Fall 16 – AMS276 Project 2

Due: 5pm Wed December 7th.

The project is to reproduce Example 4.3 (A BMT Trial) in BCLM Section 4.3.2. Please read BCLM Section 4.3.2 and the paper Thall *et al* (1995) (posted on our course webpage) carefully. It is summarized in lecture note, slides 18–29. I also provide a summary of the section below.

Let CR and TOX denote an efficacy event and an toxicity event, respectively. Using the two, we describe 4 elementary events,

$$\{A_1 = (CR,\ no\ TOX),\quad A_2 = (CR,\ TOX),\quad A_3 = (no\ CR,\ no\ TOX),\quad A_4 = (no\ CR,\ TOX)\}.$$

I follow the notation in Example 4.3. The way that BCLM Section 4.3.2 and the paper denote the four events is slightly different. Be careful when we read the book and the paper. In Example 4.3 or Section 3.1 of the paper, note that CR = {no GVHD within 100 days} and TOX = {TR within 100 days} where GVHD: graft versus host disease and TR: transplant rejection. The way that the four events are listed in Table 1 of the paper is the same as our list.

Note that efficacy is $CR = A_1 \cup A_2$ and toxicity is $TOX = A_2 \cup A_4$. Consider two treatments, experimental therapy (E) or standard therapy (S), $T \in \{E, S\}$. Let $p_T(A_j)$ denote the (unknown) probability of event A_j under treatment T and assume $(p_T(A_1), p_T(A_2), p_T(A_3), p_T(A_4)) \sim \text{Dir}(\theta_{T1}, \theta_{T2}, \theta_{T3}, \theta_{T4})$, $T \in \{E, S\}$ (also assume independence across treatments).

We know $\Pr(CR \mid T) = p_T(A_1) + p_T(A_2) \equiv \eta_T(CR)$ and $\Pr(TOX \mid T) = p_T(A_2) + p_T(A_4) \equiv \eta_T(TOX)$ for each T, and

$$\begin{aligned} \eta_T(CR) &\sim \text{Be}(\theta_{T1} + \theta_{T2}, \theta_{T3} + \theta_{T4}), \\ \eta_T(TOX) &\sim \text{Be}(\theta_{T2} + \theta_{T4}, \theta_{T1} + \theta_{T3}). \end{aligned}$$

We use posterior probabilities to determine sequential stopping. We track the two posterior probabilities;

$$\begin{aligned} \pi_n(CR) &= Pr(\eta_E(CR) > \eta_S(CR) + \delta_{CR} \mid \boldsymbol{y}^n), \\ \pi_n(TOX) &= Pr(\eta_E(TOX) > \eta_S(TOX) + \delta_{TOX} \mid \boldsymbol{y}^n), \end{aligned}$$

where y_j^n denotes the number of patients among the first n who report event A_j and let $\boldsymbol{y}^n = (y_1^n, y_2^n, y_3^n, y_4^n)$. Here, the offset δ_{CR} and δ_{TOX} are fixed by investigators and should reflect the minimum clinically meaningful improvement. After each patient cohort, the posterior probabilities $\pi(\cdot)$ are updated and compared against threshold,

$$\text{decision} = \begin{cases} \text{stop for futility} & \text{if} \quad \pi_n(CR) > L_{CR}, \\ \text{stop for toxicity} & \text{if} \quad \pi_n(TOX) > U_{TOX}, \\ \text{continue} & \text{otherwise.} \end{cases}$$

The trial that we implement is a single arm trial with all patients assigned to the experimental therapy. Thus, the parameters $\boldsymbol{\theta}_S$ never change; only the posterior on $\boldsymbol{\theta}_E$ is updated.

Set up

- $\boldsymbol{\theta}_S$

$$(p_S(A_1), p_S(A_2), p_S(A_3), p_S(A_4)) \sim \text{Dir}(\theta_{S1}, \theta_{S2}, \theta_{S3}, \theta_{S4}),$$

  where $\boldsymbol{\theta}_S \propto (2.037, 6.111, 30.555, 2.037)$. Note that $Pr(CR \mid T = S) = 0.2$ and $Pr(TOX \mid T = S) = 0.2$.

- $\boldsymbol{\theta}_E$

$$(p_E(A_1), p_E(A_2), p_E(A_3), p_E(A_4)) \sim \text{Dir}(\theta_{E1}, \theta_{E2}, \theta_{E3}, \theta_{E4}),$$

  where $\sum_{j=1}^{4} \theta_{Ej} = 4$ and $\boldsymbol{\theta}_E \propto (2.037, 6.111, 30.555, 2.037)$ (note: $\boldsymbol{\theta}_S \propto \boldsymbol{\theta}_E$ but the prior sample sizes, $\sum_j \theta_{Tj}$ are different).

- cohort size $k = 4$, maximum sample size $n_{\max} = 75$, $\delta_{CR} = 20\%$, $\delta_{TOX} = 5\%$, $L_{CR} = 2\%$, $L_{TOX} = 80\%$

- Scenarios: True probabilities of CR and TOX under E.
  - Scenario 1: $p^{\text{TRUE}}(CR) = 0.2$ and $p^{\text{TRUE}}(TOX) = 0.4$. No improvement in CR and the mean TOX probability increases from 0.2 to 0.4. $\Rightarrow$ early stopping is desirable.
  - Scenario 2: $p^{\text{TRUE}}(CR) = 0.4$ and $p^{\text{TRUE}}(TOX) = 0.2$. Improvement in mean CR probability by 0.2 and the mean TOX probability stays the same. $\Rightarrow$ early stopping is not desirable.

Implement **Algorithm 4.2** under the two simulation scenarios specified above. Run 5 simulated trials and for each run make plots of $\pi_n(CR)$ vs time and $\pi_n(TOX)$ vs time (overlay $\pi_n(CR)$ and $\pi_n(TOX)$ in one plot, may use different colors and line types, similar to Figure 4.2 page 154). In total, we make 10 plots, 5 from each scenario. Briefly comment on your plots.