Prospective inclusion of historical efficacy data in clinical trials

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Research in small populations

Clinical Trials

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- Rare diseases / sensitive populations
- Scarcity of information
- Importance of synthesis of data evidence is stressed
- $\rightarrow$ Bayesian paradigm is a natural platform
  - Bayesian methods suggested for RCTs in rare diseases
  - Operational characteristics need to be investigated
  - Type I error is a major concern

Prospective Data Synthesis

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- Incorporation of previous information in the analysis of a new (small) trial
- Prospectively including prior data at the design phase of a trial

  Goal : Control type I error & gain efficiency
- Simple Bayesian Analysis: Posterior of old study $\rightarrow$ prior for new study
- Type I error

  Initiate a new study $\rightarrow$ positive effect in old study $\rightarrow$ Type I error $\uparrow$

Bayesian type I error

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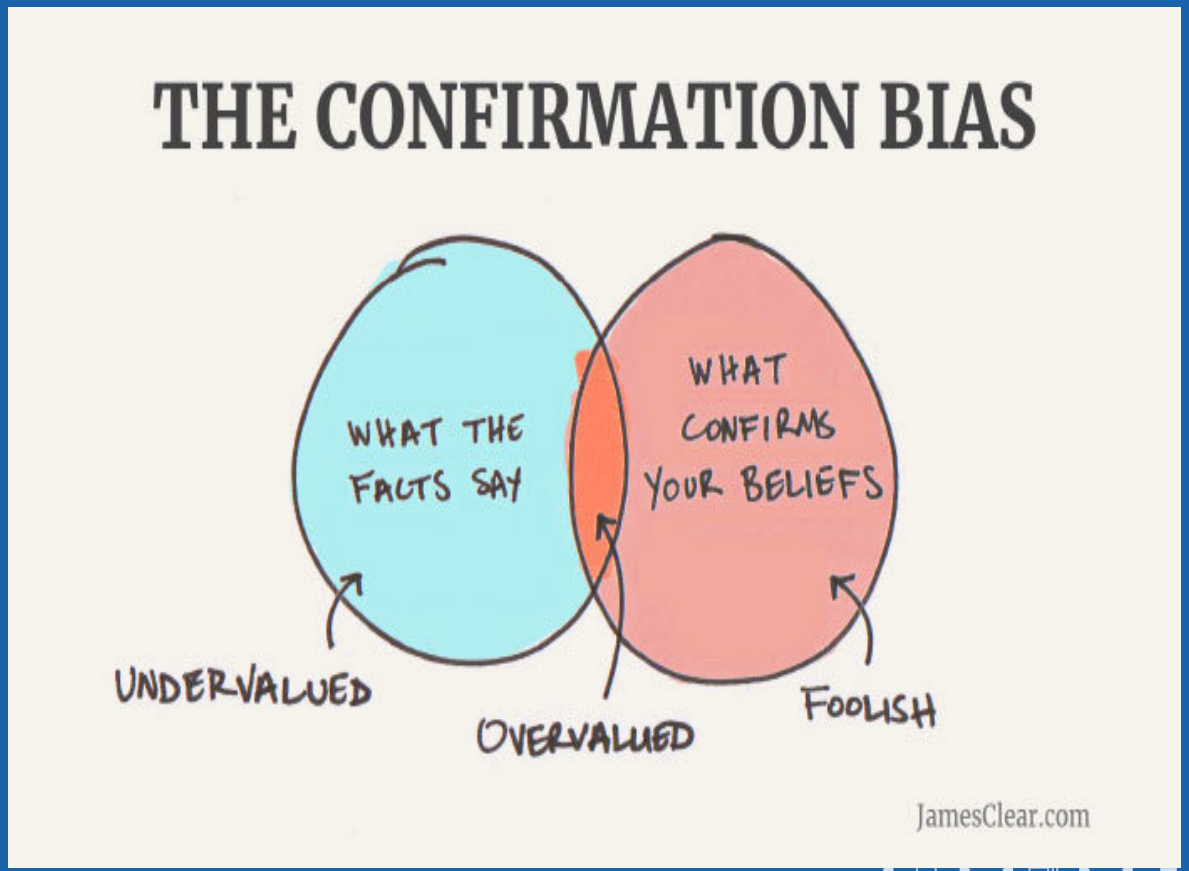
- Type I error: Probability of showing efficacy when there is actually none
- By including (synthesizing) data whith positive effect size, type I error increases



