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ClinicalBayes User & Statistical Manual

Bayesian Borrowing & Decision Framework for Clinical Trials

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Bayesian borrowing, decision rules, and operating characteristic simulations for clinical trials

1 Overview

ClinicalBayes is an interactive Shiny dashboard that implements Bayesian methods for:

- Binary endpoints (response / event)
- Continuous endpoints (two-arm)
- Dynamic borrowing of historical control data
- Posterior decision rules
- Operating characteristic (OC) simulations
- Commensurate priors (Stan)
- Meta-Analytic-Predictive (rMAP) priors and Power priors
- Normal-Inverse-Gamma models
- Exportable reporting

This manual describes:

1. **How to use the application** (User Guide)
2. **The statistical methods** (Appendix)

2 User Guide

This section explains how to navigate and use each tab inside the ClinicalBayes dashboard.

3 1. Binary Endpoints

3.1 1.1 Data & Priors

Use this tab to import **historical control studies** and prepare priors for the binary endpoint.

3.1.1 Input format

Your CSV must contain:

- `study` – study name or identifier
- `events` – number of responders
- `n` – total sample size

3.1.2 Current control data

You may enter:

- Current control responders
- Current control sample size

3.1.3 Prior Types

You can construct:

- Robust rMAP priors
- Power priors

Each prior can be updated with current control data.

3.2 1.2 rMAP-style Prior

Meta-Analytic-Predictive (MAP) priors pool historical studies by creating a **mixture of Beta posteriors**.

MAP pooling uses Beta posteriors from each historical study:

$$p_i \sim \text{Beta}(y_i + 1, n_i - y_i + 1)$$

The “robust MAP” (rMAP) adds:

- a weak Beta(1,1) component
- downweights historical data when conflict is present

The rMAP prior is:

$$p_c \sim \sum_i w_i \text{Beta}(a_i, b_i) + w_R \text{Beta}(1, 1)$$

Posterior becomes:

$$p_c | \text{data} = \sum_i w'_i \text{Beta}(a_i + y_c, b_i + n_c - y_c)$$

3.3 1.3 Power Prior

$$L(\theta | y_H, n_H)^\alpha$$

Gives:

$$p_c \sim \text{Beta}(a_0 + \alpha y_H, b_0 + \alpha(n_H - y_H))$$

Posterior:

$$p_c | \text{data} \sim \text{Beta}(a_0 + \alpha y_H + y_c, b_0 + \alpha(n_H - y_H) + n_c - y_c)$$

3.4 1.4 Binary: Decision (Δ)

Treatment difference:

$$\Delta = p_t - p_c$$

Decision rule:

$$P(\Delta > \Delta^*)$$

Outputs:

- Posterior plots
- posterior summaries
- Go / No-Go

3.5 1.5 Operating Characteristics

Monte Carlo estimates of:

- Power
- Type I error
- Borrowing behavior

Across grids of true parameters.

3.6 1.6 Commensurate Prior (Stan)

Linking framework:

$$\theta_c^{curr} \sim N(\theta_c^{hist}, \tau^{-1})$$

$$\tau \sim \text{Gamma}(a_\tau, b_\tau)$$

4 2. Continuous Endpoints

4.1 2.1 Two-arm: Data & Priors

Normal-Inverse-Gamma model:

$$(\mu, \sigma^2) \sim \text{NIG}(m_0, k_0, \alpha_0, \beta_0)$$

Supports power prior weighting.

4.2 2.2 Two-arm: Decision (Δ)

$$\Delta = \mu_t - \mu_c$$

Same posterior Go / No-Go structure.

4.3 2.3 Two-arm: Operating Characteristics

Power & Type I error under continuous endpoint.

5 Statistical Appendix

This appendix summarizes the statistical models, prior constructions, posterior computations, effective sample size (ESS) calculations, decision rules, and operating characteristic (OC) simulation algorithms implemented in ClinicalBayes.

5.1 A. Notation

- y — observed event count (binary) or observed sample mean (continuous)
- n — sample size
- p — event (control/treatment) probability, e.g., control p_c or treatment p_t
- $\Delta = p_t - p_c$ (binary) or $\Delta = \mu_t - \mu_c$ (continuous)

- H — historical data _ C — current data
 - S — number of Monte Carlo draws for simulation (posterior sample size)
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5.2 B. Binary endpoint: Beta mixtures, rMAP, and Power Prior

5.2.1 B.1 Single historical study

A historical binary study with y_H events in n_H subjects yields a Beta posterior (with flat prior Beta(1,1)):

$$p_H \mid \text{hist} \sim \text{Beta}(1 + y_H, 1 + n_H - y_H).$$

5.2.2 B.2 Mixture of historical Betas (MAP / rMAP)

Given K historical studies with (y_i, n_i) , define component Beta parameters:

$$\text{Beta}(a_i, b_i) \quad \text{with} \quad a_i = 1 + y_i, \quad b_i = 1 + n_i - y_i.$$

