Adaptive Borrowing based on Prior Effective Sample Size

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Background

- In many CMC situations, prior knowledge is available and quantifiable in the form of prior distributions
    - Method validation
    - Process validation
    - Stability analysis

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Motivation

- Prior knowledge / data can often “overwhelm” the current study data

FDA Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010)

“If the prior information for a study is based on many more patients than are to be enrolled in the study, the prior distribution may be too informative. The judgment of what constitutes too informative is a case-by-case decision. In this case, some modifications to the study design and analysis plan may be warranted.”

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Question

- Can we use prior effective sample size (ESS) as a mechanism to down-weight the prior data?
    - Not looking into the current data
    - No commensurability criterion
- This is not the same as ESS for MCMC posterior sampling
- Previous work on prior borrowing for method validation:
    - Novick et al. (2020)
    - Faya et al. (2022)

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Previous Work

- Novick et al. (2020)
  - Reduce informativeness of variance components manually
  - E.g.: divide shape and rate parameters in a gamma distribution by factor of 3
- Faya et al. (2022)
  - Method 1: Upper limit on prior probability of study success
  - Method 2: Bayesian P-value as measure of prior-data conflict (Evans and Moshonov, 2006)
  - Both methods rely on posterior predictive distribution and power prior (Ibrahim and Chen, 2000)

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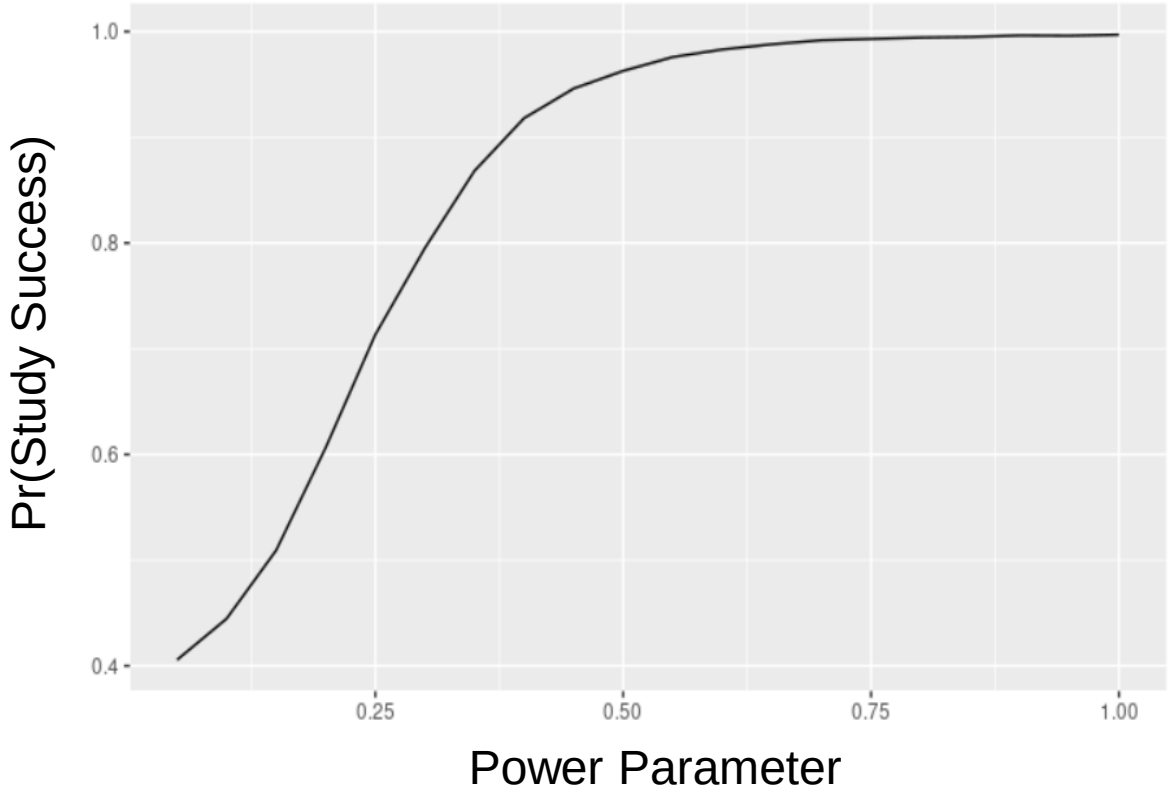
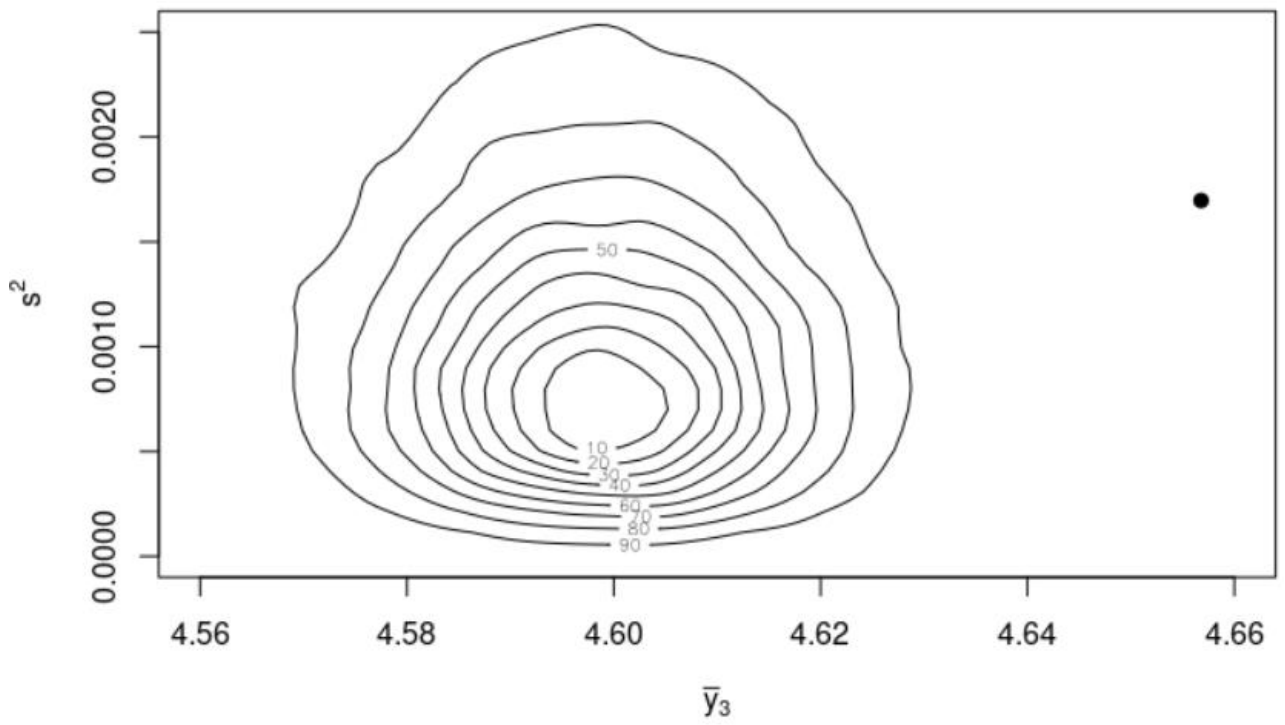
Previous Work

