Historical Data Borrowing OPC Trials

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Outline

Objective Performance Criterion (OPC) trial analyses with historical borrowing

1. OPC trials and historical borrowing
2. Historical data borrowing defined
3. Statistical methods for historical borrowing
   a) Power prior approach
   b) Discount function approaches
4. Example
5. Discussion and concluding remarks

OPC Trials and Historical Borrowing

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OPC trials

OPC trial goal:

Determine the minimum acceptable success rate for demonstrating treatment effectiveness

- Enrolling patients into studies is time consuming, expensive, and potentially dangerous
  - Need to maximize safety, i.e., do not enroll more patients than necessary to demonstrate effectiveness
- New medical treatments under investigation rarely exist in a vacuum
  - Pre-clinical trials and pilot studies
  - Clinical trials used for approval under a different regulatory body
  - Post-approval trials

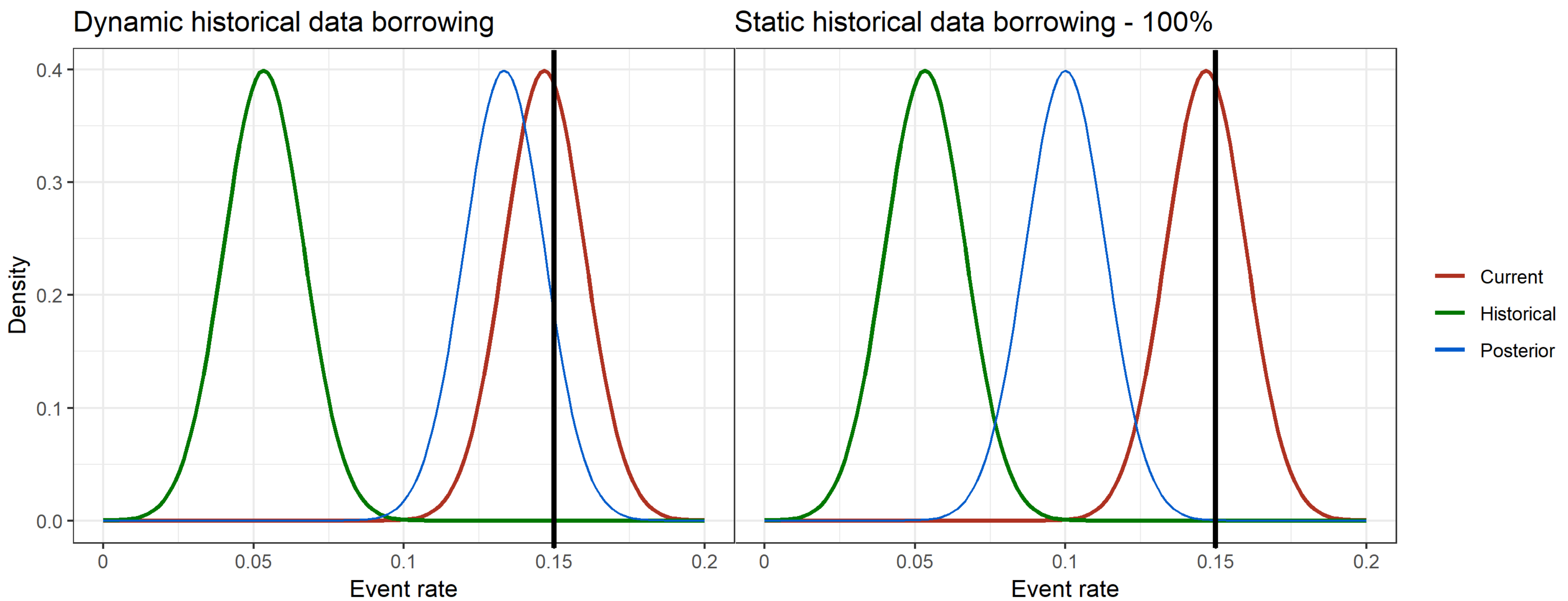
OPC trials

Historical borrowing

- *Augmenting current trial data with data collected at a previous time point*
- Typically discussed in two camps: static and dynamic
  - **Static**: choose historical data weight before collecting data
  - **Dynamic**: estimate historical data weight using new data
    - If data completely agree, give 100% weight to historical data
    - If data are disparate, give 0% weight to historical data
    - Everything in-between is a source of controversy
    - Main idea: added protection against frequentist decision errors about the current data, i.e., type 1 error and reduced power

OPC trials

Historical borrowing



OPC criterion at 0.15

OPC trials

How to determine which data are OK to borrow?