Weight each component by w_i (by default $w_i \propto n_i$ — sample size weighting):

$$w_i = \frac{n_i}{\sum_j n_j}, \quad \sum_i w_i = 1.$$

The rMAP prior adds a robust component Beta(1,1) with weight w_R . The mixture prior is:

$$\pi(p) = \sum_{i=1}^K (1 - w_R) w_i \text{Beta}(a_i, b_i) + w_R \text{Beta}(1, 1).$$

Posterior update with current data y_c, n_c (mixture-of-Betas conjugacy):

Each component updates as $\text{Beta}(a_i + y_c, b_i + n_c - y_c)$ with reweighted component weights:

$$w'_i \propto w_i \frac{B(a_i + y_c, b_i + n_c - y_c)}{B(a_i, b_i)}, \quad w'_R \propto w_R \frac{B(1 + y_c, 1 + n_c - y_c)}{B(1, 1)}$$

(normalize so weights sum to 1). In practice we sample from the posterior mixture using `rmixbeta()`.

5.2.3 B.3 Power Prior (binary)

Aggregate historical totals $Y_H = \sum_i y_i, N_H = \sum_i n_i$. For a baseline $\text{Beta}(a_0, b_0)$, the power prior with $0 \leq \alpha \leq 1$ gives:

$$\pi(p) \propto \text{Beta}(a_0, b_0) \cdot \text{Binomial}(Y_H; N_H, p)^\alpha \Rightarrow \text{Power prior } p \sim \text{Beta}(a_0 + \alpha Y_H, b_0 + \alpha(N_H - Y_H)).$$

Update with current data y_c, n_c to obtain posterior Beta:

$$p \mid \text{data} \sim \text{Beta}(a_0 + \alpha Y_H + y_c, b_0 + \alpha(N_H - Y_H) + n_c - y_c).$$

5.3 C. Effective Sample Size (ESS)

For a Beta(a, b) distribution, **ESS** is defined as:

$$\text{ESS}_{\text{Beta}} = a + b.$$

For a mixture of Betas with mixture weights w , we use the weighted average ESS:

$$\text{ESS}_{\text{mix}} = \sum_k w_k (a_k + b_k).$$

Practical interpretation: - ESS approximates the sample size of equivalent binomial data corresponding to the prior. - Incremental ESS = posterior ESS – prior ESS.

5.4 D. Decision Rule for Binary Endpoint

Define the treatment and control posteriors and compute posterior draws (Monte Carlo) for $\Delta = p_t - p_c$.

Decision rule:

$$\text{Declare efficacy if } \Pr(\Delta > \Delta^*) > \gamma,$$

where typical γ values are 0.9 to 0.99 and Δ^* is the clinically meaningful difference.

Implementation detail: - Draw S independent samples $\{p_c^{(s)}\}_{s=1}^S$ and $\{p_t^{(s)}\}_{s=1}^S$ from their posteriors (if using shared control posterior draw carefully if borrowing). - Compute $\Delta^{(s)} = p_t^{(s)} - p_c^{(s)}$. - Estimate $\Pr(\Delta > \Delta^*) \approx \frac{1}{S} \sum_{s=1}^S \mathbf{1}\{\Delta^{(s)} > \Delta^*\}$.

5.5 E. Operating Characteristics (OC) Simulation — Binary

To compute $\Pr(\text{declare efficacy})$ under a grid of true parameters ($p_c^{\text{true}}, p_t^{\text{true}}$):

Algorithm

For each grid point: 1. For iteration $b = 1 \dots B$: - Simulate current control $y_c^{(b)} \sim \text{Binomial}(n_c, p_c^{\text{true}})$. - Simulate current treatment $y_t^{(b)} \sim \text{Binomial}(n_t, p_t^{\text{true}})$. - (Re)construct the prior based on historical data (mixture or power prior). - Update posterior(s) with simulated current data. - Compute decision indicator $d^{(b)} = \mathbf{1}\{\Pr(\Delta > \Delta^*) > \gamma\}$. 2. Estimate power / operating characteristic as $\frac{1}{B} \sum_b d^{(b)}$.

Report heatmaps of $\Pr(\text{declare efficacy})$ across the grid. Also compute Type I error as the $\Pr(\text{declare efficacy})$ when $p_t^{\text{true}} = p_c^{\text{true}}$.

5.6 F. Commensurate Prior (binary, Stan)

Commensurate prior formulation (sketch):

- Work on logit scale: $\theta = \text{logit}(p)$.
- Let θ^{hist} be historical controls (estimated or modeled), and assume:

$$\theta^{curr} \mid \theta^{hist}, \tau \sim N(\theta^{hist}, \tau^{-1}).$$

Place a prior on τ (e.g., $\tau \sim \text{Gamma}(a_\tau, b_\tau)$). Larger $\tau \rightarrow$ stronger shrinkage toward historical value.

