bayesCT: An R package for Adaptive Bayesian Clinical Trials

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Objective

Adaptive Bayesian clinical trials have gained much popularity over the years due to the great deal of flexibility and power over conventional clinical trials. We are continuously developing an R package (bayesCT) for adaptive bayesian clincal trials. bayesCT package is available at **thevaachandereng.github.io/bayesCT**. bayesCT

- incorporates historical data to reduce sample size using the power prior approach
- allows early stopping for futility and early success during interim looks
- pipes for modular input to ease understanding of inputs
- parallel programming to reduce computational time

Currently, the bayesCT R package supports Gaussian, binomial and time-to-event data.

Historical Borrowing via Discount Functions

Incorporation of historical data involves weighting a likelihood, known generally as the power prior approach

$$\underbrace{\pi(\theta \mid y_0, \alpha)}_{\text{Prior}} \propto \underbrace{L(\theta \mid y_0)^{\alpha}}_{\text{Historical data likelihood}} \cdot \underbrace{\pi(\theta)}_{\text{Initial prior}}$$

- θ is the parameter of interest
- y_0 is the historical data
- α is the historical data weight

Discount function approach

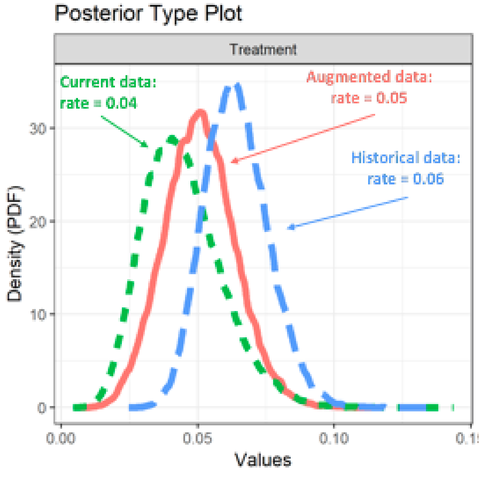
Discounting reduces the impact of the historical data likelihood on the prior

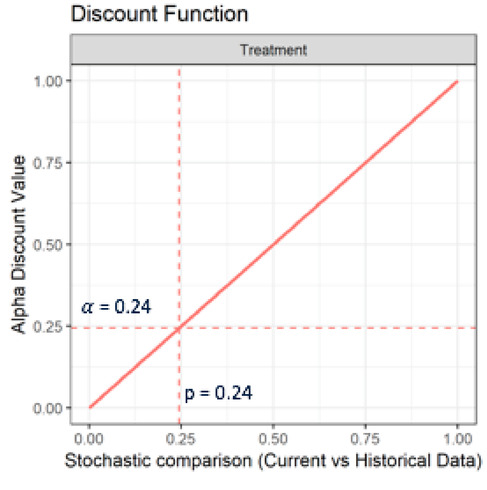
- Similarity measure p between current and historical data
- Discount function H modules the effect of the similarity on the historical data weight

Similarity measure

- Construct a surrogate statistics $\bar{\theta}$, derived from current data to facilitate the comparison between current and historical data (eg $\bar{\theta} = y/N$)
- Then, estimate p can be obtained $\quad |\bar{\theta} - \theta_0| < \delta \quad$ or $\quad \Phi(\frac{\bar{\theta}-\theta_0}{\sqrt{\sigma_0^2+\sigma^2}})$

Example with single-arm Binomial count endpoint with incorporation of historical data





Early Stopping for Futility or Early Success

Interim Analysis - Stop for Futility or Success (eg.)

$$\underbrace{P(\underbrace{\theta_T - \theta_C}_{\text{posterior treatment difference}} > \underbrace{\delta}_{\text{Margin}} \mid y, y_0, \alpha) < \underbrace{\omega}_{\text{futility rate}}}_{\text{futility}} \qquad \underbrace{P(\underbrace{\theta_T - \theta_C}_{\text{posterior treatment difference}} > \underbrace{\delta}_{\text{Margin}} \mid y, y_0, \alpha) > \underbrace{\Delta}_{\text{success rate}}}_{\text{success}}$$

Usability (Eg: OPC Trial)

Piping Modular Inputs

$$H_0 : \pi_{treatment} \geq 0.08 \qquad H_A : \pi_{treatment} < 0.08$$

```
value <-
  binomial_outcome(p_treatment_true = 0.08) %>%
  historical_binomial(y0_treatment = 5, N0_treatment = 55,
                      y0_control = NULL, N0_control = NULL,
                      discount_function = "identity") %>%
  enrollment_rate(lambda = c(0.3, 1), time = 25) %>%
  study_details(total_sample_size = 900, study_period = 50,
                interim_look = c(410, 440, 670),
                prop_loss_to_followup = 0.10, alternative = "less") %>%
  impute(no_of_impute = 25, number_mcmc = 1000) %>%
  hypothesis(delta = -0.01, futility_prob = 0.05, prob_ha = 0.95, expected_success_prob = 0.90) %>%
  BACTbinomial(no_of_sim = 110)
```

Better understanding of the inputs rather than feeding them into one big function at once!
Similar idea to dplyr, keras R package.

Enrollment

- Homogeneous Poisson process does not work well in clinical trial
- Inhomogenous with different cutoff points better fit
- Patient enrollment usually increases as time progress
- Omits enrollment date considers time zero as study initiation

$$\lambda = \begin{cases} \lambda_1, & t \in [0, t_1) \\ \lambda_2, & t \in [t_1, t_2) \\ \vdots & \\ \lambda_k & t \in [t_{k-1}, \infty) \end{cases}$$

Randomization

Randomization is important to eliminate bias in analysis (to eliminate confounders)

- Complete randomization does not work well (physician usually get better as time progress)
- Block Randomization
  - Randomize within a block and allow multiple block size
  - Allow imbalanced randomization ratio (treatment vs control)
  - Block size is a allocation group

References

Carlin, B. P., Berry, S. M., Lee, J. J., & Muller, P. (2010). *Bayesian adaptive methods for clinical trials*. CRC press.