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# Robust incorporation of external information in hypothesis testing

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# Information borrowing

- **External information** is often available when designing a trial (historical/concurrent trial, real world evidence, expert opinion...)
- Incorporation can improve **trial efficiency**
- Bayesian paradigm offers natural framework to incorporate it through **informative prior distributions**
- However: **potential for heterogeneity** (prior-data conflict)
- Assessment and control of the amount of borrowed information is crucial

# Robust borrowing

- Various robust methods available (meta-analytic, power, commensurate priors...), dynamic approaches adaptively discount potentially conflicting prior information
- **Choice/estimation of borrowing parameters/distributions** required
- Small changes in the borrowing parameter **should not induce sharp changes** in metric of interest (O'Hagan, 2010; Travis et al., 2023)
- Different rationales for adaptation (covariates, full Bayes, empirical Bayes..)

Frequentist operating characteristics (OCs) often evaluated to ensure reasonable behaviour under the **worst possible scenario**

# Targeting test error rates

- Typically **not possible to gain power via borrowing while controlling type I error (TIE) rate** (Kopp-Schneider et al., 2020)
- True for both dynamic and static mechanisms
- **Gains only possible under assumptions** about consistency
- **External information is typically valuable**: *some* trust is present
- One possibility: use trust in external information as a rationale for TIE inflation

Stronger trust/information → Stronger inflation

# Set-up

$$\theta \sim \pi(\theta) = N(\mu_\theta, \sigma_\theta), \quad \bar{y} \sim N(\theta, \sigma/\sqrt{n}), \quad \theta|y \sim \pi(\theta|\bar{y}) = N(\mu_{\theta|y}, \sigma_{\theta|y})$$

$$H_0 : \theta \leq 0 \text{ vs } H_1 : \theta > 0$$

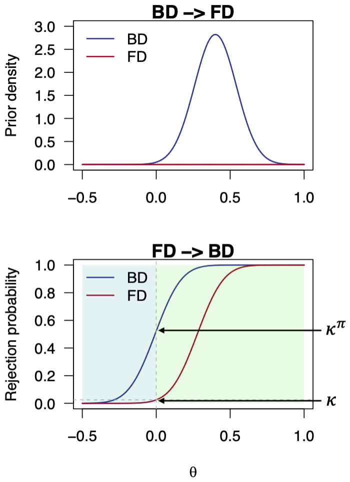
- **Decision**: reject or keep $H_0$
- **Optimal test decision** depends on $y$, $\kappa$, and prior/paradigm:
  - Bayesian **(BD)**: reject if $P^\pi(H_0|\text{data}) \leq \kappa$
  - Frequentist **(FD)**: decision such that TIE $\leq \kappa$ and power maximised
- $\kappa$ from TIE and TIIE **costs**

# Two routes

**Duality between $\pi$ and $\kappa$** (Berger, 1985):

1. BD $\rightarrow$ FD: fix $\kappa$, $\pi \rightarrow \pi_0$, where $\pi_0$ prior inducing FD
2. **FD $\rightarrow$ BD: fix $\pi_0$, $\kappa \rightarrow \kappa^\pi$ where $\kappa^\pi$ TIE under BD**

Note: in **one-arm** intermediate solutions in (1) and (2) can be made equivalent through tuning of (fixed) borrowing parameter(s).



# Compromise decision

Under $\pi_0$, **compromise decision (CD) threshold** (Calderazzo et al., 2023)

$$\kappa^{w} = (1 - w)\kappa + w\kappa^{\pi},$$

where $w \in [0, 1]$, $\kappa$ gives FD, while $\kappa^{\pi}$ gives BD.

Properties:

- With fixed $w$: $\kappa^{w}$ is also TIE rate.
- **Linearly relates** borrowing parameter $w$ and TIE rate inflation.
- $w$ can be pre-specified, or dynamically estimated.
- We can always **cap TIE rate at pre-specified value**

# One-arm testing - $w$ fixed

- $\bar{y} \sim N(\theta, \sigma/\sqrt{n})$
- $\pi = N(\mu_\theta, \sigma_\theta)$
- $\pi_0$: vague prior $N(0, \sigma_{\pi_0})$, $\sigma_{\pi_0} \to \infty$
- **Threshold inducing BD**

$$\kappa^\pi = 1 - \Phi\left(-\frac{\sigma\mu_\theta}{\sqrt{n}\sigma_\theta^2} + z_{1-\kappa}\sqrt{1 + \frac{\sigma^2}{n\sigma_\theta^2}}\right)$$

- **CD threshold**, with upper bound:

$$\kappa^w = \min[(1-w)\kappa + w\kappa^\pi, \kappa^{bound}],$$

where $\kappa^{bound}$ is the maximum allowable TIE rate.

