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Bayesian Nonparametric Bivariate Meta -Analysis

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Abstract: In the meta-analysis of clinical trials, usually the data of each trail summarized by one or more outcome measure estimates which reported along with their standard errors. In the case that summary data are multi-dimensional, usually, the data analysis will be performed in the form of a number of separated univariate analysis. In such a case the correlation between summary statistics would be ignored. In contrast, a multivariate meta-analysis model, use from these correlations synthesizes the outcomes, jointly to estimate the multiple pooled effects simultaneously. In this paper, we present a nonparametric Bayesian bivariate random effect meta-analysis.

Keywords: Bayesian Nonparametric, Gibbs algorithm, Meta-analysis, Bivariate Distribution, Bayesian Model Selection

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1. Introduction

Meta- analysis may be broadly defined as the quantitative review and analysis of the results of related but independent studies (Normand 1999). In every meta-analysis the point estimates of the effect size will differ between different studies present in the analysis, one cause for this is sampling error, however, often there is more, i.e. real differences exist between studies, which is called heterogeneity. DerSimonian and Laird (1986) introduced a statistical model for dealing with this heterogeneity, which called "random effects model".

In meta- analysis, specially in meta- analysis of clinical trails, the data in each trail summarized by one or more outcome measure estimates along with their standard errors. If the summary data are multi-dimensional, usually the data analysis is restricted to a number of separated univariate analysis (Arends 2006).

Houwelingen et al. (1993) were the first that consider multivariate random effect meta-analysis. They introduced a bivariate linear random effect model for the joint analysis of one estimated outcome measure per treatment group. These results often to the synthesis of multiple summary statistics, that are correlated (Gleser and Olkin 1994), which was ignored by performing separate meta-analysis for each outcome. In contrast a multivariate meta-analysis model, like that of Berkey et al. (1998) Utilizes the correlation and jointly synthesizes the outcomes, to estimate the multiple pooled effects simultaneously. Glas et al. (2003) apply a bivariate meta-analysis model to a systematic review of tumor markers. However all Bayesian bivariate models that we know are parametric. The purpose of this paper is to present a bivariate Bayesian nonparametric random effect meta-analysis.

Bayesian nonparametric and semiparametric univariate meta-analysis have been studied by authors like as Muller et al. (2004), Burr and Doss(2005) and Ohlsen et al. (2006). Remaining of this paper organized as follows. In section 2 we will present our model. In section 3 we will compute the posterior distributions. In section 4 we will study a simulated example, and finally in section 5 we will employ our proposal model for a real example.

2. Data structure and model

The Dirichlet process (Ferguson 1973) has been overwhelming mechanism used as the prior for the unknown distribution in the model specification, especially when we use from multinomial distribution. In meta-analysis literature, this prior was used for various models, too, which between them we can mention at Burr and Doss (2005) and Ohlsen et al. (2006). In this paper we will generalize following

model of Burr and Doss (2005) to a bivariate meta-analysis.

$$\begin{aligned} D_i|\psi_i &\overset{ind}{\sim} N(\psi_i, \sigma_i^2) \quad i = 1, ..., m; \\ \psi_i|F &\overset{ind}{\sim} F \quad i = 1, ..., m; \\ F|\mu, \tau &\overset{ind}{\sim} D_{MN(\mu,\tau^2)}; \\ \mu|\tau &\overset{ind}{\sim} N(c, d\tau^2); \\ \gamma = {}^{1}\!/_{\tau^2} &\overset{ind}{\sim} \Gamma(a, b). \end{aligned} \tag{2.1}$$

To do this we first bring the definition of mixture of Dirichlet process which was introduced by Antoniak (1974) and Sethuraman constructive definition of Dirichlet process (Sethuraman 1994), which will be used in posterior computations.

Definition 1: Let H_θ for $\theta \in \Theta \subset \Re^k$ be a parametric family of distributions on the real line, and λ be a distribution on Θ. Suppose that for each θ, we have $M_\theta > 0$ be known weights, and let $\alpha_\theta = M_\theta H_\theta$. If θ is chosen from λ, and F is chosen from D_{α_θ}, the Dirichlet process with parameter α_θ (Ferguson 1973, 1974), then we say that the prior on F is a mixture of Dirichlet processes (Antoniak 1974). In other words mixture of Dirichlet processes, is a Dirichlet process which its measure parameter is itself a random variable.

