Bayesian Inference for Network Meta-Regression Using Multivariate Random Effects with Applications to Cholesterol Lowering Drugs

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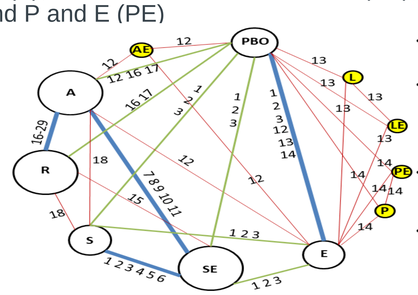
Abstract

Low-density lipoprotein cholesterol (LDL-C) has been identified as a causative factor for atherosclerosis and related coronary heart disease. Statin drugs inhibit cholesterol synthesis in the liver, while Ezetimibe inhibits the absorption of cholesterol by the small intestine. Many clinical trials have been carried out on safety and efficacy evaluation of cholesterol lowering drugs. To synthesize the results from different clinical trials, we examine treatment level network meta-data from 29 double-blind, randomized clinical trials on patients with primary hypercholesterolemia. We propose a new approach to carry out Bayesian inference for arm-based network meta-regression. We develop a new strategy of grouping the variances of random effects, in which we first formulate possible sets of the groups of the treatments based on their clinical mechanisms and then use Bayesian model comparison criteria to select the best set of groups. The proposed approach is especially useful when some treatment arms are involved in only a single trial. A Markov chain Monte Carlo sampling algorithm is developed to carry out the posterior computations. The correlation matrix is generated from its full conditional distribution via partial correlations. The proposed methodology is further applied to analyze the network meta-data from 29 trials.

Introduction & Network Meta-Data

- **Network meta-analysis (NMA)** is an analysis of synthesizing information from multiple sources.
  - NMA is known as multiple/mixed treatment comparisons
  - Extend the pairwise meta-analysis for (trt_A,trt_P) trials to data structures that include (trt_A,trt_P), (trt_B,trt_P), (trt_A,trt_B) and even (trt_A,trt_B,trt_P) trials
  - Direct and indirect comparisons co-exist
  - When there is no direct comparison between two treatments
  - When direct comparison exists, but does not provide enough information for a substantial statistical analysis
  - NMA can “borrow strength” from indirect comparisons
  - NMA allows for simultaneously comparisons and even ranking of several treatments
- **The Network Meta-Data** includes 29 double-blind, randomized, active or placebo controlled clinical trials on adult with hypercholesterolemia
  - Elevated cholesterol levels are associated with coronary heart disease
  - Cardiovascular diseases are the number one killers in US
  - It is arm-by-trial level aggregate data. The main outcome is mean percent change from baseline in LDL-C
  - The data has 11 treatment arms including placebo (PBO), simvastatin (S), atorvastatin (A), lovastatin (L), rosuvastatin (R), pravastatin (P), Ezetimibe (E), the combinations of S and E (SE), A and E (AE), L and E (LE), and P and E (PE)



- Each node represents a treatment in the network meta-data.
- Each edge represents a direct comparison between the treatments it connects, and the involved trial IDs are listed for each head-to-head comparison.
- The node size is proportional to the total sample size of the treatment across the network
- The width of the edge is related to the number of the trials providing the direct comparisons.

Network Meta-Regression Model

- **Notation**
  - Suppose the network meta-data include K randomized trials and a set of treatments $\mathcal{I}$= {0, 1, 2, …, T} from all K trials
  - Assume that the kth trial has T_k treatments, which are denoted by $\mathcal{I}_k$= {t_{k1}, t_{k2}, …, t_{kTk} ; $t_{k\ell} \in \mathcal{I}$, ℓ=1, 2, … T_k}
  - Let $y_{kt_{kl}}$and $S^2_{kt_{kl}}$ denote the aggregate sample mean and sample variance for the $t_{k\ell}$th treatment in the kth trial
  - Let $x_{kt_{kl}}$ represents the aggregate arm-level covariates
- Random effects network meta-regression model

$$y_{kt_{kl}} = x'_{kt_{kl}}\beta + \gamma_{kt_{kl}} + \varepsilon_{kt_{kl}},\ \varepsilon_{kt_{kl}} \sim N\left(0, {}^{\sigma^2_k t_{k\ell}}\!/_{n_k t_{k\ell}}\right) \quad (1)$$

$$\text{and } \frac{(n_{kt_{kl}}-1)s^2_{kt_{kl}}}{\sigma^2_k t_{k\ell}} \sim \chi^2_{(n_{kt_{kl}}-1)} \quad (2)$$

$$\text{and } \gamma_{kt_{kl}} \sim N_{T+1}(\gamma, \Omega) \quad (3)$$

- Assume that the random effect, $\gamma_{kt_{kl}}$, is independent of $\varepsilon_{kt_{kl}}$ and follows a multivariate normal distribution with a (T+1) dimensional vector of overall effects and a (T+1)x(T+1) positive definite covariance matrix Ω
- The random effect captures the dependence of $y_{kt_{kl}}$’s within trial and the heterogeneity across trials[1]
- The major challenge for proposed model is that only part of the Ω can be estimated due to the fact that some treatments are only included in a single trial, for example, treatment arms: L, LE, P, PE, SE
- Propose a grouping methodology – formulate possible sets of groups of treatments according to clinical mechanisms of action