Example

Pediatric clinical trial

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- Spinal anesthesia in children

  Sensitive population

	NEW		OLD	
	C group	T group	C group	T group
Intervention	isobaric bupivacaine	+clonidine $2\mu g/kg$	hyperbaric bupivacaine	+clonidine $2\mu g/kg$
Population	children 10-15		children 6-15	

- Primary outcome: Mean difference in duration of sensory block
- Observed standardized effect in old study: 0.76

Basic Definition

Discarding prior data

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- New data D_1, old data D_0, $L(\theta|D_*)$ likelihood for θ

$$\pi(\theta|D_0,\gamma) \propto L(\theta|D_0)^{\gamma}\pi_0(\theta)$$
$$\pi(\theta|D_1,D_0,\gamma) \propto L(\theta|D_1)L(\theta|D_0)^{\gamma}\pi_0(\theta)$$

- $\gamma \in [0,1]$ **power parameter**, controls amount of historical data that enter calculation of posterior

  Normal conjugate: $Var(\theta|D_0,\gamma) = \frac{1}{\gamma}Var(\theta|D_0)$

Extensions
Fixed vs Random γ

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- Initial idea: γ fixed and known, sensitivity analyses
- Thus: control the amount of historical data, fixed and known
- Good start, but problem remains

  γ can be fixed for required type I error
  Other features of inference (bias, coverage of intervals) remain problematic for large discrepancies
- Solution: *Dynamic* borrowing
- Determine the amount of borrowing based on the similarity between old and new data

Box's p-values (1980)

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- Prior Predictive p-value (ppp)
- Quantify conflict (or agreement) between prior and data, based on value of statistic $T(D_1)$
- What is the probability that such or more extreme result is observed given the ~~null hypothesis~~ prior distribution
- Calculated on the basis of the prior predictive distribution for $T(D_1)$

$$ppp = 2\min\{Pr_{D_1|D_0}\left(T(D_1) \geq T(D_1^{obs})\right), Pr_{D_1|D_0}\left(T(D_1) \leq T(D_1^{obs})\right)\}$$

Prior-Data Conflict Calibrated Power Priors

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- Adjust prior, through γ, so that the conflict with observed data is not more than a prespecified value
- Reminder: γ adjusts the spread of the prior, can be set to wide enough so that observed value is not conflicting

$$\hat{\gamma}_{PDCCPP}(c) = \min\left[\max_{\hat{\gamma}}\{\hat{\gamma} : ppp|\hat{\gamma} \geq c\}, 1\right]$$