Method 1



Method 2



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Prior Effective Sample Size (ESS)

- Morita et al. (2008)
  - Prior distribution of interest $p(\theta)$
  - ε-information prior, or a vague prior $q_0(\theta)$
  - Posterior distribution $q_m(\theta|\boldsymbol{y})$ from $q_0(\theta)$ and hypothetical data sample $\boldsymbol{y}$ of sample size m
  - ESS is the value of m that makes $q_m(\theta|\boldsymbol{y})$ similar to $p(\theta)$

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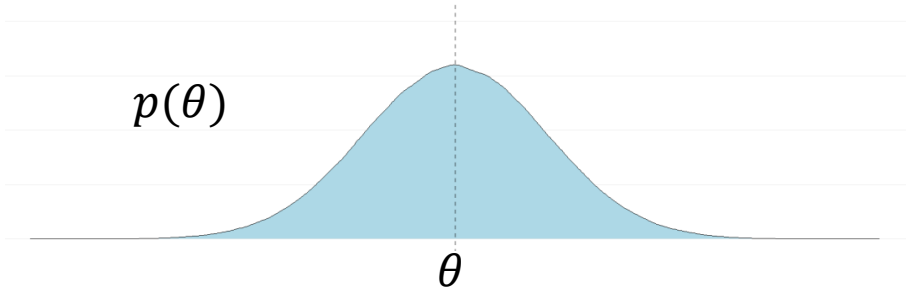
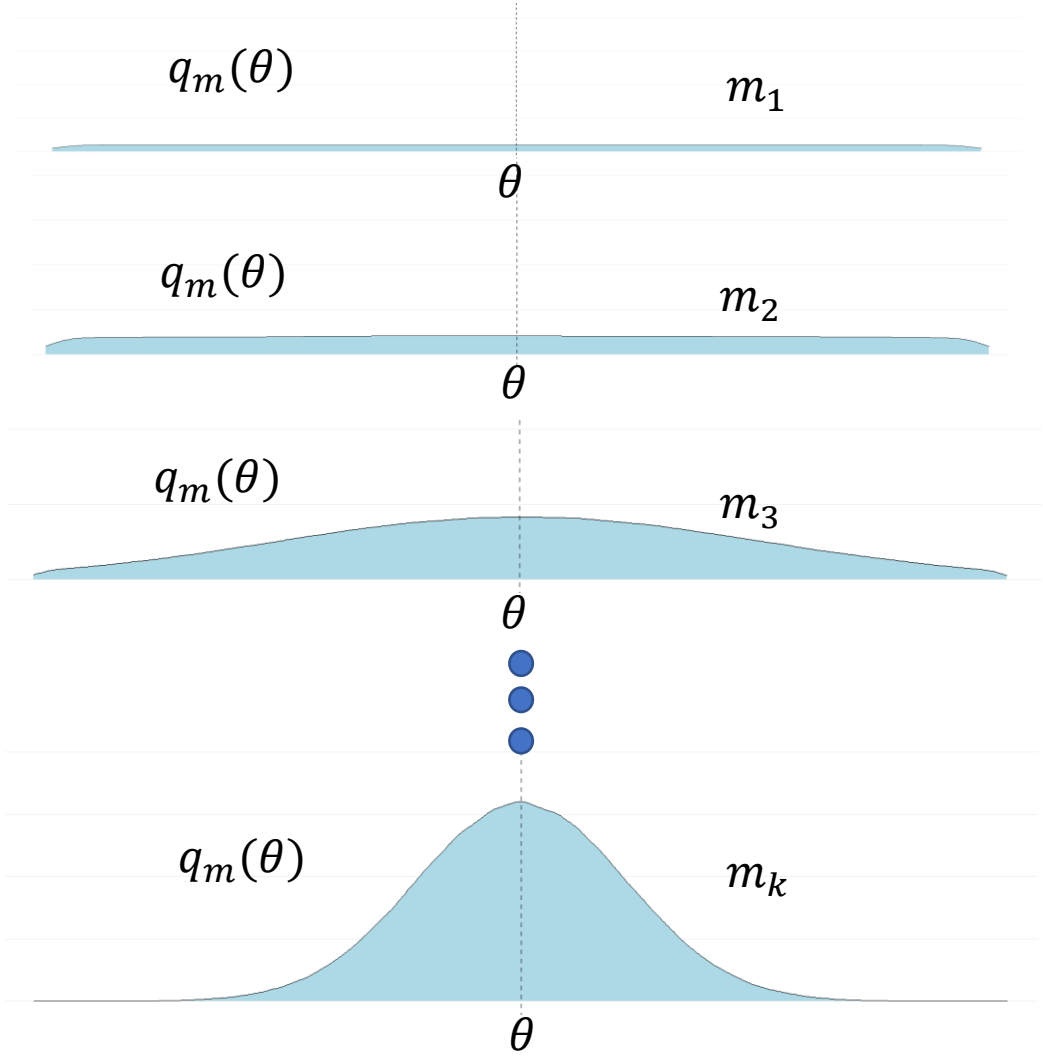
Prior Effective Sample Size (ESS)

- Morita et al. (2008)





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Prior Effective Sample Size (ESS)

- Morita et al. (2008)

