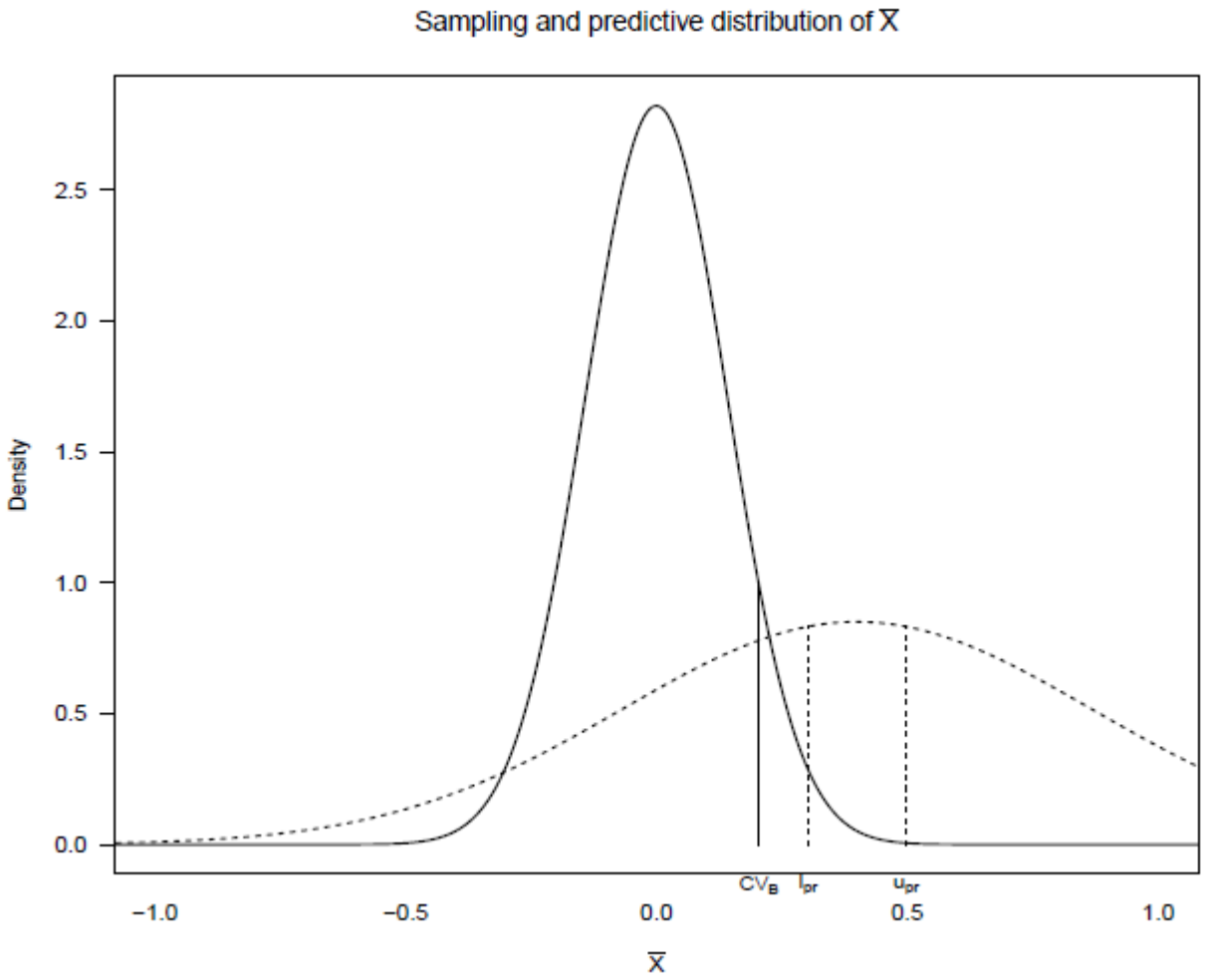

Figure 1: Sampling (solid line) and predictive (dashed line) distributions of $\bar{X}$ for $\mu_T = 0, \mu_0 = 0.4, \sigma^2 = 1, \eta = 0.95, n_0 = 5, n_1 = 50$ and $z_{c/2} \approx 0.2$ so $c \approx 0.84$.

Calibrated power prior

- Prior tuning allows controlling Type 1 error

- Potential advantage:
  - Precision (in terms of means squared error) more robust across a range of assumptions of the true treatment effect.

  - Increased precision if prior assumptions of treatment effect are true.