Bayesian Inference

- **Computation Development**
  - Assume that β^*, Ω, and $\sum(k)$, k = 1, 2, …, K are independent a priori and $\beta^* \sim N_{p+T+1}(0, 100000 I_{p+T+1})$, $\sum(k) = \text{diag}\left(\frac{\sigma^2_{kt_{k1}}}{n_{kt_{k1}}}, \frac{\sigma^2_{kt_{k2}}}{n_{kt_{k2}}}, \ldots \frac{\sigma^2_{kt_{kT^k}}}{n_{kt_{kT^k}}}\right)$, assume that $\sigma^2_{kt_{kl}} \sim$ IG(0.0001, 0.0001)
  - The analytical evaluation of the posterior distribution of $\theta = (\beta^*, \Omega, \sum^*)$ is not available
  - We develop a Markov chain Monte Carlo (MCMC) sampling algorithm and use a modified collapsed Gibbs sampling technique
- **Bayesian Model Comparison**
  - The grouping of the T + 1 variances into G groups motivates the idea of model comparison to select the appropriate grouping
  - We use the deviance information criterion (DIC)[2] and the logarithm of the pseudo marginal likelihood (LPML)[3] for model comparison

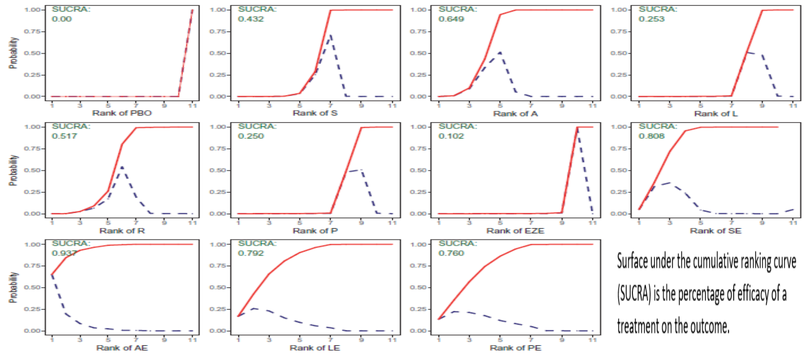
Analysis of the Network Meta-Data

- Let $y_{kt_{kl}}$ be the mean percent change in LDL-C from the baseline for the $t_{k\ell}$th treatment in the kth trial
- The vector of covariates is $x_{kt_{kl}}$= $(1, (bl\_ldlc)_{kt_{kl}}, (bl\_hdlc)_{kt_{kl}}, (bl\_tg)_{kt_{kl}}, (age)_{kt_{kl}}, (male)_{kt_{kl}}, (BMI)_{kt_{kl}}, (potency\_med)_{kt_{kl}}, (potency\_high)_{kt_{kl}}, (duration)_{kt_{kl}})^T$, and the corresponding regression coefficient vector is β

Model Comparison Table

Model	Description	DIC	LPML
M1 (G=1)	Random effects for all 11 arms have the same variance	381.3	-165.3
M2 (G=4)	PBO, EZE, SE/AE/LE/PE, S/A/L/R/P	377.8	-164.7
M3 (G=5)	PBO, EZE, SE/AE/LE/PE, A/L/R/P, S	373.2	-161.9
M4 (G=5)	PBO, EZE, SE/AE/LE/PE, S/A/L/P, R	371.5	-161.9
M5 (G=5)	PBO, EZE, SE/AE/LE/PE, S/L/R/P, A	377.9	-164.9
M6 (G=6)	PBO, EZE, SE/AE/LE/PE, A/L/P, S, R	369.7	-161.2
M7 (G=6)	PBO, EZE, SE/AE/LE/PE, R/L/P, S, A	371.8	-161.6
M8 (G=6)	PBO, EZE, SE/AE/LE/PE, S/L/P, A, R	368.3	-160.5

Plots of Ranking Probabilities for All Treatment Arms Under Model M8



Surface under the cumulative ranking curve (SUCRA) is the percentage of efficacy of a treatment on the outcome.

Conclusions

- Statin drugs are effective but statin drugs in combination with Ezetimibe are even more effective in reducing LDL-C
- The combinations of atorvastatin+EZE and simvastatin+EZE are the top two treatments for cholesterol lowering
- The proposed methodology is quite general and can be applied in any meta-analysis setting including a wide range of scientific applications

References

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