    1. Apply normal/Laplace approximations to $p(\theta)$ and $q_m(\theta|\boldsymbol{y})$
    2. Compute absolute differences between the precisions of the two Laplace approximations for different m
    3. The m that minimizes the absolute difference becomes the prior ESS
    4. Equivalent to matching the curvatures of $p(\theta)$ and $q_m(\theta|\boldsymbol{y})$, evaluated at prior mean

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Prior Effective Sample Size (ESS)

- Penello et al. (2008)

$$ESS_{prior} = N\frac{Var(\theta|data, prior\ information\ ignored)}{Var(\theta|data, prior\ information\ utilized)} - N$$

  - At the design stage, pre-posterior analysis of ESS
  - Average ESS over the prior distribution and the data
    1. Generate parameters from the informative prior distribution
    2. Simulate data with the parameters generated above
    3. Compute ESS based on posterior variances, given current study design *N*
    4. Repeat 1-3 to obtain ESS distribution

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Prior Effective Sample Size (ESS)

- Hobbs et al. (2013)
  - Reference posterior $q^*(\theta|\boldsymbol{y}) \propto p^*(\theta)L(\theta|\boldsymbol{y})$ with vague prior $p^*(\theta)$ and current data sample $\boldsymbol{y}$ of size n
  - p^* denotes posterior precision of the reference posterior
  - Inference posterior $q(\theta|\boldsymbol{y}) \propto p(\theta)L(\theta|\boldsymbol{y})$ with informative prior $p(\theta)$ and current data sample $\boldsymbol{y}$ of size n
  - p denote the posterior precision of the inference posterior
  - $ESS = N\left(\frac{p}{p^*} - 1\right)$

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Proposal

- Use the power parameter (from the power prior) as a lever to adjust the prior ESS relative to the study size

$$ESS_{prior} = N\frac{Var(\theta|D, vague\ prior)}{Var(\theta|D, power\ prior)} - N$$

- Power Prior

$$\pi(\theta|D) = L(\theta|D)^{a}\pi(\theta)$$

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Proposal

- If we want historical data to be equally weighted with current data:
  - Choose a such that $ESS \approx N$
- If we want historical data to be half of the weight of current data:
  - Choose a such that $ESS \approx \frac{N}{2}$
- Note that decision is not made based on the “similarity” between historical and current data

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Example: Intermediate Precision Study

- Suppose $N = 8$ for intermediate precision study
- $y \sim normal(\log(100), \sigma_T)$
- Informative prior for σ_T based on case study from Novick et al. (2020)
- Apply Pennello and Thompson (2020) method with power prior

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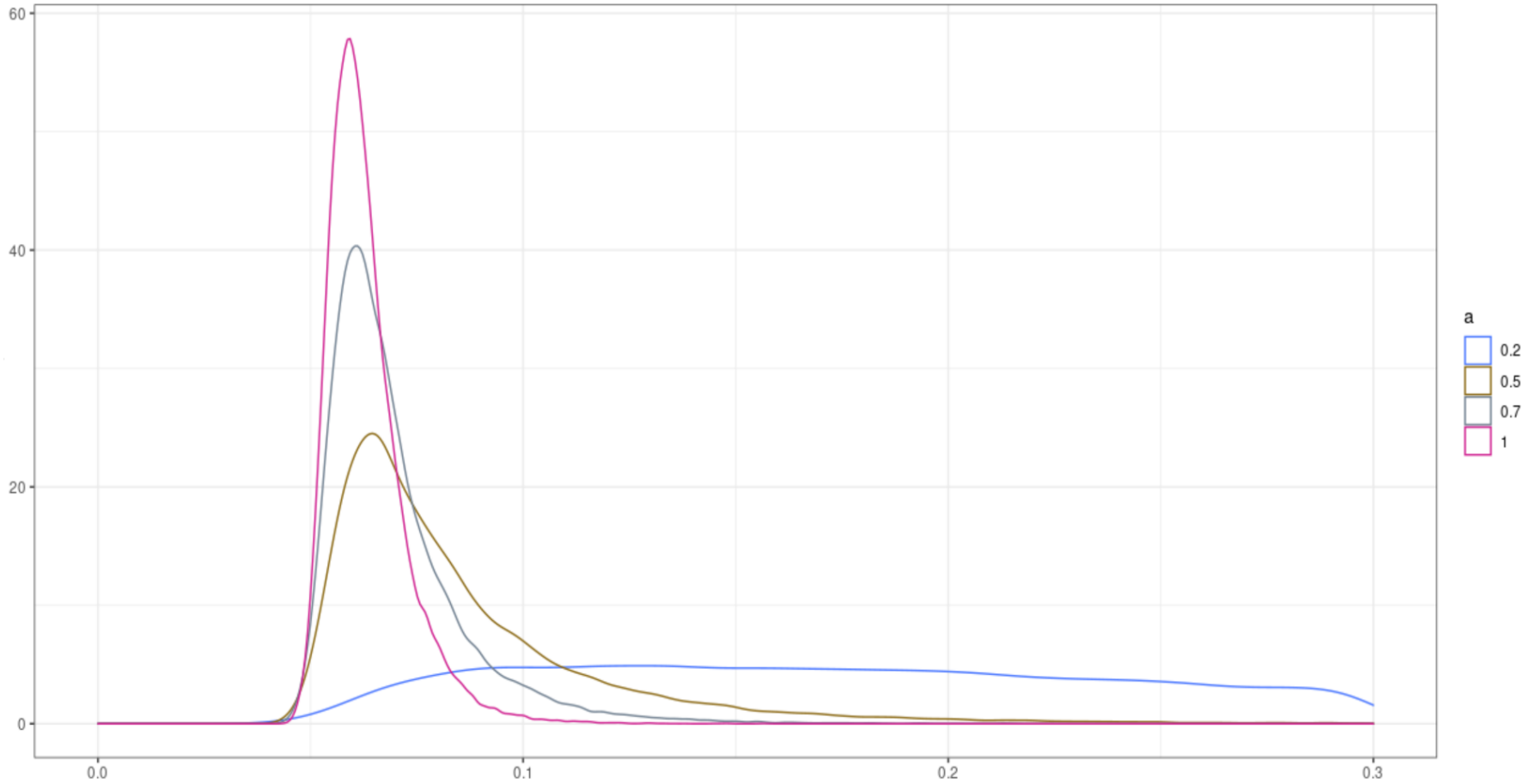
Example: Intermediate Precision Study

Power priors for σ_T



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Example: Intermediate Precision Study

1. Generate large number $i = 1, \ldots, M$ of parameters σ_T from posterior of σ_T.
2. For each σ_T^i ,generate a data sample $\boldsymbol{y} \sim normal(\log(100), \sigma_T^i)$, of size *N*.
3. For each sample $\boldsymbol{y}$ generated above, compute $Var(\sigma_T | y, vague\ prior)$.
4. Similarly, use each $\boldsymbol{y}$ generated above to get $Var(\sigma_T | y, power\ prior)$.
5. Compute Monte Carlo estimate for ESS $\approx \frac{\sum_{i=1}^{M} N \frac{Var(\sigma_T | y, vague\ prior)}{Var(\sigma_T | y, power\ prior)} - N}{M}$.
6. Repeat the above process for different a, N.

