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Information borrowing in Bayesian clinical trials: choice of tuning parameters for the robust mixture prior

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dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

Borrowing external data

- Bayesian clinical trial designs increasingly used:
  - save resources
  - timely delivery of new treatments to patients
- Borrowing external data
- Bayesian methods provide a natural way: use of informative priors
- Challenge: heterogeneity between external and current studies (aka **prior-data conflict**)

Dynamic borrowing

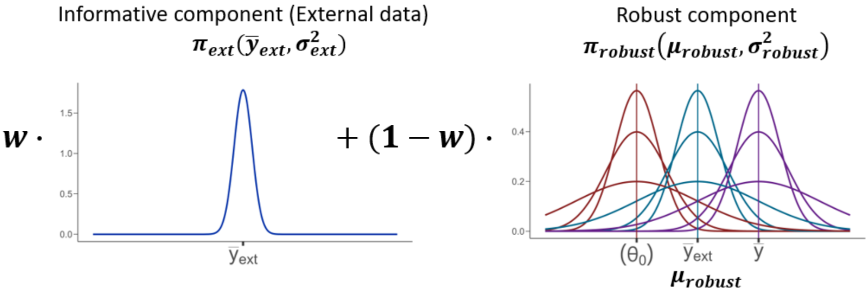
- Prior-data conflict remedy: Dynamic borrowing
- Borrow most when the current and external data are observed to be similar and least otherwise
- Examples of such methods:
  - Robust mixture prior (see Schmidli et al., 2014)
  - Power prior (see Ibrahim and Chen, 2000)
  - Commensurate prior (see Hobbs et al., 2012)
  - Compromise decision (see Calderazzo et al., 2024)
  - ....

All these methods depend on choices of borrowing parameters that influence their behaviour.

Robust mixture prior

For a parameter of interest θ, the mixture prior is given as follows (see Schmidli et al., 2014) :

$$\pi_{\text{mixture}}(\theta) = w\pi_{\text{ext}}(\theta) + (1-w)\pi_{\text{robust}}(\theta)$$



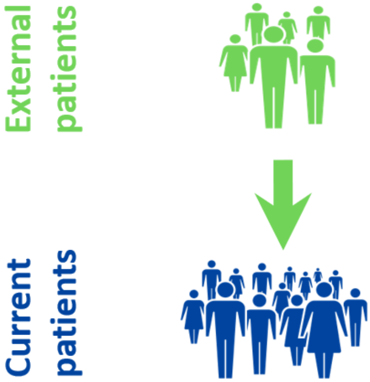
Posterior also a mixture: $\pi_{\text{mixture}}(\theta|y) = \tilde{w}\pi_{\text{ext}}(\theta|y) + (1-\tilde{w})\pi_{\text{robust}}(\theta|y)$

Scoping review

- Scoping review about use of robust Bayesian methods in Phase II trials (submitted)
- Robust mixture prior among the most used methods
- In some cases,
  - rationale for the choice of prior weight missing/not clear
  - exact prior specification of robust component not reported
- Poor reporting of borrowing parameters in general

Preprint

One-arm trial



Impact of robust component's parameter choices (Weru et al., 2026)

Prior weight on informative component $\boldsymbol{w}$

$0.25, 0.5, 0.75$

Location of robust component

- $\mu_{robust} = \bar{y}_{ext}$
- $\mu_{robust} = Null\ hypothesis\ value$
- $\mu_{robust} = \bar{y}$ (Current observed mean)

Variance of robust component

- Unit-information
- Very-dispersed

Operating characteristics

- Type I error rate
- Power
- Root Mean Squared Error (RMSE)
- Potential multi-modality of posterior distribution

Set-up ($H_0: \theta \leq 0$ vs $H_1: \theta > 0$)

