BAYESIAN MODELING FOR BENEFIT-RISK BALANCE ANALYSIS: ROSIGLITAZONE FOR TYPE II DIABETES

K. Vamvourelis, K. Kalogeropoulos, L. Phillips

THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Regulating Diabetes Treatments

1999 Rosiglitazone gets US approval
2000 Rosiglitazone gets European approval
2007 New evidence for risks arises [Nissen and Wolski, 2007]
2010 European regulators revert their recommendation
2011 US regulators partially revert their recommendation
2013 US regulators undo reversion

How to assess a drug?

- measurements Y_{ij} from a clinical trial for $j: 1, \dots, J$ favorable/unfavorable effects on $i: 1, \dots, N$ subjects
- the goal is to combine Y_{ij}'s into a single value, termed *drug preference score*

Standard practice is to use MCDA to do this, e.g. [Mussen et al., 2007]

MCDA in practice

1. Transform each variable to $[0, 100]$ with a linear mapping $c_j(\cdot)$
   a if Y_{ij} is continuous we assume $Y_{ij} \sim \mathcal{N}(\mu_j, \sigma_j^2)$ and take $c_j(Y_{ij}) = c_j(\mu_j)$,
   b if Y_{ij} is binary we assume $Y_{ij} \sim$ Bernoulli(μ_j) and take $c_j(Y_{ij}) = c_j(\mu_j)$
2. Construct the *preference score* the weighted sum $S = \sum_j w_j \cdot c_j(\mu_j)$ where w_j are appropriate weights
3. Compare the *preference score* for a control and treatment group, s^C and s^T respectively.

Note that $c_j(\cdot)$ and w_j are given by subject matter experts and reflect their clinical judgement

Issues

- The above model assumes independence of effects
- Not realistic, e.g. for Nausea and Dyspepsia.

Goal: Calculate $P(s^C < s^T|y)$ taking into account

- dependencies between effects
- individual variability

Parameter uncertainty - a Bayesian approach

The previous procedure ignores sampling variability so [Phillips et al., 2013] proposed the following Bayesian approach:

- Assume independence between effects.
- Assign $U(0,1)$ and $\propto 1$ priors on μ_j for binary and continuous cases respectively. Assume σ_j^2 known from the sample variance.
- The posterior for $\mu = (\mu_1, \dots, \mu_J)$ is then a product of either $\mathcal{N}(\bar{Y}_j, \frac{S_j^2}{N})$ or Beta$(T_j + 1, N - T_j + 1)$, where $T_j = \sum_i Y_{ij}$.
- Calculate $P(s^T > s^C|y)$ using Monte Carlo
  1. draw K samples of μ^C and μ^T from their posterior,
  2. for each sample compute the corresponding s^T and s^C,
  3. report the relative frequency of the event $s^T > s^C$.

Model for Mixed-type Data

For binary data:

$$\begin{cases} Y_{ij} \sim \text{Bernoulli}(\eta_j), \; i = 1, \dots, N, \; Y_{ij} \text{ independent, for fixed } j \\ h_j(\eta_j) = \mu_j + Z_{ij}, \end{cases} \quad (1)$$

For continuous variables:

$$Y_{ij} = \mu_j + Z_{ij}, \; i = 1, \dots, N. \quad (2)$$

where the distribution of Z is assumed[1] to be

$$Z_{i:} \sim \mathcal{N}_J(0_J, \Sigma), \quad (3)$$

where Σ is a $J \times J$ covariance matrix, 0_J is a row J-dimensional vector with zeros and $Z_{i:}$ are independent $\forall i$.

[1] other options are available, e.g. a multivariate t

Challenges

- Parametrisation according to covariance is non likelihood identifiable.
- Related work [Talhouk et al., 2012, Chib and Greenberg, 1998] on the probit model. The diagonal elements of Σ are set to 1. A Gibbs sampler is provided by [Talhouk et al., 2012].
- We extend to the case of mixed variable and adapt to MCDA setting.
  - Both logit and probit links can be used.
  - Random walk metropolis step for each $Z_{i:}$, Gibbs steps elsewhere.
  - Implemented in Python and Stan.

Model Objectives

The aim is to sample from (for control and treatment groups)

$$\pi(\mu, \Sigma, Z|Y) \propto f(Y|Z, \mu, \Sigma)\pi(Z|\Sigma)\pi(\mu)\pi(\Sigma) \quad (4)$$

so that we can in turn sample from score posterior.