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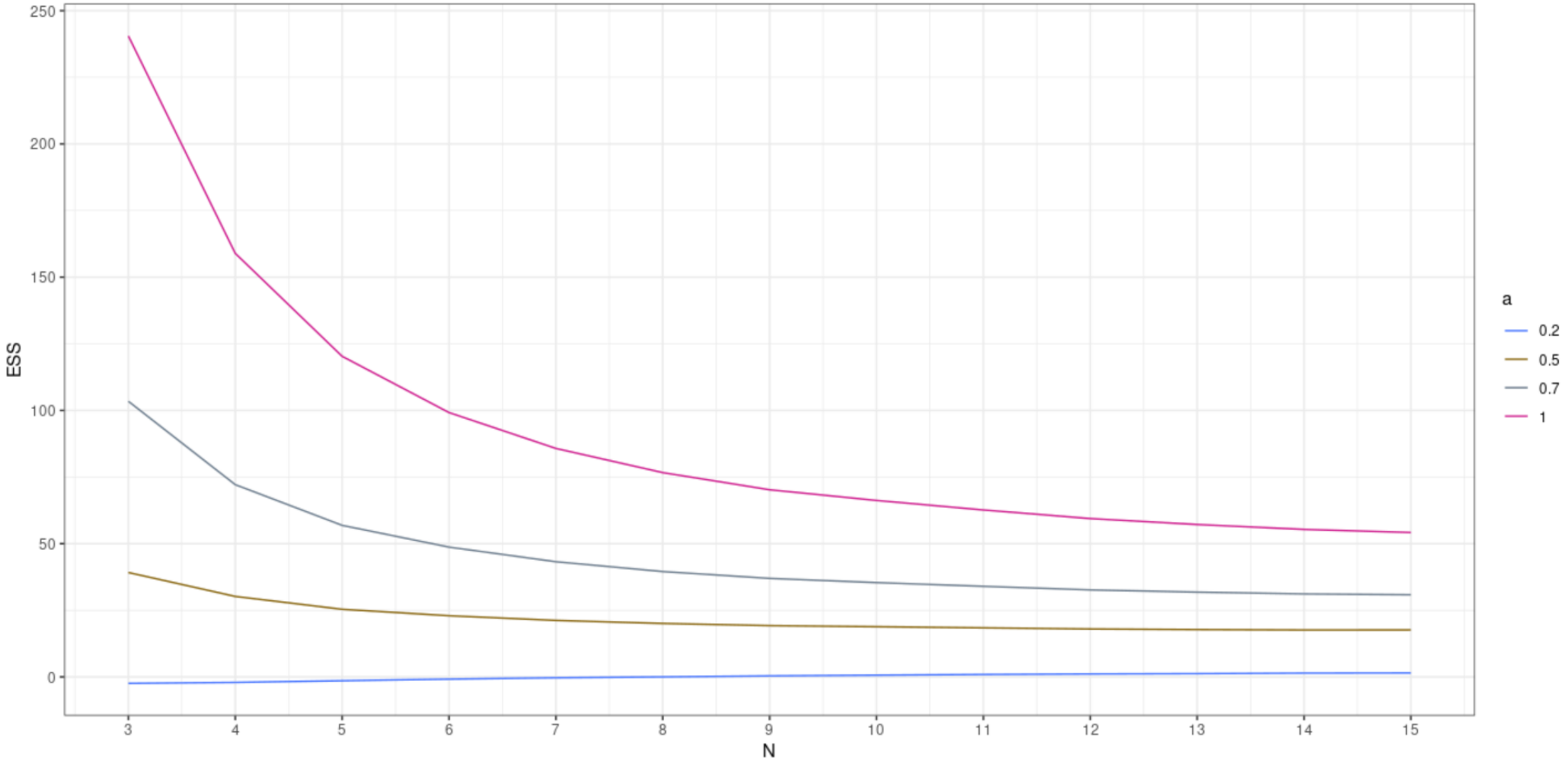
Example: Intermediate Precision Study