Definition 2: Let α be a nonzero finite measure on (χ, β). Let $\beta(B) = \frac{\alpha(B)}{\alpha(\lambda)}$ be the normalized probability measure arising from α . Let N be the set of positive integers and F be the σ -field of all subsets of N. Let $\{\Omega, S, Q\}$ be a probability space supporting a collection of random variables $(\theta, Y, I) = ((\theta_j, Y_j), j = 1, ..., I)$, taking values in $(([0, 1] \times \chi)^\infty \times N, (\varepsilon \times B)^\infty \times F)$, with a joint distribution defined as follows. The random variables $(\theta_1, \theta_2, ...)$ are independently and identically distributed with a common Beta distribution $Beta\,(1, \alpha(\chi))$.

The random variables $(Y_1, Y_2, ...)$ are independent of the $(\theta_1, \theta_2, ...)$ and i.i.d. among themselves with common distribution β . Let $p_1 = \theta_1$ and $p_n = \theta_n \prod_{1 \le m \le n-1} (1 - \theta_m)$ for $n = 2, 3, ...$. Let $P\,(I = n|(\theta, Y)) = p_n$, for $n = 1, 2, ...$. Define

$$p(\theta, Y; \beta) = p(B) = \sum_{n=1}^{\infty} p_n \delta_{Y_n}(B) \tag{2.2}$$

Where $\delta_x(.)$ stands for the probability measure degenerate at x .We will denote the random measure in (2.2) by p for simplicity of notations . Random measure p have a Dirichlet distribution.

As usual in the meta-analysis literature we will take a normal distribution on the first level of our model and a Dirichlet process prior to introduce the following Bayesian nonparametric bivariate hierarchical model. It was typically supported

by some theoretical result, for example the asymptotic normality of maximum likelihood estimates.

$$D_i|\beta_i^{(1)},\beta_i^{(2)} \overset{ind}{\sim} N_2(\beta_i^{(1)}X_i^{(1)},\beta_i^{(2)}X_i^{(2)},{\sigma_i^{(1)}}^2,{\sigma_i^{(2)}}^2,\rho_i) \;\; i=1,...,m; \tag{2.3}$$

$$\beta_i^{(j)}|F^{(j)} \overset{ind}{\sim} F^{(j)} \;\; j=1,2 \;\; and \;\; i=1,...,m; \tag{2.4}$$

$$F^{(j)}|\mu^{(j)},\tau^{(j)} \overset{ind}{\sim} D_{MN(\mu^{(j)},{\tau^{(j)}}^2)} \;\; j=1,2; \tag{2.5}$$

$$\mu^{(j)}|\tau^{(j)} \overset{ind}{\sim} N(c^{(j)},d^{(j)}{\tau^{(j)}}^2); \tag{2.6}$$

$$\gamma^{(j)} = {}^{1}\!\Big/_{{\tau^{(j)}}^2} \overset{ind}{\sim} \Gamma(a^{(j)},b^{(j)}). \tag{2.7}$$

Where $a^{(j)},b^{(j)},d^{(j)}>0$ and $-\infty<c^{(j)}<\infty$ are arbitrary but fixed.

In this model we estimate $\sigma_i^{(j)}$'s and ρ_i's along with data, which due to DerSimonian and Laird (1986) have a little effect, if the number of studies wasn't little. Note that following Burr and Doss (2005), we adopt that subscripting a distribution indicates conditioning. The main question is whether the mean of $F^{(j)}$'s, the distributions of study-specific effects, is different from 0 or not. Now, we will compute posterior distributions.

3. The Posterior Computations

Using the well known fact that (Burr and Doss 2005):

If $X_1,...,X_m$ are $\overset{iid}{\sim} F$, $F\sim D_{MH}$, then

$$\pi(X_i|X_{-(i)}) = \frac{MH+\sum_{j\neq i}\delta_{X_j}}{M+m-1} \tag{3.8}$$

and

$$\begin{aligned}\pi_{\{\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)}\}}(D_i|\beta_i^{(1)},\beta_i^{(2)}) &= \pi(D_i|\beta_i^{(1)},\beta_i^{(2)}) \\ &= N_2(\beta_i^{(1)}X_i^{(1)},\beta_i^{(2)}X_i^{(2)},{\sigma_i^{(1)}}^2,{\sigma_i^{(2)}}^2,\rho_i)\end{aligned} \tag{3.9}$$

Where first equality in equation (3.9) is because $\beta_{(-i)}^{(j)},\mu^{(j)},\tau^{(j)}$, only through their effects on $\beta_i^{(j)}$, affectD_i, and the last equality is just the model statement (2.3). Now, we combine equations (3.8) and (3.9) to achieve

$$\pi_D(\beta_i^{(1)},\beta_i^{(2)}|\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\;\tau^{(1)},\tau^{(2)}).$$