- Can't address everything here (topic worthy of its own session)
- Data should be representative
- Expert opinion and guidance
  - Can inform an upper tolerable limit on amount of weight to give to historical data
- Data should not be cherry picked
- Data could arise from sources including literature search, pilot study, etc.

Historical Data Borrowing Via Discount Functions

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Historical data borrowing

Running example: designing reliability analysis

Historical Data

- $N_0 = 100$ observations
- $y_0 = 7$ failures
- Failure rate: $\theta_0 = 0.07$

Current Data

- N observations
- y failures
- Failure rate: θ

- OPC criterion:
  - Failure rate $\theta < 0.15$
- Statistically: upper bound of 95% CI around θ is less than 0.15

Historical data borrowing

Incorporation of historical data involves weighting a likelihood

$$\underbrace{\pi\left(\theta \mid \boldsymbol{y}_0, \alpha\right)}_{\text{Prior}} \propto \underbrace{L\left(\theta \mid \boldsymbol{y}_0\right)^{\alpha}}_{\text{Historical data likelihood}} \underbrace{\pi\left(\theta\right)}_{\text{Initial prior}}$$

- θ is the parameter of interest
- $\boldsymbol{y}_0$ is the historical data
- α is the historical data weight

- Known generally as the **power prior** approach

Historical data borrowing

Incorporation of historical data involves weighting a likelihood

$$\pi\left(\theta \mid \boldsymbol{y}, \boldsymbol{y}_0, \alpha\right) \propto L\left(\theta \mid \boldsymbol{y}\right) \pi\left(\theta \mid \boldsymbol{y}_0, \alpha\right)$$

- $\boldsymbol{y}$ is the current data

- Here, we'll explore the case when α is held fixed
- Discount functions are concerned with how α is estimated

Historical data borrowing via discounting

Discount function approach

- *Discounting* reduces the impact of the historical data likelihood on the prior

1. Similarity measure p between current/historical data

$$p = g\left(\tilde{\theta},\, \theta_0\right)$$

2. Discount function H modulates the effect of the similarity on the historical data weight

$$\alpha = H\left(p\right)$$

Historical data borrowing via discounting

Similarity measure

- First, construct a surrogate statistic, $\tilde{\theta}$, derived from y to facilitate the comparison between the current and historical data
  - E.g., $\tilde{\theta} = y/N$

- Similarity measure function examples $g(\tilde{\theta}, \theta_0)$:
  - $|\tilde{\theta} - \theta_0| < \delta$
  - $\Phi\left(\frac{\tilde{\theta}-\theta_0}{\sqrt{\tilde{\sigma}^2+\sigma_0^2}}\right)$