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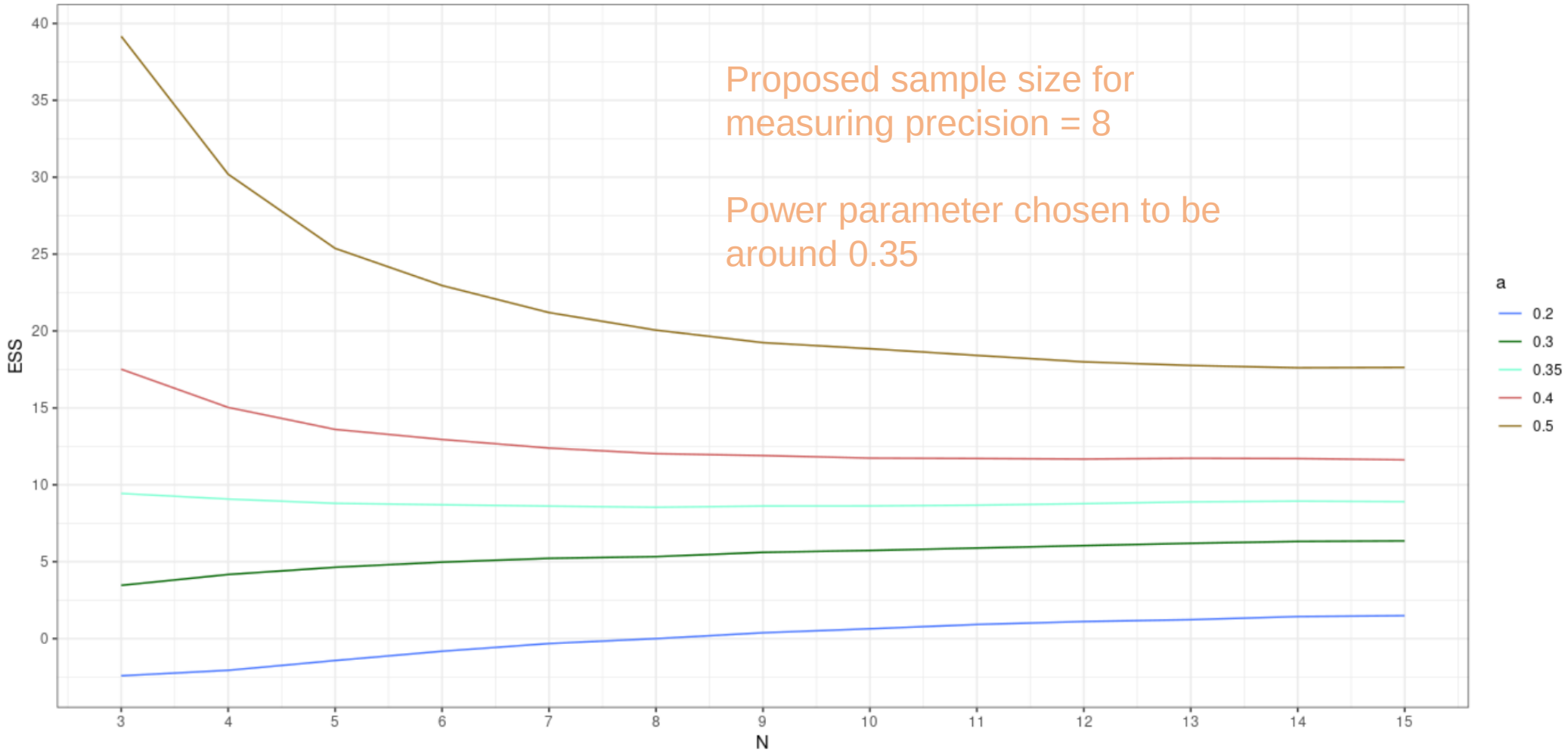
Example: Intermediate Precision Study



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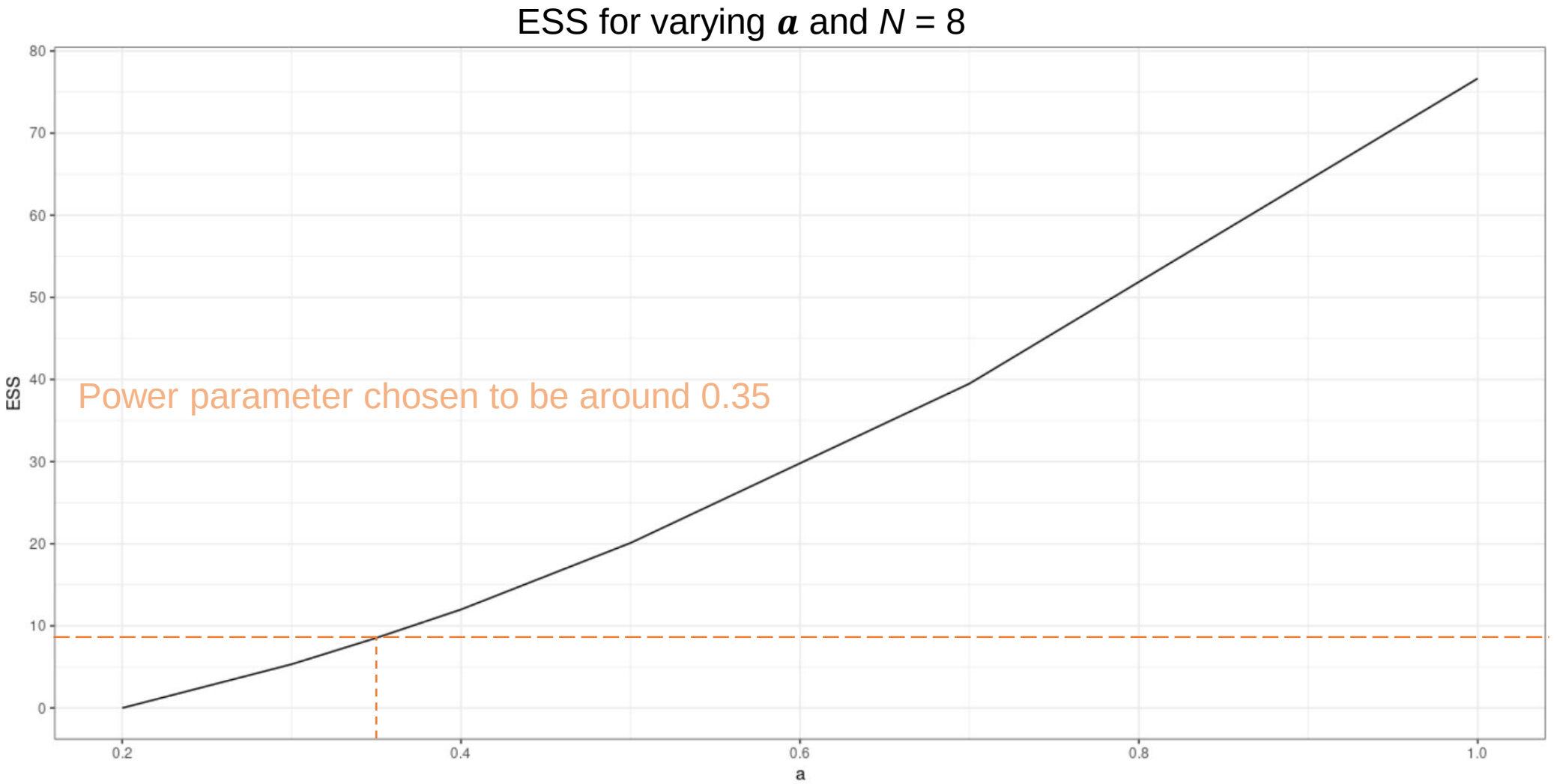
Example: Intermediate Precision Study



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Posterior Predictive Variance