Keeping conflict fixed

Illustration

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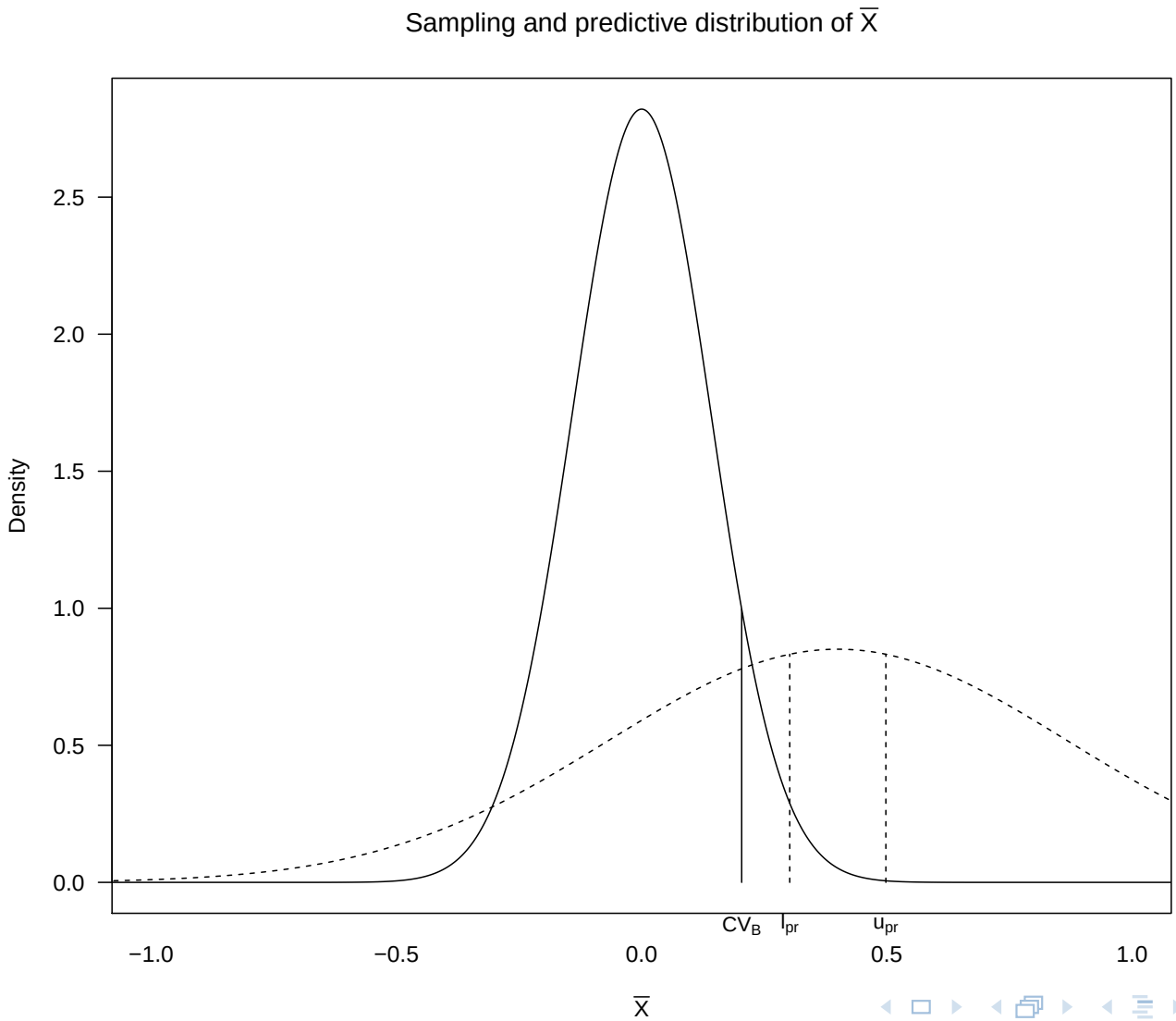