Historical data borrowing via discounting

Discount function examples $H(p)$

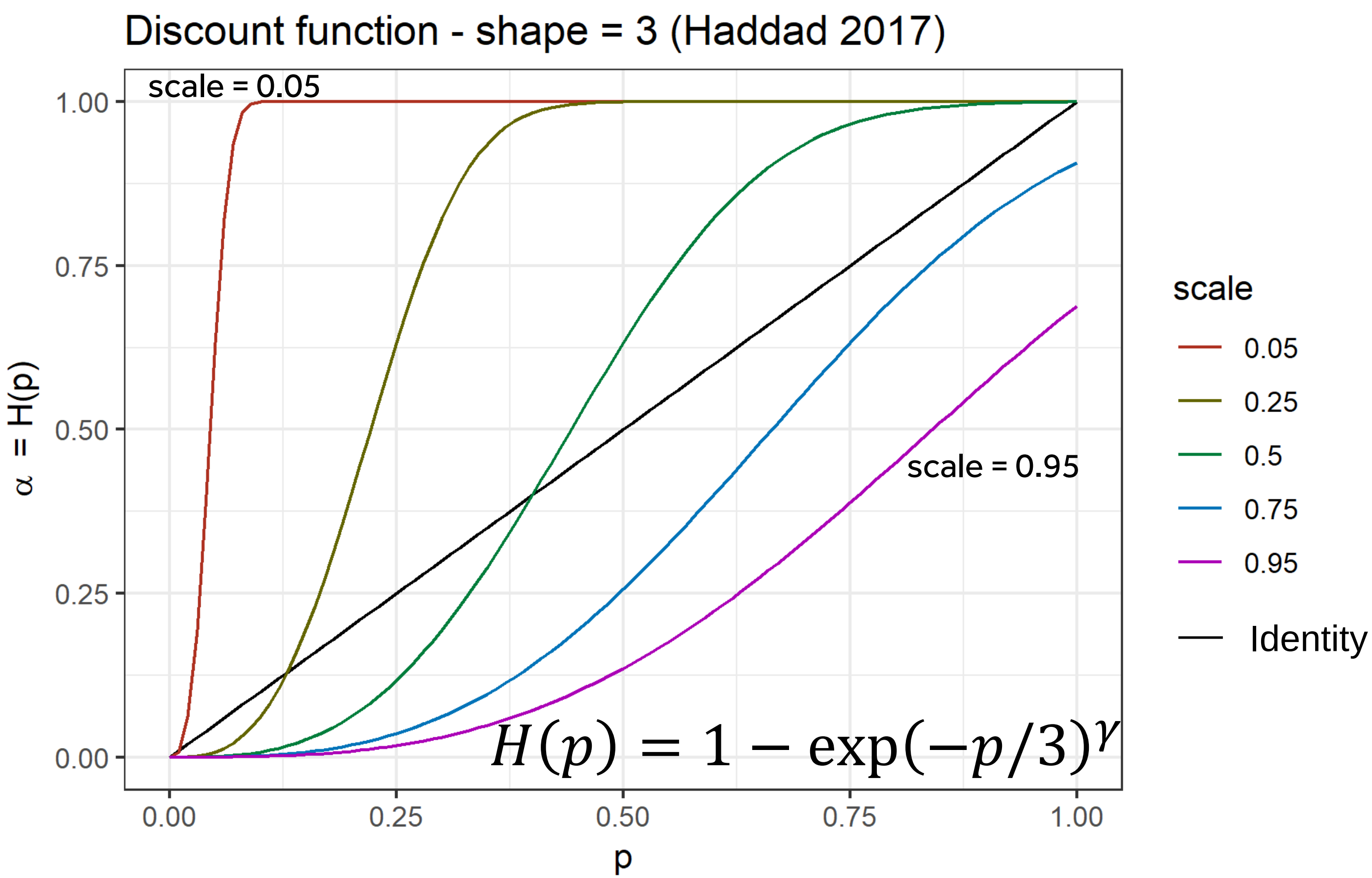
- $1 - \exp(-p/\lambda)^{\gamma}$
  - Weibull CDF (Haddad et. al. 2017)
  - λ is the shape and γ is the scale, both tuning parameters

- $p^{k/p}$
  - k a tuning parameter (Liu et al. 2018)