We can then

1. compute $P(s^T > s^C|y)$ as before.
2. compute $P(s^T_{N+1} > s^C_{N+1}|y)$ for a future individual $N+1$ based on

$$\pi(Z_{N+1}|y) = \int\int \pi(Z_{N+1:}|\mu, \Sigma)\pi(\mu, \Sigma|y) \, d\mu \, d\Sigma$$

3. compute $P(s^T_{N+1} > s^C_{N+1}|y, \widehat{\mu}, \widehat{\Sigma})$ based on Bayes or ML estimators of $\widehat{\mu}, \widehat{\Sigma}$.[2]

[2] This can be done by frequentist approach, e.g. in Mplus [Muthen and Muthen, 1998]

Gibbs Algorithm for Mixed Data

- $\pi(\mu|\Sigma, Z) \sim (\mu_n, \Sigma_n)$ for conjugate prior $\mu \sim (\mu_0, \Sigma_0)$ where

$$\mu_n = (\Sigma_0^{-1} + n\Sigma^{-1})^{-1}(\Sigma_0^{-1}\mu_0 + n\Sigma^{-1}\bar{Z})$$
$$\Sigma_n = (\Sigma_0^{-1} + n\Sigma^{-1})^{-1}$$

- $\pi(R|\mu, Z)$

$$D = \text{diag}(d_1, \dots, d_J), \text{ where } d_i^2 \sim ((k+1)/2(R^{-1})_{ii}/2)$$
$$\pi(\Sigma|W) = (\Sigma; 2 + N, W'W + I_J - \xi^{-1}M'M)$$
$$R = D\Sigma D \text{ where } D = \text{diag}(d_1, \dots, d_J) \text{ with } d_i = (\Sigma_{ii})^{-1/2}$$

- Set $\Sigma = SRS$ where $S = \text{concatenation}(\sigma, \mathbf{1})$
- $\pi(Z|\mu, \Sigma, Y)$ We sample each row z_i separately using a Metropolis-Hastings algorithm. The proposal comes from the conditional Normal $N(z|y, \mu, \Sigma)$ and the becomes

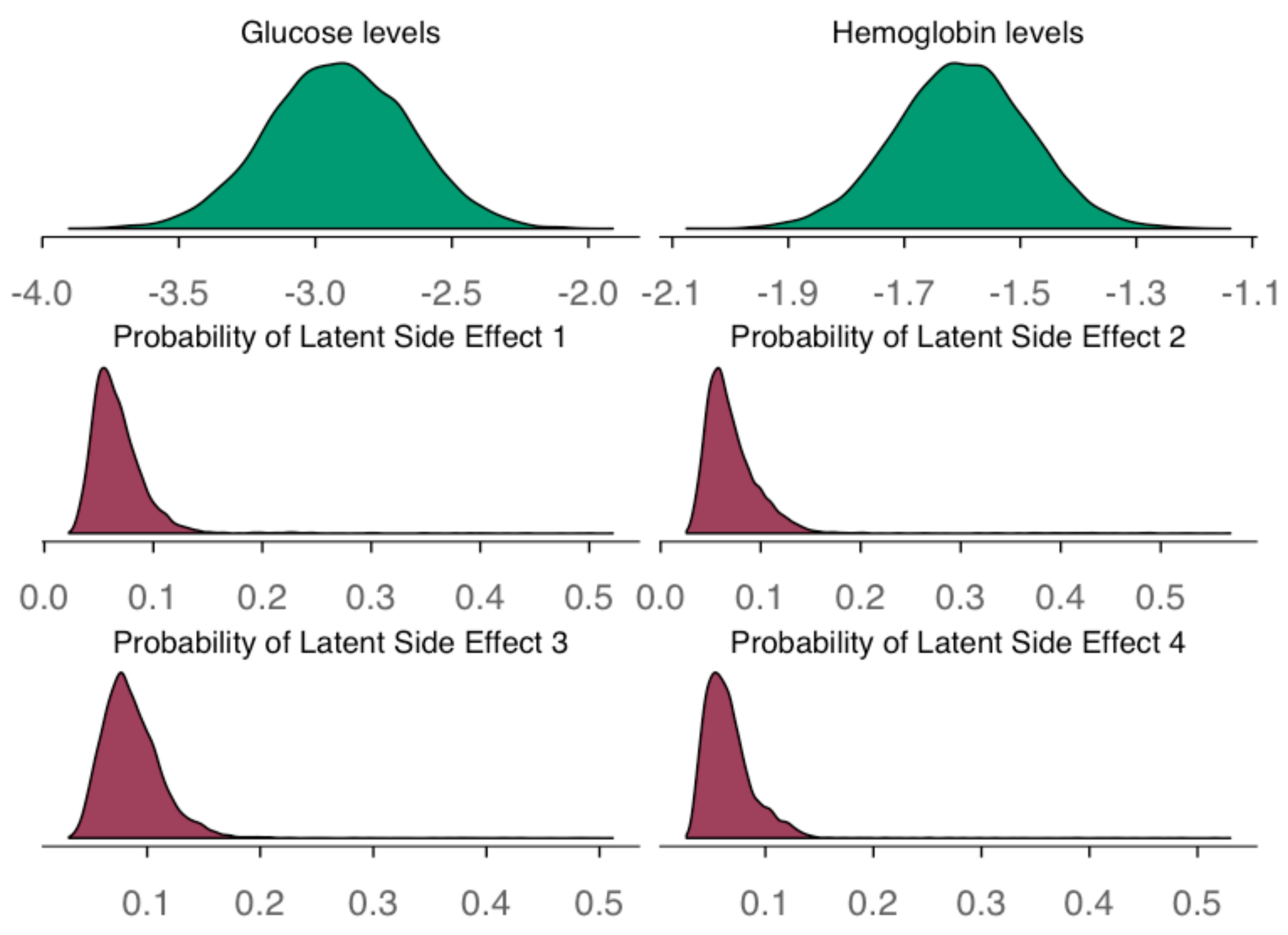
$$\pi(z|y, \mu, \Sigma) \propto f(y|z) \cdot \pi(z|\mu, \Sigma)$$
$$= \prod_{j=1}^{J}\prod_{k=1}^{N} h^{-1}(z_{kj})^{y_{kj}}(1 - h^{-1}(z_{kj}))^{(1-y_{kj})} \cdot N(z|\mu, R)$$
$$= \prod_{j=1}^{J}\prod_{k=1}^{N} \eta_{kj}^{y_{kj}}(1 - \eta_{kj})^{(1-y_{kj})} \cdot N(Z|\mu, \Sigma)$$