- Normal endpoint with known variance, $\sigma^2 = 1$:

$$\bar{y} \sim N(\theta, 1/n_{\text{current}}), \quad n_{\text{current}} = 20$$

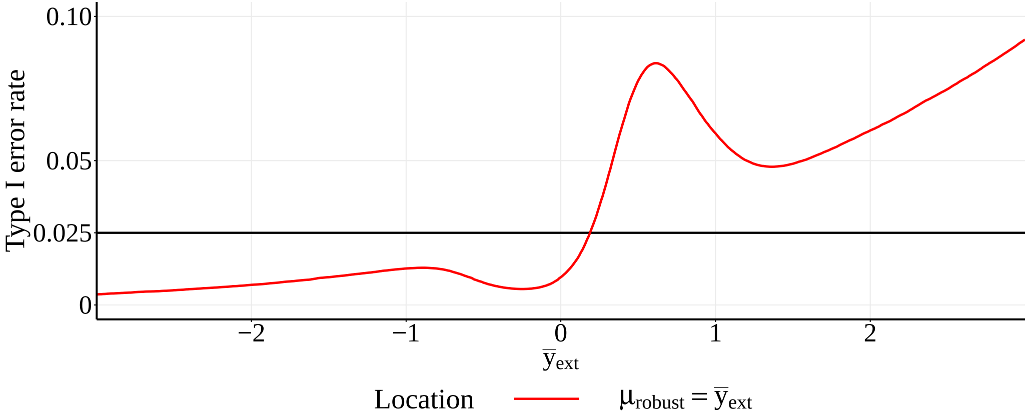
  Mixture prior:

$$\pi_{\text{ext}}(\theta) \sim N(\mu_{\text{ext}}, 1/n_{\text{ext}}),$$
$$\pi_{\text{robust}}(\theta) \sim N(\mu_{\text{robust}}, 1/n_{\text{robust}})$$
$$n_{\text{ext}} = 15 \quad \text{and} \quad \text{unit-information:} \quad n_{\text{robust}} = 1$$

- Since we evaluate Type I error, to generate the data $\theta = \theta_0 = 0$.

Testing θ ($H_0 : \theta \leq 0$ vs $H_1 : \theta > 0$): Type I error rate

$\pi_{\text{robust}}(\theta) \sim N(\mu_{\text{robust}}, 1/n_{\text{robust}})$, unit-information: $n_{robust} = 1$, $w = 0.5$



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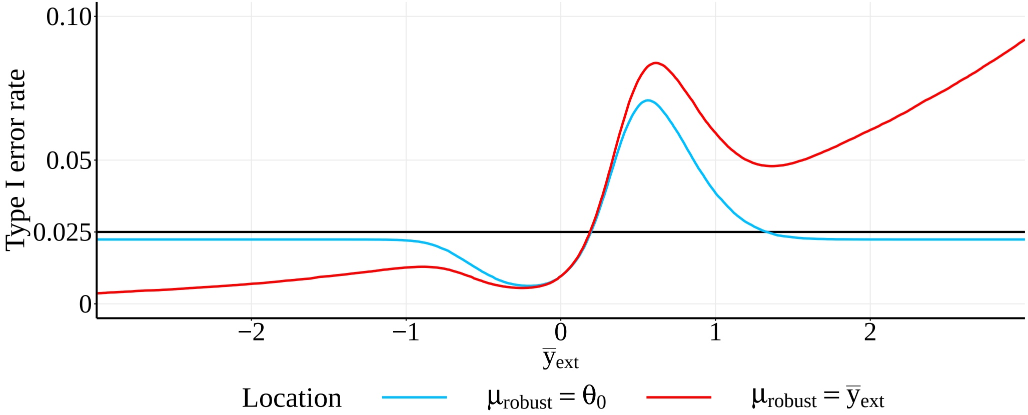