- p
  - The identity function

Historical data borrowing via discounting

Discount function examples



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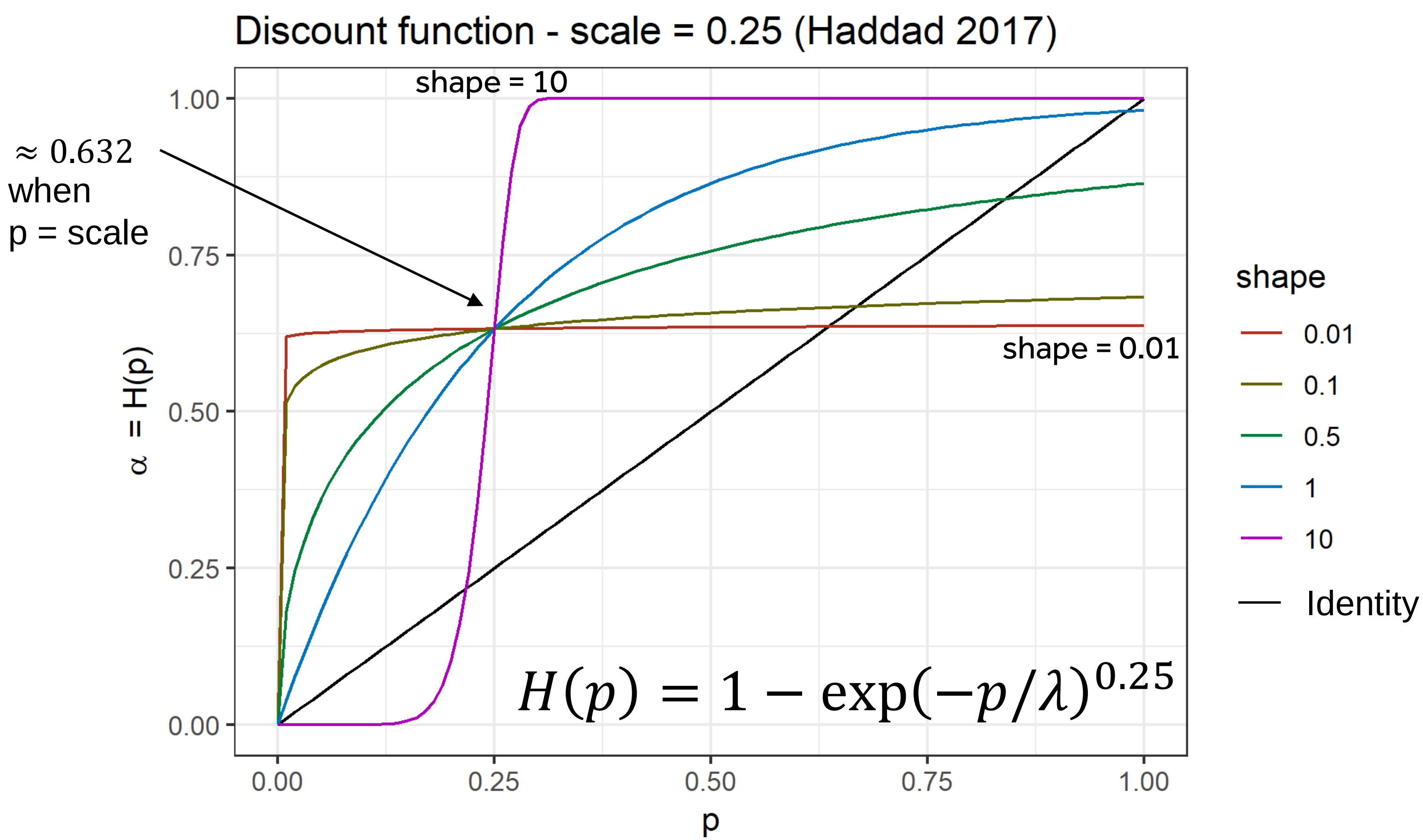
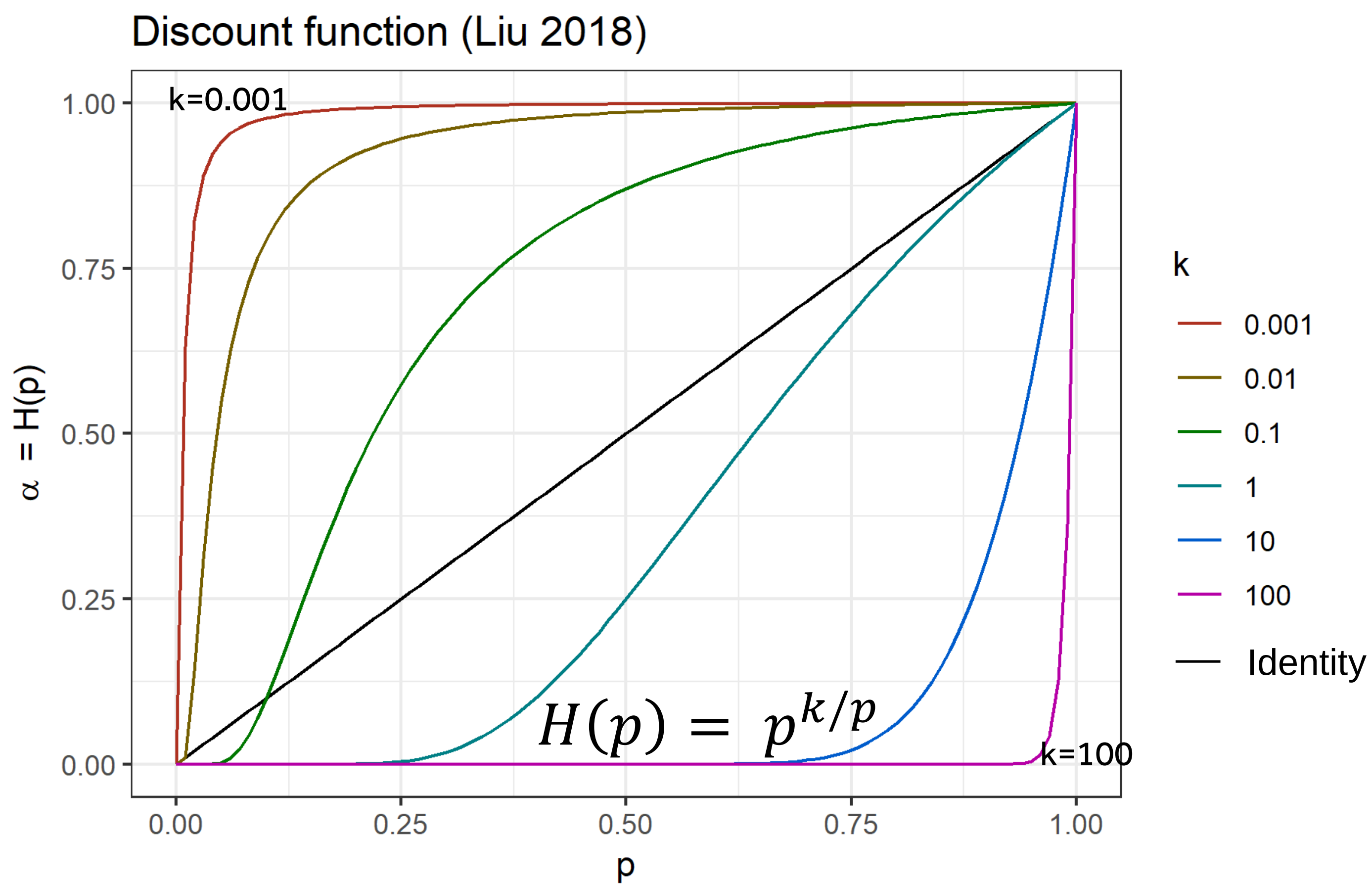
Historical data borrowing via discounting