# Extension: Two-arm testing

Treatment vs Control:

- $\bar{y}_C \sim N(\theta_C, \sigma/\sqrt{n_C}), \bar{y}_T \sim N(\theta_T, \sigma/\sqrt{n_T})$
- $\pi_C = N(\mu_C, \sigma_C), \pi_T = N(\mu_T, \sigma_T)$

$$H_0 : \theta_T - \theta_C \leq 0 \text{ vs } H_1 : \theta_T - \theta_C > 0$$

**Reduction to one-arm**

- Methodology directly applicable
- Not possible when borrowing on control only

**Two-arm**

- More complex: TIE rate typically depends on $\theta_C$
- Static borrowing: TIE rate typically reaches 1

We can still compromise/cap TIE rates

# Two-arm testing - $w$ fixed

Treatment vs Control: $\theta = \theta_T - \theta_C$

- $\pi_C = N(\mu_C, \sigma_C)$, $\pi_T = N(\mu_T, \sigma_T)$; $\sigma^2_{\theta|\bar{y}_C,\bar{y}_T}$ posterior variance for $\theta$
- $\pi_{0,C}$, $\pi_{0,T}$: vague priors
- **Threshold inducing BD**

$$\kappa^{\pi} = 1 - \Phi\left(\frac{\left(\frac{\sigma^2}{n_T\sigma_T^2}+1\right)\left[\bar{y}_C\left(\frac{n_C\sigma_C^2}{\sigma^2+n_C\sigma_C^2} - \frac{n_T\sigma_T^2}{\sigma^2+n_T\sigma_T^2}\right) - \frac{\mu_{\pi_T}\sigma^2}{\sigma^2+n_T\sigma_T^2} + \frac{\mu_{\pi_C}\sigma^2}{\sigma^2+n_C\sigma_C^2} + z_{1-\kappa}\sigma_{\theta|\bar{y}_C,\bar{y}_T}\right]}{\sqrt{\sigma^2/n_T + \sigma^2/n_C}}\right)$$

- **CD threshold**, data dependent:

$$\kappa^{w}(\bar{y}_C) = \min[(1-w)\kappa + w\kappa^{\pi}(\bar{y}_C), \kappa^{bound}]$$

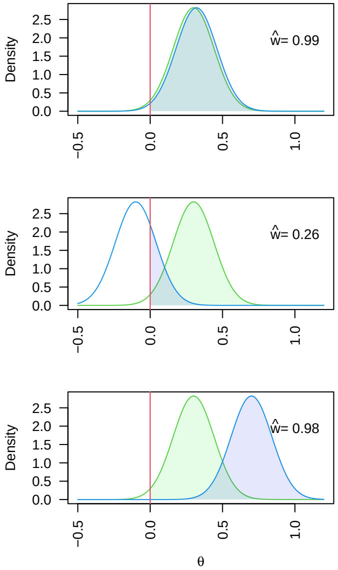
CD TIE rate approximate but $\leq \kappa^{bound}$

# Dynamic borrowing

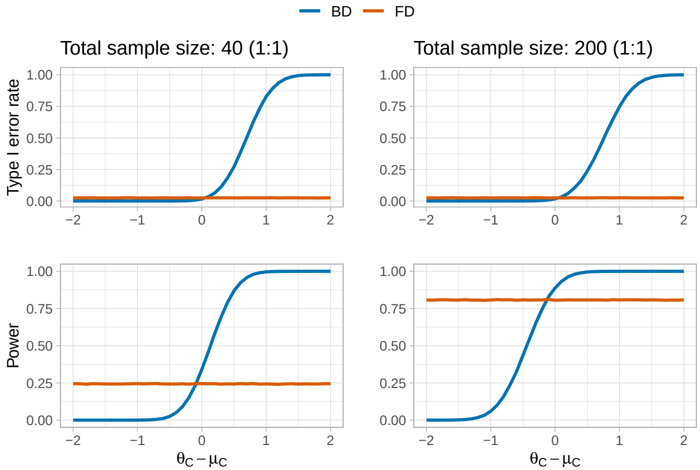
- *w* **reflects trust in external information**
- Any measure of similarity between current and external data can be used
- **CD-Adapt dynamic approach**

