Bayesian Methods for Clinical Trials

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Practical 4: Borrowing of information in basket trials

Recall the BRAF-V600 basket trial in Lecture 9. It is a phase II PoC trial to smultaneously evaluate the efficacy of vemurafenib, a novel anti-cancer treatment, in several patient subpopulations. The primary endpoint is binary: response or non-response.
Open the R script titled `BasketTrials.R` and ensure that the JAGS model files, `StandardHM.txt`, `EXNEX.txt` and `Stand-alone.txt`, are in the working directory (Use `setwd()` to modify if necessary). For each substudy, the Bayesian analysis model returns the posterior mean of response rate together with a credible interval.

(a) Read the `StandardHM.txt` and `EXNEX.txt` scripts to understand how these Bayesian models are fitted for borrowing of information.

(b) Use the code written in `BasketTrials.R` to run an analysis for the BRAF-V600 trial.

```
# BRAF-V600 basket trial data
> nMod = 6
> r = c(8, 1, 6, 0, 2, 6)
> n = c(20, 8, 18, 10, 7, 32)
```

Set $\mu \sim N(0, 10^2)$, $\tau^2 \sim HN(0.125)$ to implement the standard hierarchical model and, additionally, the prior mixture weight as (0.5, 0.5) to implement the EXNEX model. For comparison, implement the stand-alone analysis model.

What are the posterior mean for the response rate, denoted by p_k, per substudy $k = 1, \ldots, 7$? What are the posterior probabilities that $\Pr(p_k > 0.25 \mid \text{data})$?

(c) Install and load the 'bmabasket' package in R. Using the bma() function, run an analysis for the BRAF-V600 trial using Bayesian model averaging. What are the posterior means of the response rates per substudy? What are the posterior probabilities that $\mathbb{P}(p_k > 0.25|\text{data})$?

(d) Retain the prior specification unchanged from (b). Analyse the hypothetical datasets below using the standard hierarchical modelling approach, EXNEX model, BMA and stand-alone analyis. Again, what are the posterior mean for the response rate, denoted by p_k, per substudy $k = 1, \ldots, 5$? What are the posterior probabilities that $\Pr(p_k > 0.25 \mid \text{data})$?

Hypothetical dataset of a consistency scenario:

	Substudy 1	Substudy 2	Substudy 3	Substudy 4	Substudy 5
Number of patients	10	10	20	20	17
Number of responses	5	4	12	7	9

Hypothetical dataset of an inconsistency scenario:

	Substudy 1	Substudy 2	Substudy 3	Substudy 4	Substudy 5
Number of patients	10	10	20	20	17
Number of responses	2	7	15	4	5

(e) Compare the resulting posterior mean estimate and posterior standard deviation under both scenarios. What do you notice about the relative advantages and disadvantages of each analysis model?

(f) Set the argument of `Prior.tau.HN` to a larger value, for example, 0.25. What impact does this change have on the posterior means and credible intervals?

(g) When using the EXNEX for analysis, set the argument of `pMix` to a range of large values, for example, 0.8, for the probability of exchangeability. How does this quantity affect the results?

(h) How would you expect the subtrial-wise type I error rate and statistical power to change using analysis models that permit borrowing of information? Perform a small-scale simulation study to develop intuition.

(i) Do you have any suggestions on how to better control for a type I error?