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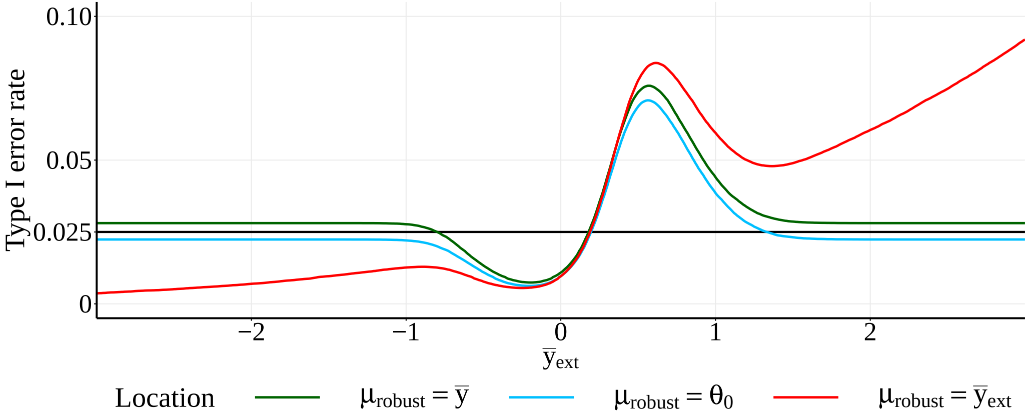
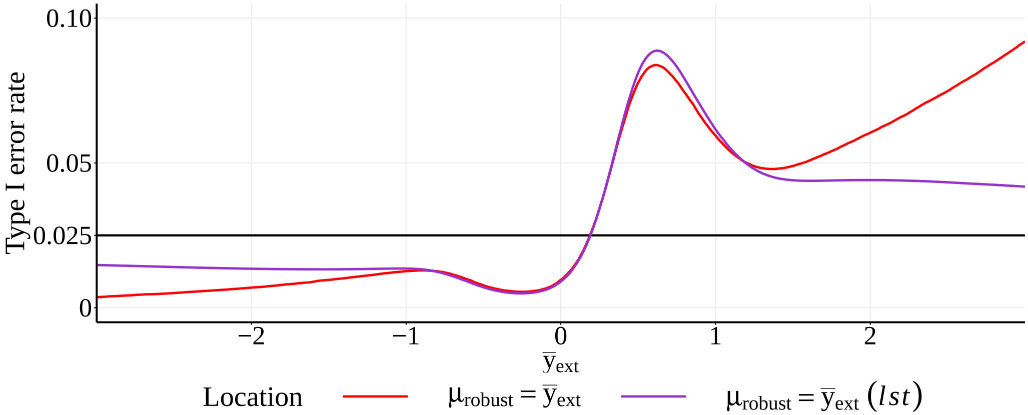


t-distribution for robust component

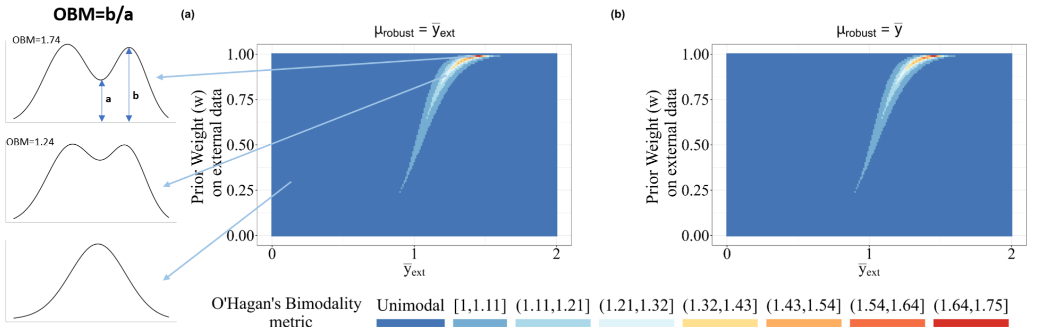
$\pi_{\text{robust}}(\theta) \sim lst(\mu, \sigma, \nu)$, $\sigma = 1$, $\nu = 3$, $w = 0.5$ (*lst* short for location scale t distribution)



Requires MCMC.

Bimodality of posterior distribution

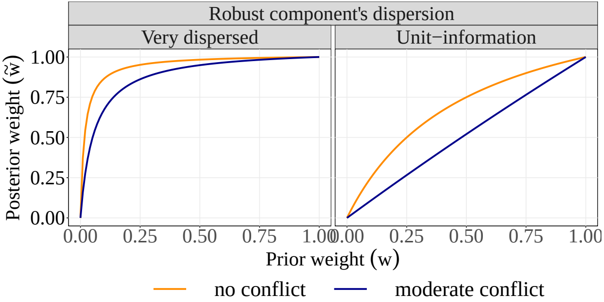
- Mixture prior $\longrightarrow$ Posterior also mixture
- O'Hagan's Bimodality Metric (OBM): minimum ratio of each mode's density to antimode's density (see O'Hagan and Forster, 2004)



Here, $\bar{y} = \theta$

Robust component’s dispersion

- Robust component should not be too vague ⟶ high posterior weight given to informative component (even when there’s conflict) (see e.g Röver et al., 2019, Mutsvari et al., 2016)
- Unit-information prior has been proposed (Kass and Wasserman, 1995)



Also in the paper:

- Importance of robust component’s location decreases with increasing dispersion.
- Bimodality more likely with less precise robust component.