- Use variance ratio for predictive distribution for computing ESS:

$$ESS_{prior} = N\frac{Var\left(\tilde{y}|\boldsymbol{y}, prior\ information\ ignored\right)}{Var\left(\tilde{y}|\boldsymbol{y}, prior\ information\ utilized\right)} - N$$

- Using vague and informative priors yields little difference in predictive variance

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Simple Example

- Normal-normal example with a known data variance σ^2 :
  - Prior for $\mu \sim normal(\mu_0, \sigma_0^2)$
  - Likelihood is $p(\mu|\boldsymbol{y}) = (2\pi\sigma^2)^{-n/2} exp\left\{-\frac{1}{2\sigma^2}\sum_{i=1}^{n}(x_i - \mu)^2\right\}$
  - Posterior for $\mu \sim normal\left(\left[\frac{\frac{\sigma_0^2}{n}}{\frac{\sigma^2}{n}+\sigma_0^2}\bar{y} + \frac{\sigma^2}{\frac{\sigma^2}{n}+\sigma_0^2}\mu_0\right] = \mu_n,\ \frac{1}{\frac{n}{\sigma^2}+\frac{1}{\sigma_0^2}} = \sigma_n^2\right)$
  - Posterior predictive for $\tilde{y} \sim normal(\mu_n, \sigma_n^2 + \sigma^2)$
  - The posterior predictive variances are close for priors with varying σ_0^2

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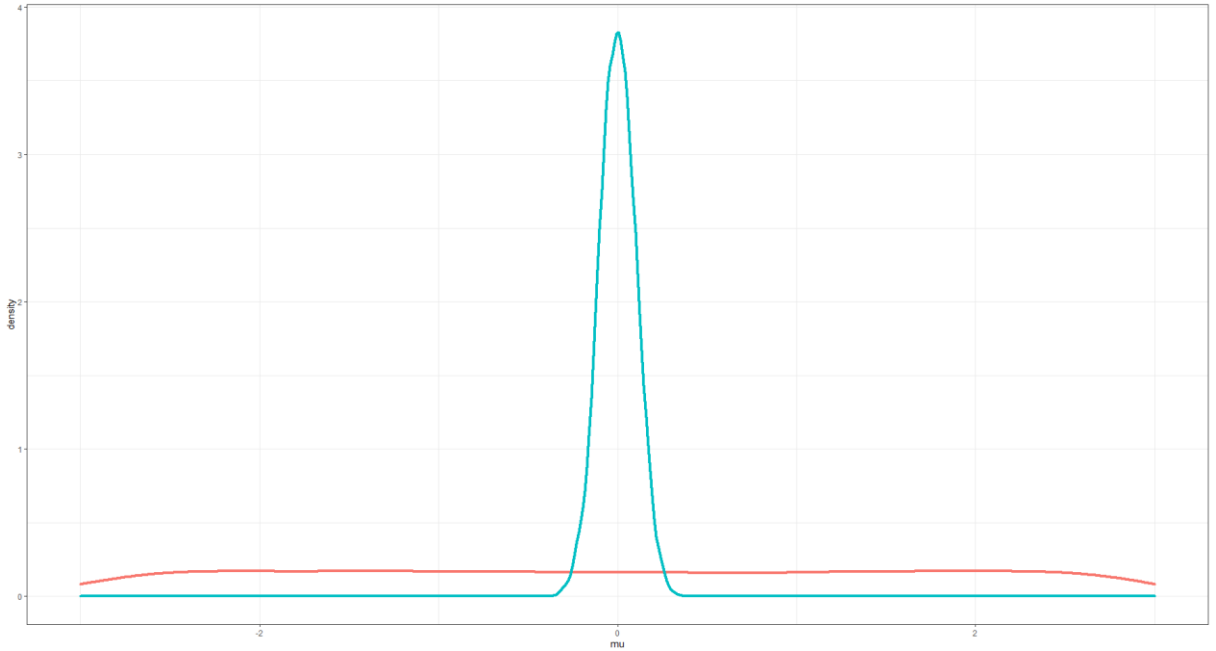
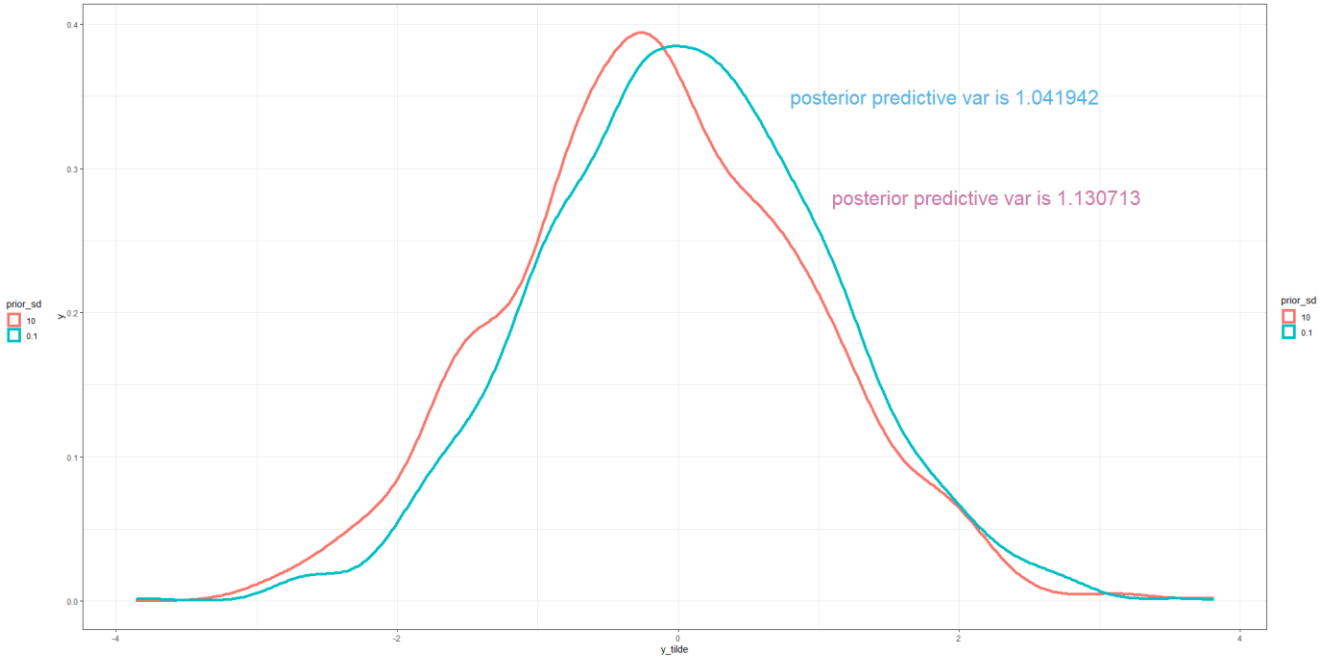
Posterior Predictive Variance-normal mean