Type I error
Illustration

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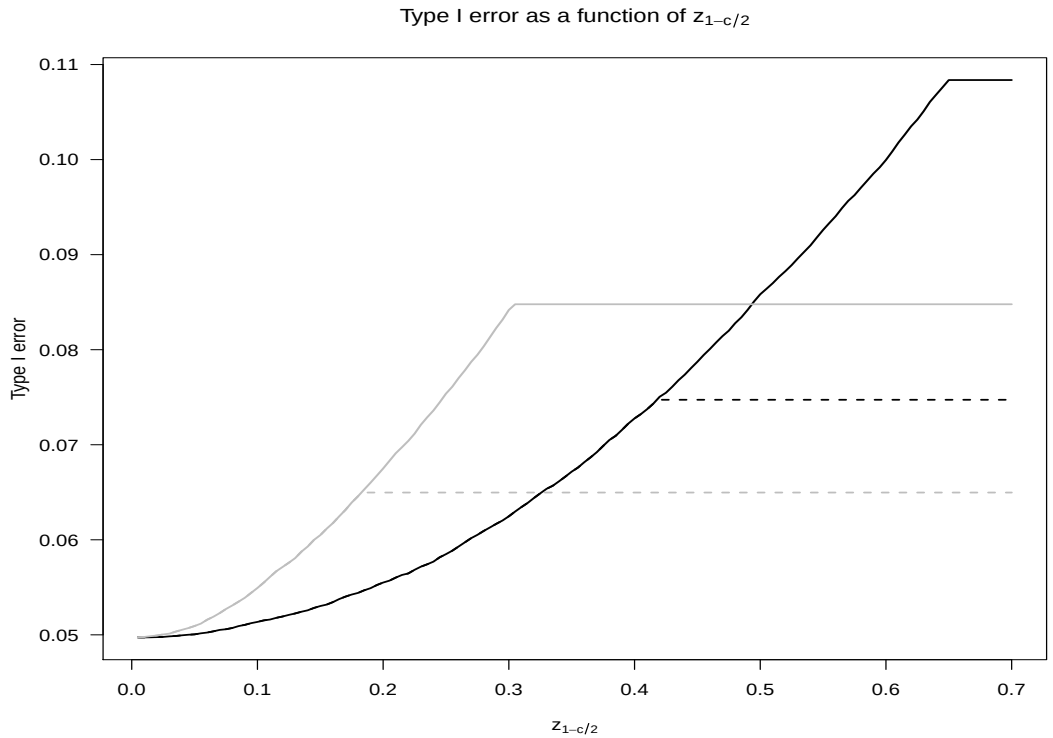

Type I error for PDCCPP when $n_0 = 10$ (solid lines) and $n_0 = 5$ (dashed lines) for $\mu_0 = .4$ (black lines) and for $\mu_0 = .3$ (grey lines) for a range of $z_{1-c/2}$; $\sigma^2 = 1, \eta = 0.95$ and $n_1 = 50$.

Comparison with other methods

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Type I error could be controlled by:

- fixed γ so that type I error is controlled
- Test-then-pool approach (**TtP**), only fully borrow when observed value is not significantly different than prior [1]

  Choose significance level of TtP so that type I error of new trial is controlled
- No borrowing ($\gamma = 0$)
- Full borrowing ($\gamma = 1$)