Borrowing to control arm (Hybrid-control trials)

Impact of robust component's parameter choices (Weru et al., 2026)

Prior weight on informative component w

$0.25, 0.5, 0.75$

Location of robust component

- $\mu_{robust} = \bar{y}_{ext}$
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Variance of robust component

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Operating characteristics

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Set-up ($H_0 : \theta_t \leq \theta_c$ versus $H_1 : \theta_t > \theta_c$)

- External data available for the control arm
- Normal endpoint with known variance, $\sigma^2 = 1$:

$$y_t|\theta_t, \sigma_t \sim N(\theta_t, \sigma_t^2), \quad y_c|\theta_c, \sigma_c \sim N(\theta_c, \sigma_c^2), \quad \sigma_t^2 = \sigma_c^2 = \sigma^2$$
$$n_t = n_c = 20$$

Mixture prior:

$$\pi_{\text{ext}}(\theta) \sim N(\mu_{\text{ext}}, 1/n_{\text{ext}}),$$
$$\pi_{\text{robust}}(\theta) \sim N(\mu_{\text{robust}}, 1/n_{\text{robust}})$$
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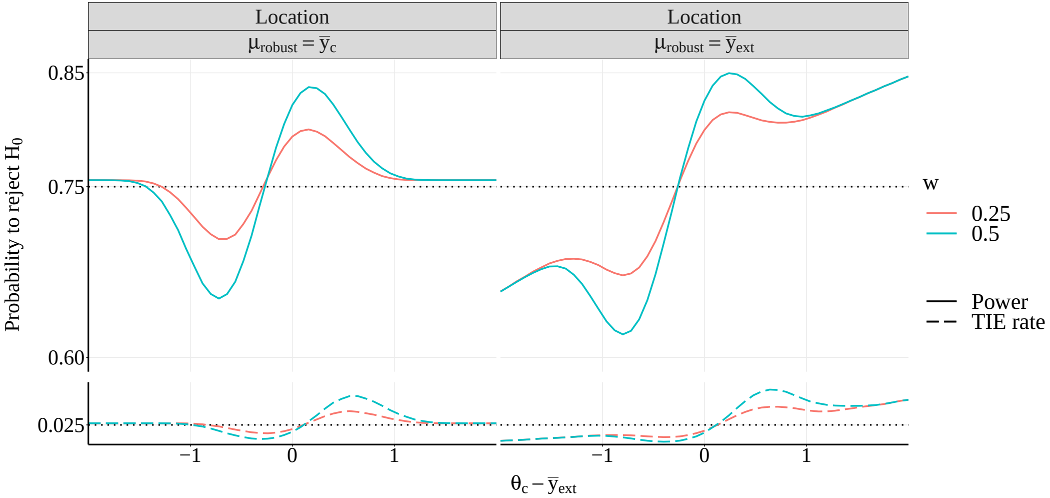
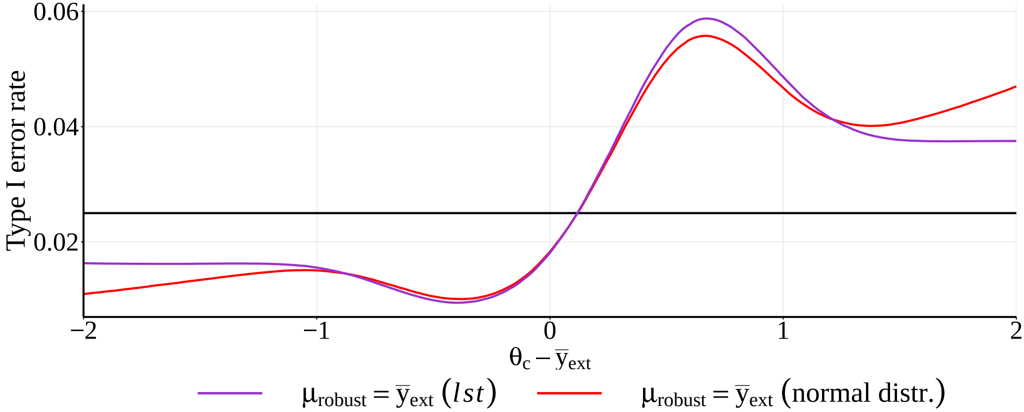
TIE rate and power