Stan is used to fit the hierarchical model and returns posteriors for θ^{curr} , $\theta^{treatment}$, τ , and Δ . Posterior inference and decision rule are applied to posterior draws.

5.7 G. Continuous endpoint: Normal–Inverse–Gamma (NIG) conjugate model

5.7.1 G.1 NIG prior parameterization

An NIG prior can be parameterized as:

$$\begin{aligned}\sigma^2 &\sim \text{Inverse-Gamma}(a_0, b_0) \\ \mu \mid \sigma^2 &\sim N(m_0, \sigma^2/k_0)\end{aligned}$$

This yields the joint NIG prior on (μ, σ^2) with parameters (m_0, k_0, a_0, b_0) .

5.7.2 G.2 Posterior update with data (sample mean \bar{y} , sample variance s^2 , n)

Given prior (m_0, k_0, a_0, b_0) and observed data (\bar{y}, s^2, n) :

$$\begin{aligned}k_N &= k_0 + n \\ m_N &= \frac{k_0 m_0 + n \bar{y}}{k_N} \\ a_N &= a_0 + \frac{n}{2} \\ b_N &= b_0 + \frac{1}{2} \left[(n-1)s^2 + \frac{k_0 n (\bar{y} - m_0)^2}{k_N} \right]\end{aligned}$$

Posterior: $(\mu, \sigma^2) \sim \text{NIG}(m_N, k_N, a_N, b_N)$.

5.7.3 G.3 Drawing posterior samples

To obtain Monte Carlo draws: 1. Draw $\sigma^2 \sim \text{Inverse-Gamma}(a_N, b_N)$ (or sample $1/\sigma^2 \sim \text{Gamma}(a_N, b_N)$ and invert). 2. For each σ^2 , draw $\mu \sim N(m_N, \sigma^2/k_N)$.

Then compute $\Delta^{(s)} = \mu_t^{(s)} - \mu_c^{(s)}$ and apply the decision threshold.

5.7.4 G.4 Borrowing (power prior on control)

Given historical control summary (\bar{y}_H, s_H^2, n_H) and power parameter α , convert to an effective prior for control by treating $n_{eff} = \alpha n_H$ and building the corresponding NIG prior update from the historical summary, then use that as the prior for the current-control posterior update.

5.8 H. Decision rule (continuous)

Same rule format as binary:

Declare efficacy if $\Pr(\Delta > \Delta^*) > \gamma$

Estimate by Monte Carlo using posterior draws from the NIG posterior for both arms.

5.9 I. Practical examples (numerical)

5.9.1 I.1 Binary example (rMAP)

- Historical: study1 (8/40), study2 (15/75)
- Current control: 12/50
- Treatment: 30/100
- Robust weight $w_R = 0.10$ (10% Beta(1,1))
- Build rMAP mixture and posterior; draw 50,000 samples per posterior and compute $\Pr(\Delta > 0.10)$.

Result (example output format; compute in app): - Posterior mean $p_c \approx 0.24$ - Posterior mean $p_t \approx 0.30$ - Estimated $\Pr(\Delta > 0.10) \approx 0.67 \rightarrow$ decision depends on γ chosen.

5.9.2 I.2 Continuous example (NIG)

- Historical control summary: $\bar{y}_H = 1.2, s_H = 1.5, n_H = 60$.
 - Current control: $\bar{y}_c = 1.1, s_c = 1.4, n_c = 50$.
 - Treatment: $\bar{y}_t = 1.4, s_t = 1.45, n_t = 100$.
 - Use power prior $\alpha = 0.5$ for control priors.
 - Collect posterior samples and compute $\Pr(\mu_t - \mu_c > 0.1)$.
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5.10 J. Implementation notes & numerical stability

- Use vectorized sampling (large S draws) to approximate posterior probabilities.
 - Implement checks on input CSVs: require study, events, n columns and $0 \leq \text{events} \leq n$.
 - When working with tiny prior parameters (e.g., a0, b0 near zero), avoid exact zero to preserve conjugacy numerically.
 - For commensurate Stan models, monitor R-hat, effective sample size and posterior trace plots.
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5.11 K. References for further reading

- Schmidli et al., “Robust meta-analytic predictive priors in clinical trials” (Biometrical Journal).
 - Ibrahim & Chen, “Power prior distributions for regression models” (Journal of Statistical Planning and Inference).
 - Hobbs et al., “Commensurate priors for borrowing historical information in clinical trials” (Biostatistics).
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6 Workflow Diagram

```
## Workflow: Upload data → Priors → Current data → Posterior → Decision → OC  
→ Report
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