Different priors for normal mean



μ

Posterior predictive distributions for a new observation for a simulated sample with n = 10



$\tilde{y}$

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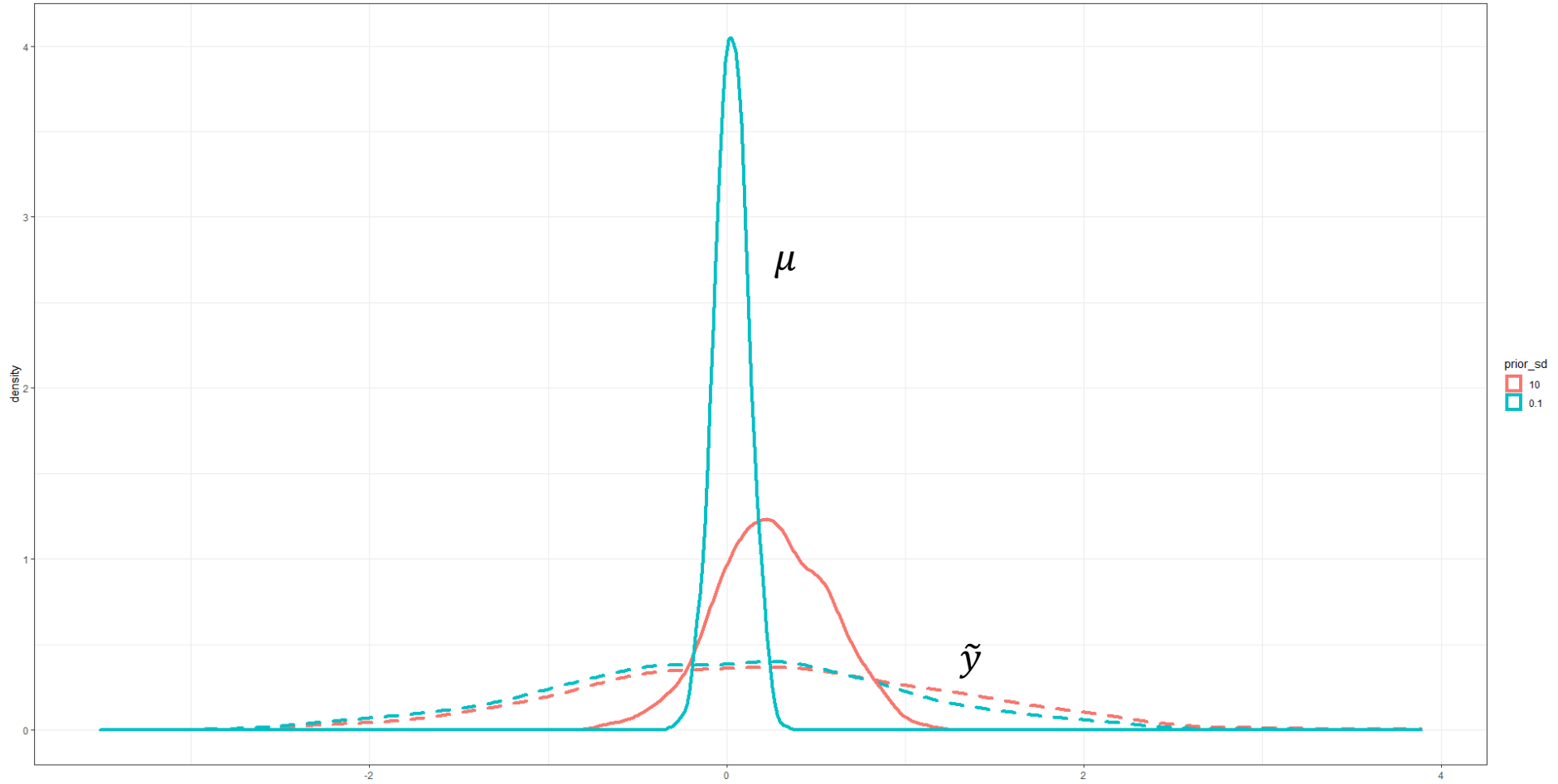
Posterior Predictive Variance-normal mean



Posterior distributions for normal SD (solid) and posterior predictive distributions for a new observations, the priors considered are normal(0, 0.1) (blue) and normal(0, 10) (red) for a simulated sample with n = 10