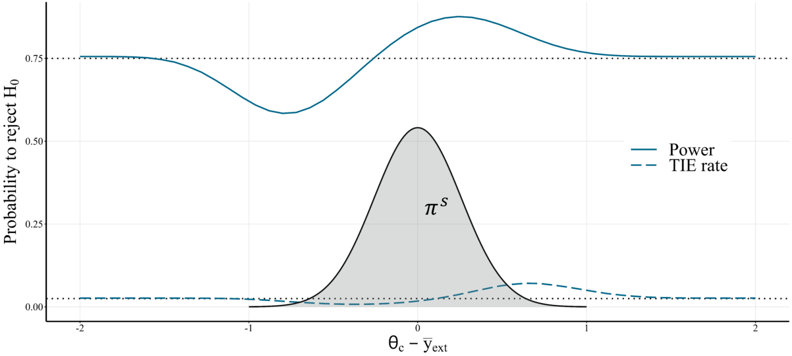
t-distribution for robust component

$\pi_{\text{robust}}(\theta) \sim lst(\mu, \sigma, \nu), \quad \sigma = 1, \nu = 3, w = 0.5$ (*lst* short for location scale t distribution)



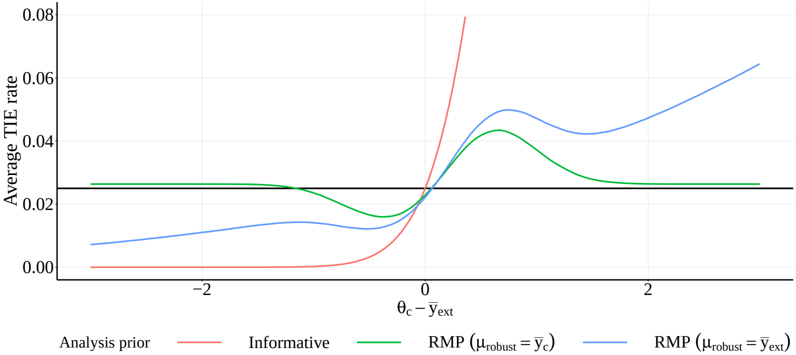
Average Type I error rate

- Bayesian metrics have been proposed (see e.g. Berry et al., 2010; Best et al., 2025; Calderazzo et al., 2020)
- Sampling/Design prior needed: used to generate a value of the parameter which is then used to generate the data



Average Type I error rate

- Informative component (external data) as design prior
- Different analysis priors



If design and analysis priors match, average type I error rate is controlled at 2.5% (Best et al., 2025) .

Summary

- Parameters of robust component in mixture prior need careful thought.
- With small current sample size, impact of the unit-information prior on the posterior will be more pronounced.
- Location of robust component: most favourable behaviour depends on whether testing or estimation
  - Testing:
    μ_{robust} at Null hypothesis value (one-arm trial)
    μ_{robust} at current control observed mean (hybrid-control trial)
  - Estimation: $\mu_{\text{robust}} = \bar{y}$ (See Weru et al. (2026) for estimation framework)
- t-distribution more robust: choice of scale and degrees of freedom.
- Bimodality in the posterior distribution can arise and can complicate decision making.

Thank you!