Discount function examples



Historical data borrowing via discounting

Discount function examples



Historical data borrowing via discounting

Why discount functions?

- Computationally efficient
  - Do not require monitoring posterior chains for convergence – especially useful when powering adaptive trials
- Allow for easily controlling type 1 error and power
- Open source software is freely available
  - See the `bayesDP` R package on CRAN
  - Implemented for binary, continuous, and survival data
- Easy for clinicians to understand

Examples

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Reliability example

Reliability data

- Determine required enrollment sample size so that the total effective sample size is 300
  - Total effective sample size = $N + \alpha N_0$
- Recall historical data:
  - $y_0/N_0 = 0.07$
  - $y_0 = 7$
  - $N_0 = 100$

- Trial success declared if upper limit of 95% CI < 0.15

Reliability example

Reliability data

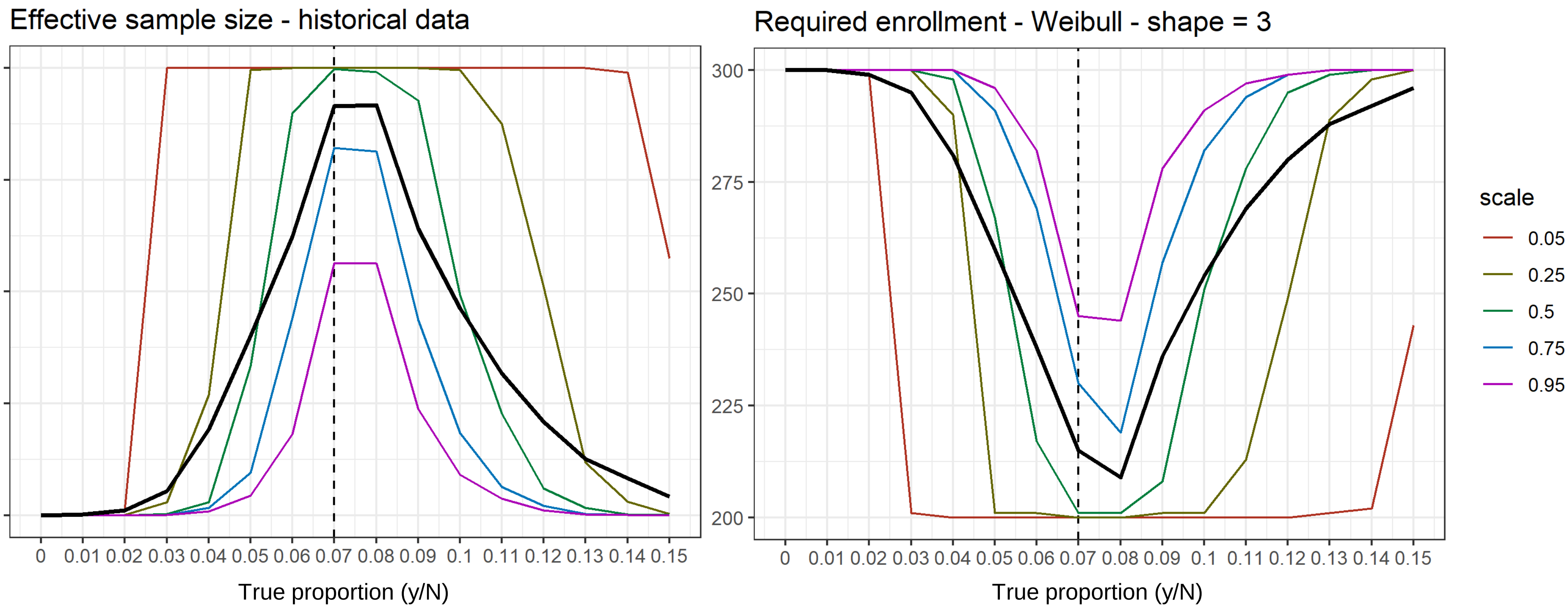
- Prior and posterior: Beta-Binomial model
  - Hyperparameters a = b = 1

$$\pi\left(\theta \mid \boldsymbol{y}_0, \boldsymbol{\alpha}\right) \propto \underbrace{\mathcal{B}eta\left(\theta \mid \boldsymbol{\alpha}\boldsymbol{y}_0 + a, \boldsymbol{\alpha}\left(\boldsymbol{N}_0 - \boldsymbol{y}_0\right) + b\right)}_{\text{Updated prior}}$$

$$\pi\left(\theta \mid \boldsymbol{y}, \boldsymbol{y}_0, \boldsymbol{\alpha}\right) \propto \underbrace{\mathcal{B}eta\left(\theta \mid \boldsymbol{y} + \boldsymbol{\alpha}\boldsymbol{y}_0 + a, \boldsymbol{N} + \boldsymbol{\alpha}\left(\boldsymbol{N}_0 - \boldsymbol{y}_0\right) + b\right)}_{\text{Posterior}}$$