  $$\hat{w} = 1 - |P^{\pi}(\theta > 0|y) - P^{\pi^{adapted}}(\theta > 0|y)|$$

  $\pi^{adapted} = N(\bar{y}, \sigma^2_{\pi})$ (one-arm) or
  $\pi^{adapted} = MVN([\bar{y}_C, \bar{y}_T], \text{diag}(\sigma^2_C, \sigma^2_T))$ (two-arm)
- Tailored to the **overall impact** of the prior on **posterior tail probabilities**



# Two-arm simulation

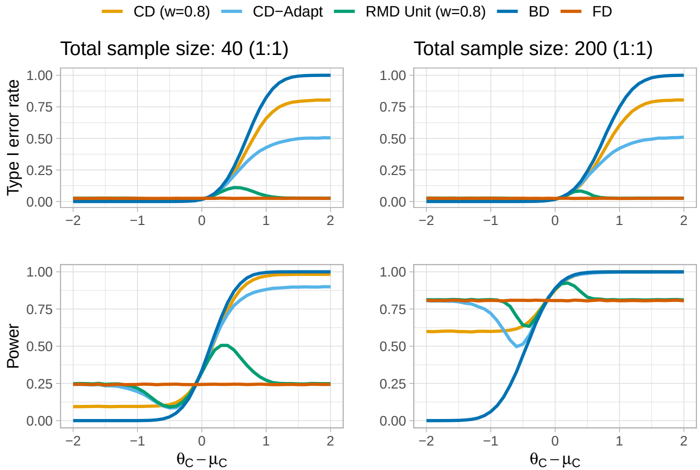



$\sigma^2 = 1$.

Informative prior on the **control arm only**: $\sigma_C^2 = \sigma^2/50$.

# Two-arm simulation

$\kappa^{bound} = 1$

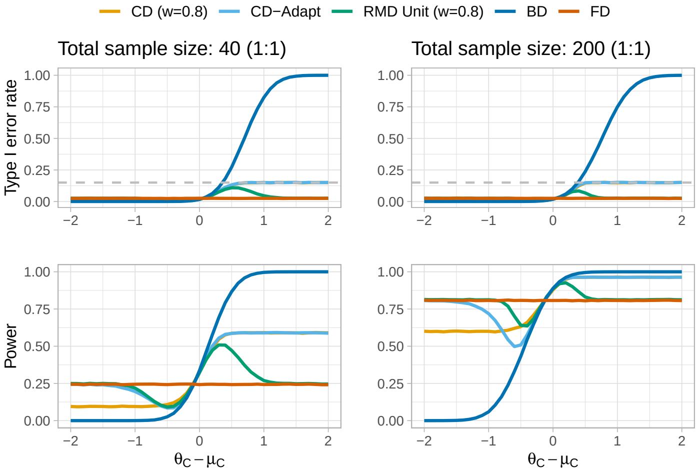



$\sigma^2 = 1$. Informative prior on the **control arm only**: $\sigma_C^2 = \sigma^2/50$.

RMD Unit: $0.8N(\mu_C, \sigma_C) + 0.2N(\mu_C, \sigma)$.

# Two-arm simulation

$\kappa^{bound} = 0.15$

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# Discussion & Outlook

- CD **relates borrowing weight to TIE rate** inflation
- Extension to **binomial outcomes** for both one- and two-arm available
- **Tailored to testing**: estimation would require a different CD
- CD tunes **test decisions** rather than the prior:
  - Directly applicable when **borrowing on both arms** with arbitrary biases
  - TIE rate for the BD in two-arm situations can be unbounded:
    $\rightarrow$ Possibility to **borrow locally but bound TIE rates** can be useful also under BD
  - When **TIE varies with $\theta_C$: fraction of borrowed information** also does
    $\rightarrow$ The focus is on controlling **impact** of borrowing on TIE rate
- Outlook: quantification of informativeness in terms of **effective sample size** (ESS)
  $\rightarrow$ Informativeness related to impact

# References

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