[1] Viele et. al, 2014

Comparison: MSE

Illustration

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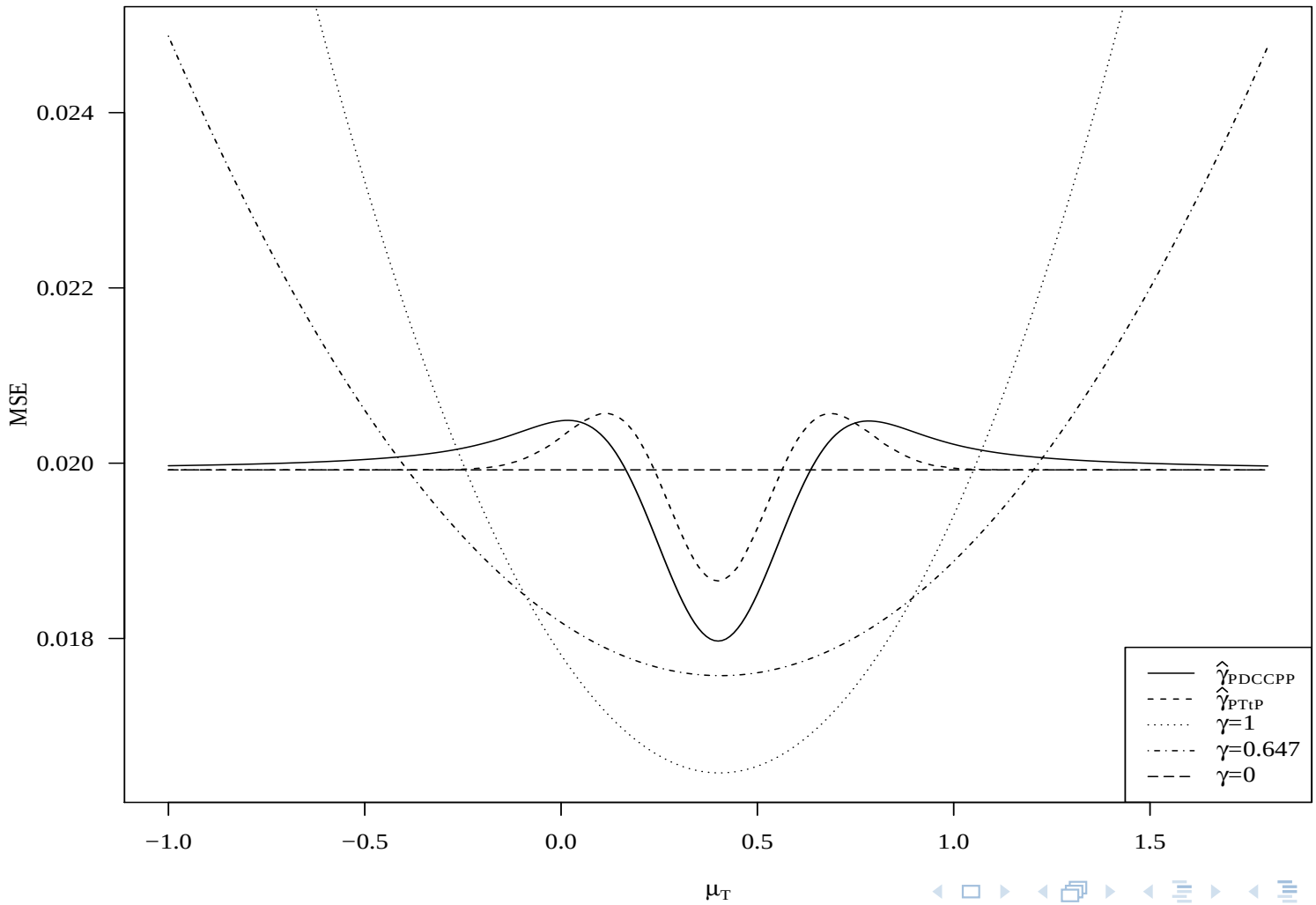

Example

Treatment effect level - 2 arm trial, $\delta_0 = 0.76$, $\eta = 0.975$

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	$\hat{\delta}$=0.580	
$\alpha_d \mid z_{1-c/2}$	0.035	0.040
$z^d_{1-c/2}$	0.385	0.475
$\hat{\gamma}$	0.557	0.992
$\delta_1 \mid \hat{\gamma}$	0.619	0.640
$Pr(\delta > 0 \mid \hat{\gamma})$	0.999	0.999
95% CrI $\mid \hat{\gamma}$	(0.35,0.88)	(0.39,0.89)
No borrowing		
$\delta_1 \mid \gamma = 0$	0.580	
$Pr(\delta > 0 \mid \gamma = 0)$	0.996	
95% CrI $\mid \gamma = 0$	(0.28,0.88)	
Full borrowing		
$\delta_1 \mid \gamma = 1$	0.640	
$Pr(\delta > 0 \mid \gamma = 1)$	0.999	
95% CrI $\mid \gamma = 1$	(0.39,0.89)	

General Comments

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- Combining data with controlling type I error by pre-specified maximum conflict (ppp)
- Only treatment effect discussed, alternatively per group (borrow historical controls)
- Straightforward to other models if predictive distributions available
- Essentially: Bias/Variance Trade-off (assuming same type I error)

References

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Gravestock I and Held L, Adaptive Power priors with empirical Bayes for clinical trials, *Pharmaceutical Statistics*, 2017

Viele et. al, Use of historical data for assessing treatment effects, *Pharmaceutical Statistics*, 2014

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Thank you!