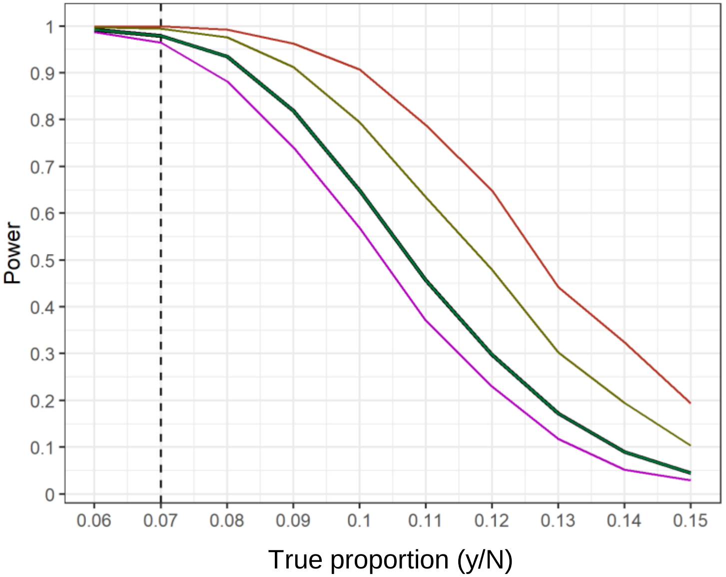
Reliability example

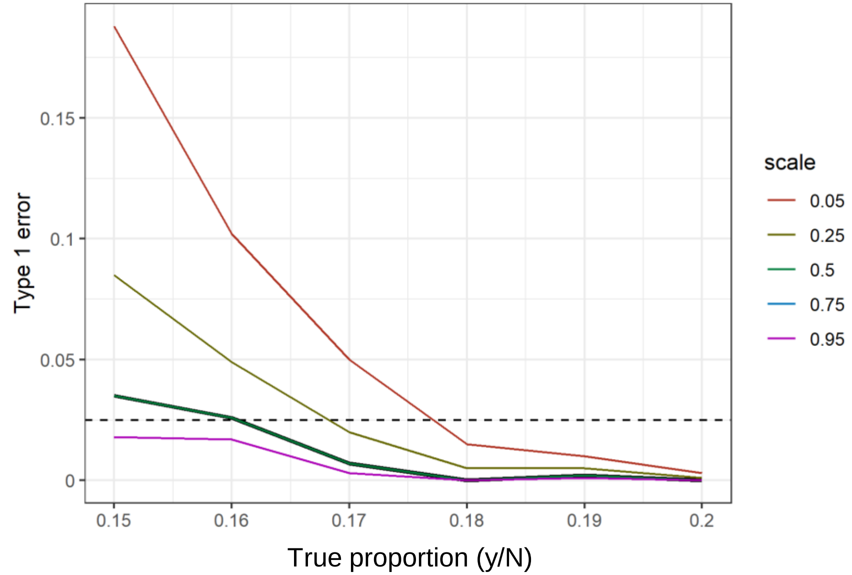
Effective sample size and required enrollment