Calibrated power prior: MSE

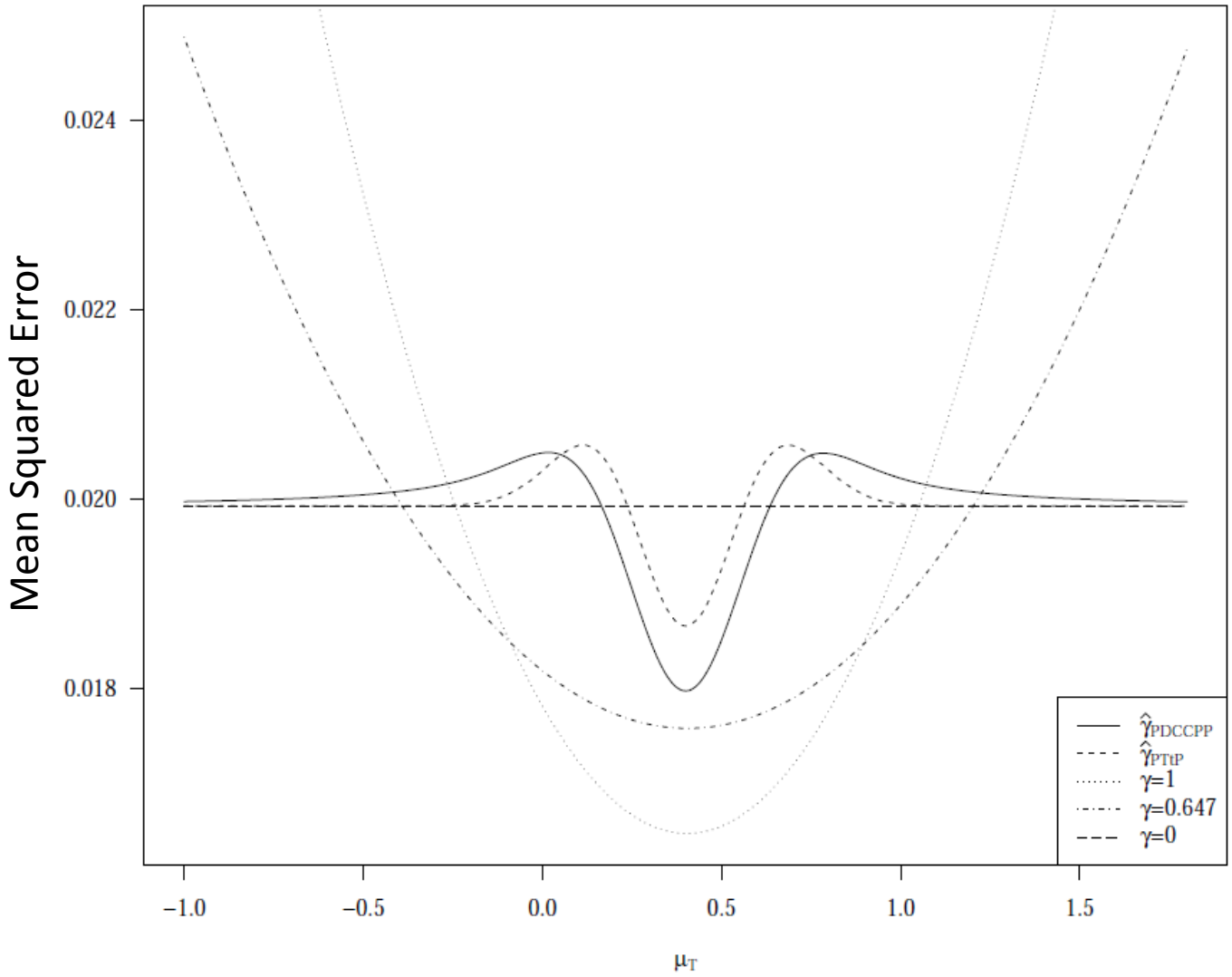

Figure 5.4: MSE for different values of γ, as a function of μ_T. The $PDCCPP$ and $PTtP$ estimates are calibrated to have a type I error of 6.5%, and so is the fixed γ of 0.647; $\mu_0 = .4$, $\sigma^2 = 1, \eta = 0.95$ $n_0 = 5$ and $n_1 = 50$.

Discussion

1. Prospectively defined inclusion of prior data (with weighting) might be attractive in a sparse setting.

2. Likely to provide more robust estimate of treatment effect under heterogeneity, whilst retaining precision.

3. Conceptual and optimisation questions open.