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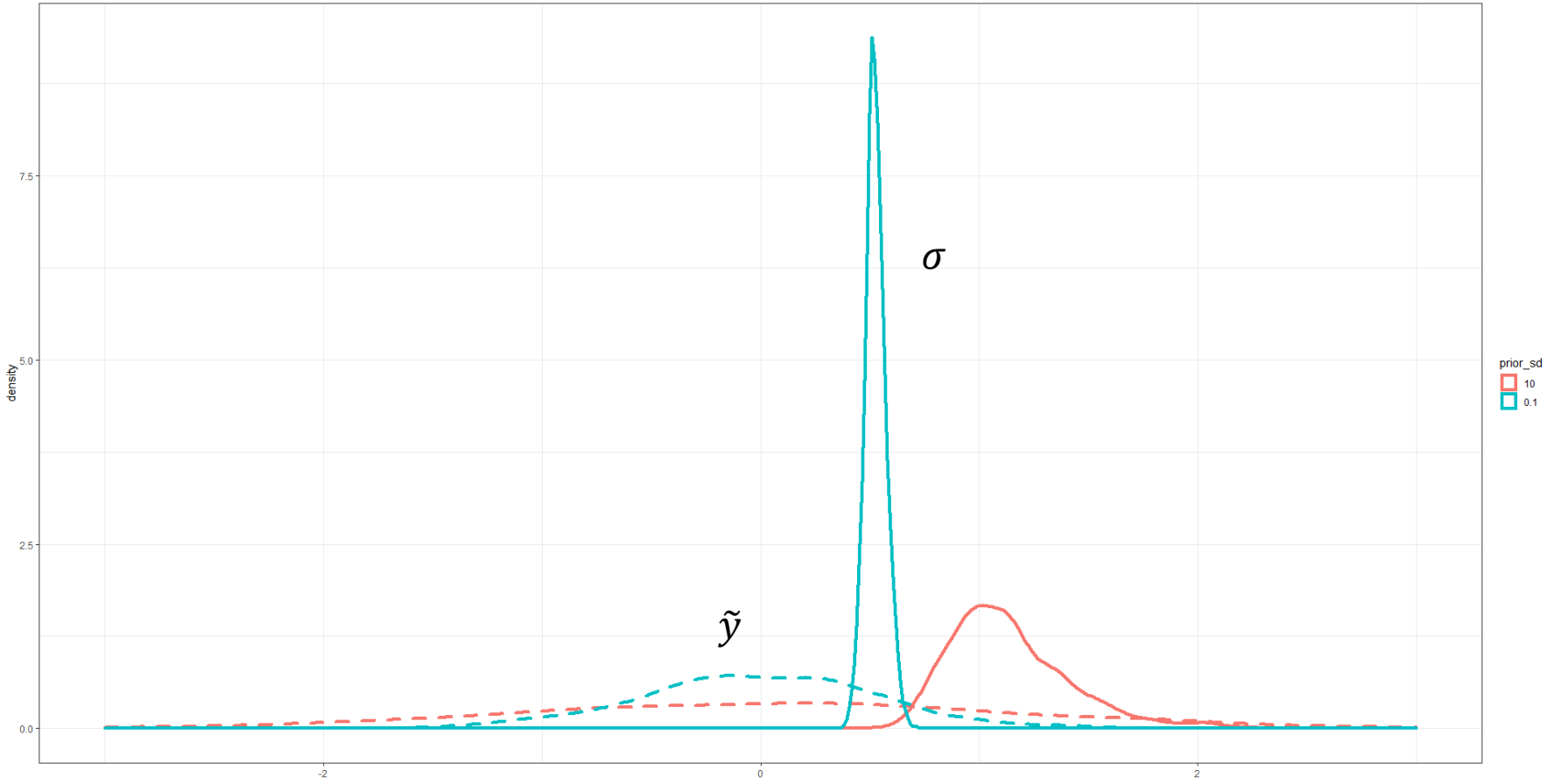
Posterior Predictive Variance-normal SD



Posterior distributions for normal SD (solid) and posterior predictive distributions for a new observations, the priors considered are half normal(0, 0.1) (blue) and half normal(0, 10) (red) for a simulated sample with n = 10

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Conclusion

- ESS-based methods have been explored and employed in the clinical space for many years
- There are opportunities to apply ESS-based method in the nonclinical space
- Adaptive borrowing based on ESS avoids criticism of prior-data similarity approaches
- Use prior data that is relevant and representative of the commercial method / process – don’t leave it up to an algorithm to decide
- Size of current study determines weight of prior data
- Can we use the posterior predictive distribution?

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Future Work

- Correlated joint prior for variance components, as per Demirhan et al. (2015), a generalized multivariate log-gamma model:
  - $\boldsymbol{\theta} = (\theta_1 = \log({\sigma_A}^2), \theta_2 = \log({\sigma_D}^2), \theta_3 = \log({\sigma_E}^2)) \sim GMVLG\ (\delta, \nu, \boldsymbol{\lambda}^T, \boldsymbol{\eta}^T)$
  - $P(\boldsymbol{\theta}) \propto\ \delta^{\nu} \sum_{m=0}^{\infty} \frac{(1-\delta)^m \prod_{j=1}^{3} \eta_j {\lambda_j}^{-\nu-m}}{\left(\Gamma(\nu+m)\right)^{3-1}\Gamma(\upsilon)m!} \exp\left((\upsilon+m)\sum_{j=1}^{3}\eta_j\theta_j\ - \sum_{j=1}^{3}\frac{1}{\lambda_j}\exp(\eta_j\theta_j)\right)$
  - $\nu > 0, \lambda_j > 0, \eta_j > 0$, for $j = 1,2,3,\ \delta = \det(\boldsymbol{\Omega})^{\frac{1}{3-1}}$
  - $\boldsymbol{\Omega} = \begin{pmatrix} 1 & \sqrt{|\rho_{12}|} & \sqrt{|\rho_{13}|} \\ \sqrt{|\rho_{12}|} & 1 & \sqrt{|\rho_{23}|} \\ \sqrt{|\rho_{13|}} & \sqrt{|\rho_{23}|} & 1 \end{pmatrix}$

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References

Evans, M., & Moshonov, H. (2006), “Checking for Prior-data Conflict,” Bayesian Analysis, 1(4), 893-914.

Faya, P., Novick, S., Seaman, J. W., Peterson, J. J., Pourmohamad, T., Banton, D., & Zheng, Y. (2022). Continuous Method Validation: Beyond One-Time Studies to Characterize Analytical Methods. Statistics in Biopharmaceutical Research, 1–9. https://doi.org/10.1080/19466315.2022.2036637

Hobbs, B. P., Carlin, B. P., & Sargent, D. J. (2013). Adaptive adjustment of the randomization ratio using historical control data. Clinical Trials, 10(3), 430–440. https://doi.org/10.1177/1740774513483934

Ibrahim, J. G., & Chen, M. H. (2000), “Power Prior Distributions for Regression Models,” Statistical Science, 15(1), 46-60.

Morita, S., Thall, P. F., & Müller, P. (2008). Determining the Effective Sample Size of a Parametric Prior. Biometrics, 64(2), 595–602. https://doi.org/10.1111/j.1541-0420.2007.00888.x

Novick, S. J., Christian, E., Farmer, E., & Tejada, M. (2020). A Bayesian Statistical Approach to Continuous Qualification of a Bioassay. PDA Journal of Pharmaceutical Science and Technology, 75(1), 8–23. https://doi.org/10.5731/pdajpst.2019.011221

Pennello, G., & Thompson, L. (2007). Experience with Reviewing Bayesian Medical Device Trials. Journal of Biopharmaceutical Statistics, 18(1), 81–115. https://doi.org/10.1080/10543400701668274

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Questions?

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