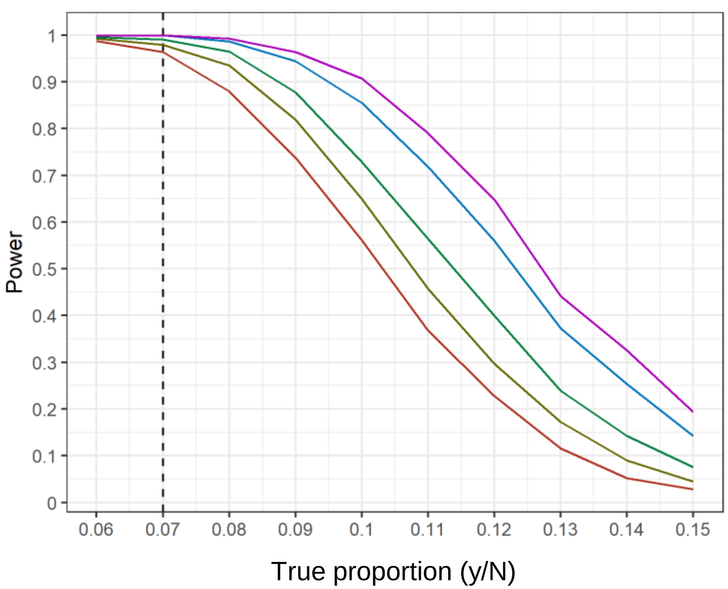
- Solid black line is the identity function

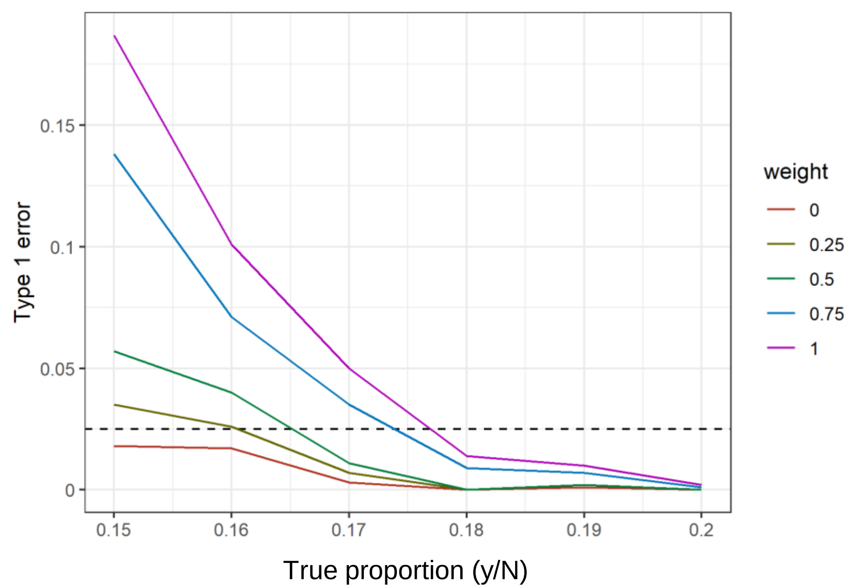
Reliability example – Power/Type 1 Error





Weibull discount function





Fixed weights

Discussion and Concluding Remarks

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Discussion and concluding remarks

Concerns

- Cherry picking historical data
  - Dynamic borrowing is a natural safeguard to prevent historical data borrowing when previously observed data is not compatible with the current data
- Type 1 error inflation
  - Depends on historical data
  - With dynamic borrowing, type 1 error inflation is limited but not guaranteed to not exist
- Historical borrowing weight based on outcome of interest
  - In the context of 2+ arm trials, this can be alleviated by basing the weight on a comparison within arm only

Discussion and concluding remarks

Other borrowing methods

- Hierarchical model
- Commensurate prior (Hobbs et al. 2012)
- Propensity score matching (Lin et al. 2018)

Additional uses

- Incorporation into adaptive trial designs
- Weighting more than one arm of a trial
- Other data types:
  - Continuous data with/without covariate adjustment
  - Survival data

Discussion and concluding remarks

Conclusion

- Historical borrowing via discounting is a computationally efficient method for incorporating historical data into a trial
  - In the context of Empirical Bayes, the estimation procedure follows the Bayesian formality
- The method is easy to implement and easy to understand
- Other methods can be difficult to implement
  - Especially in the context of adaptive trials

- Discount function methods implemented in the `bayesDP` R package

References

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