- sample each column separately

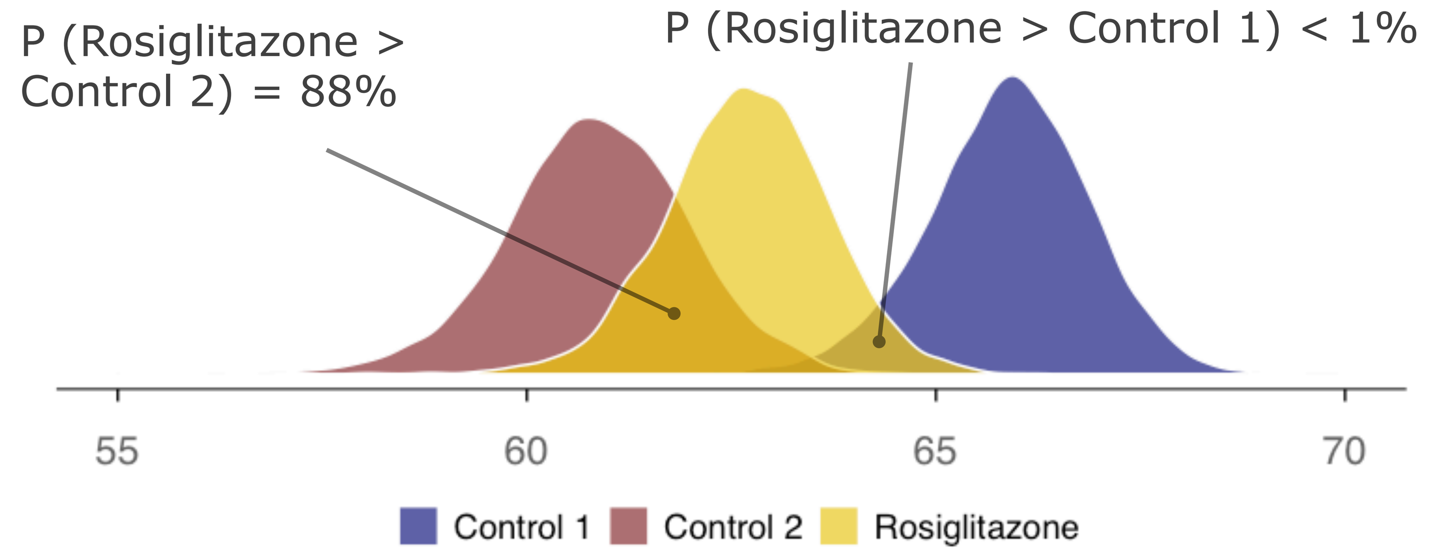
$$\sigma_j^2 \sim \text{IG}(\alpha, \beta), \text{(conjugate prior)}$$
$$p(\sigma_j^2|y_j, \mu) \sim \text{IG}\big(\alpha + \frac{n}{2}; \beta + \frac{1}{2}\sum_{i=1}^{n}(y_j - \mu)^2\big)$$

Posterior Samples for Rosiglitazone Group

Dataset from clinical trial to compare Rosiglitazone to two existing treatments



MCDA Total Score



Future work

- Develop sequential Monte Carlo as alternative, e.g. SMC[2] [Chopin et al., 2011].
- Develop algorithms for model choice (via Bayes factors) or predictive performance assessment. Can be done by Sequential Monte Carlo.
- Compare with reduced dimension models such as factor analysis (e.g. separate factors for favourable and unfavourable effects).
- Potential applications in sequential sampling design.