Weru et al. (2026).
Statistics in Biopharmaceutical Research, 1-25

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Back-up slides

Testing θ ($H_0 : \theta \leq 0$ vs $H_1 : \theta > 0$): Type I error rate

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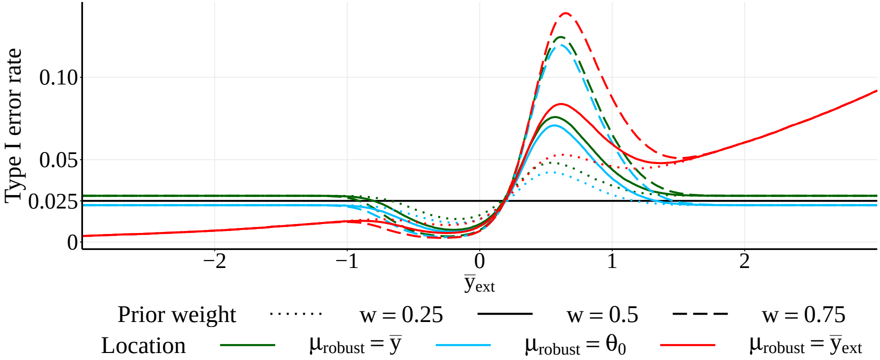
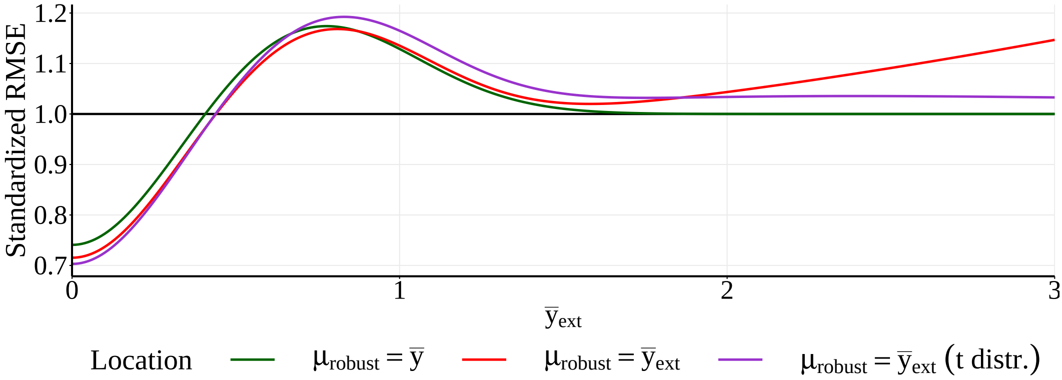


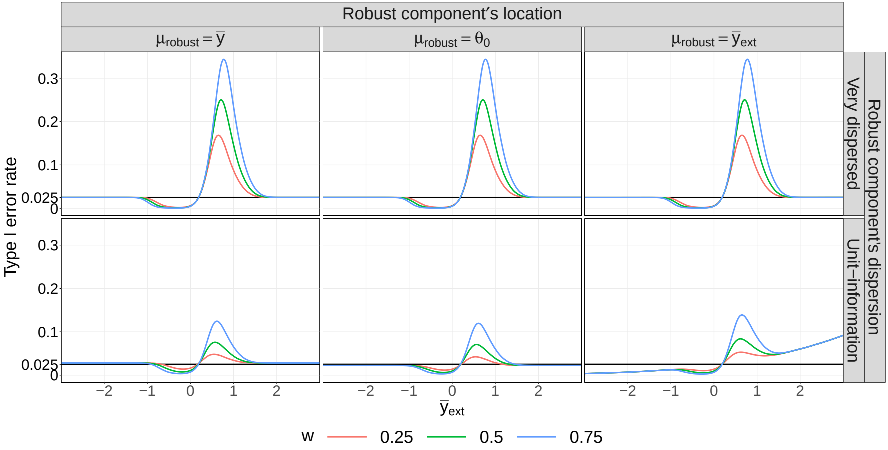
Estimating θ: Root Mean Squared error (RMSE)

$\pi_{\text{robust}}(\theta) \sim N(\mu_{\text{robust}}, 1/n_{\text{robust}})$, unit-information: $n_{robust} = 1$, $w = 0.5$



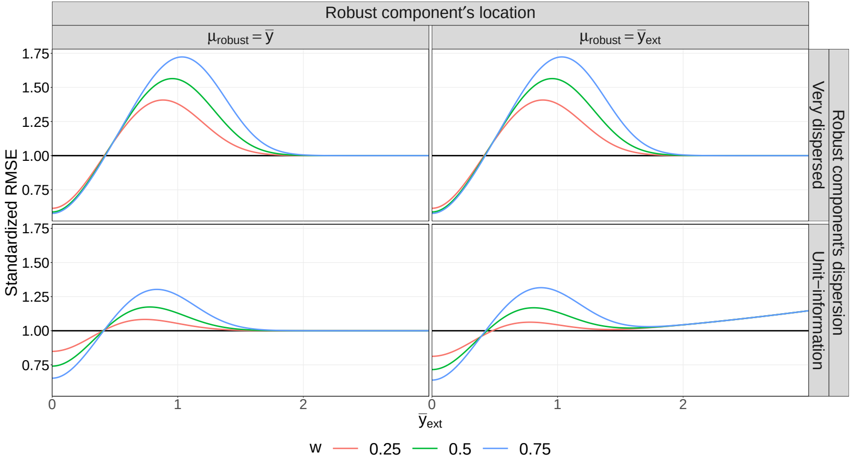
With $\mu_{\text{robust}} = \bar{y}$, RMSE better

Type I error rate: robust component's dispersion



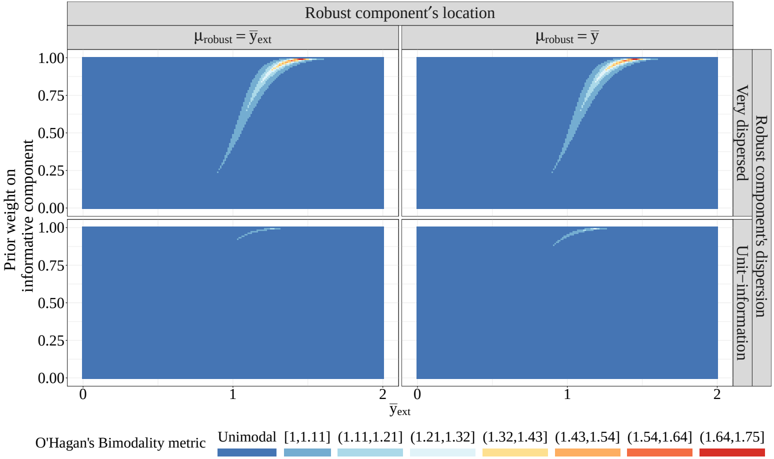
Importance of robust component's location decreases with increasing dispersion.

RMSE: robust component's dispersion



Location of robust component less important if component's precision is low

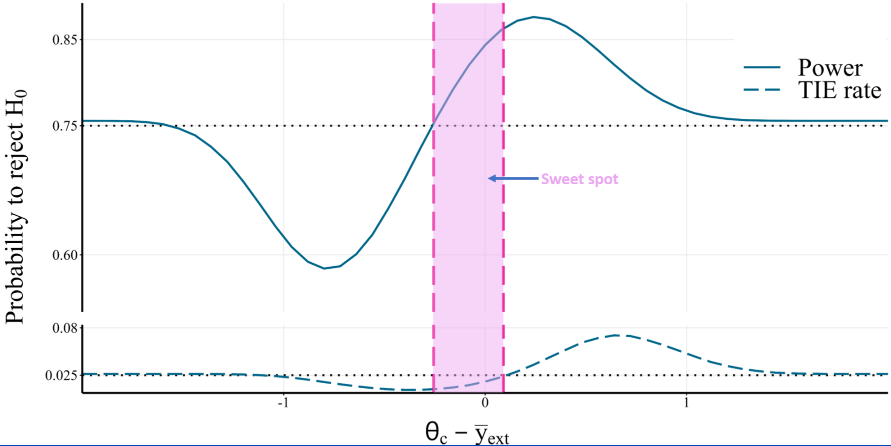
Bimodality: robust component’s dispersion



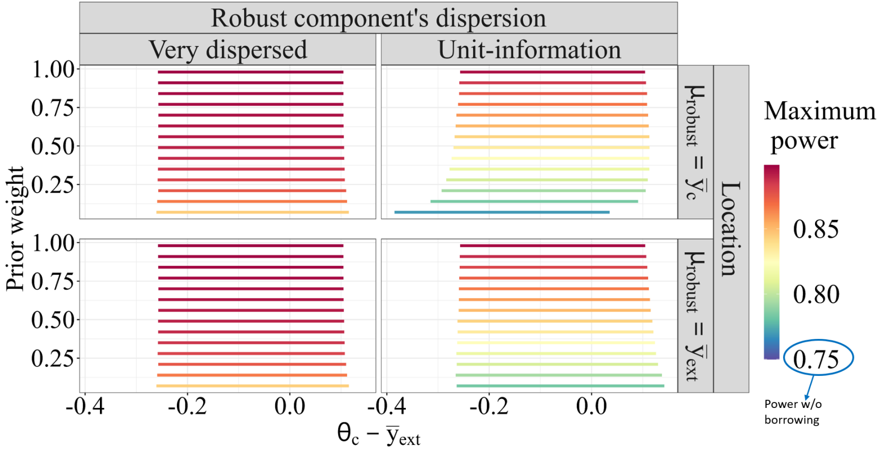
Bimodality more likely with less precise robust components and when μ_{ext} and μ_{robust} differ.

Sweet spot

In the hybrid-control setting, a "sweet spot" exists where gains in power and reductions in TIE rate are possible



Sweet spot



Robust component parameter choices impact length and position of sweet spot