Theorem: Under above situations, the posterior distribution of $(\beta_i^{(1)},\beta_i^{(2)})$ given other values of $(\boldsymbol{\beta}^{(1)},\boldsymbol{\beta}^{(2)})$, $(\mu^{(1)},\mu^{(2)})$, $(\tau^{(1)},\tau^{(2)})$ and the data is in the form of:

$$\pi_D(\beta_i^{(1)},\beta_i^{(2)}|\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)}) \propto$$

$$C^{(1,2)}N(A_i^{(1)},A_i^{(2)},B_i^{2(1)},B_i^{2(2)},\rho_i)$$

$$+\frac{M}{(M+m-1)^2}\sum_{k\neq i}\delta_{\beta_k^{(2)}}N_2(\beta_i^{(1)}X_i^{(1)},\beta_k^{(2)}X_k^{(2)},\sigma_i^{2(1)},\sigma_i^{2(2)},\rho_i)N(\mu^{(1)},\tau^{2(1)})$$

$$+\frac{M}{(M+m-1)^2}\sum_{k\neq i}\delta_{\beta_k^{(1)}}N_2(\beta_k^{(1)}X_k^{(1)},\beta_i^{(2)}X_i^{(2)},\sigma_i^{2(1)},\sigma_i^{2(2)},\rho_i)N(\mu^{(2)},\tau^{2(1)})$$

$$+\frac{M^2}{(M+m-1)^2}\sum_{k\neq i}\sum_{h\neq i}\delta_{\beta_k^{(1)}}\delta_{\beta_k^{(2)}}N_2(\beta_k^{(1)}X_k^{(1)},\beta_h^{(2)}X_h^{(2)},\sigma_i^{2(1)},\sigma_i^{2(2)},\rho_i)$$

Where

$$A_i^{(1)}=\frac{(1-\rho_i^2)\sigma_i^{2(1)}\mu^{(1)}+\tau^{2(1)}D_i^{(1)}X_i^{(1)}}{(1-\rho_i^2)\sigma_i^{2(1)}+\tau^{2(1)}X_i^{2(1)}} \qquad B_i^{2(1)}=\frac{\sigma_i^{2(1)}\tau^{2(1)}}{(1-\rho_i^2)\sigma_i^{2(1)}+\tau^{2(1)}X_i^{2(1)}} \tag{3.10}$$

$$A_i^{(2)}=\frac{(1-\rho_i^2)\sigma_i^{2(2)}\mu^{(2)}+\tau^{2(2)}D_i^{(2)}X_i^{(2)}}{(1-\rho_i^2)\sigma_i^{2(2)}+\tau^{2(2)}X_i^{2(2)}} \qquad B_i^{2(2)}=\frac{\sigma_i^{2(2)}\tau^{2(2)}}{(1-\rho_i^2)\sigma_i^{2(2)}+\tau^{2(2)}X_i^{2(2)}} \tag{3.11}$$

$$\begin{aligned}C^{(1,2)}=\tfrac{M^2}{(M+m-1)^2}&N(\mu^{(1)}X_i^{(1)},(1-\rho_i^2)\sigma_i^{2(1)}+\tau^{2(1)}X_i^{2(1)})\\&\times N(\mu^{(2)}X_i^{(2)},(1-\rho_i^2)\sigma_i^{2(2)}+\tau^{2(2)}X_i^{2(2)})e^R\end{aligned} \tag{3.12}$$

and

$$R=\frac{\rho_i}{(1-\rho_i^2)}\{\left(\frac{D_i^{(1)}-\beta_i^{(1)}X_i^{(1)}}{\sigma_i^{(1)}}\right)\left(\frac{D_i^{(2)}-\beta_i^{(2)}X_i^{(2)}}{\sigma_i^{(2)}}\right)$$
$$-B_i^{-(1)}B_i^{-(2)}\left(\beta_i^{(1)}-A_i^{(1)}\right)\left(\beta_i^{(2)}-A_i^{(2)}\right)\}$$

Proof:

$$\pi_D(\beta_i^{(1)},\beta_i^{(2)}|\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)}) \propto$$

$$\pi(\beta_i^{(1)},\beta_i^{(2)}|\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)})$$

$$\times L(D|\beta_i^{(1)},\beta_i^{(2)},\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)})$$

$$\begin{aligned}\propto \pi(\beta_i^{(1)}|\beta_{(-i)}^{(1)},\mu^{(1)},\tau^{(1)})&\pi(\beta_i^{(2)}|\beta_{(-i)}^{(2)},\mu^{(2)},\tau^{(2)})\\&\times L(D|\beta_i^{(1)},\beta_i^{(2)},\beta_{(-i)}^{(1)},\beta_{(-i)}^{(2)},\mu^{(1)},\mu^{(2)},\tau^{(1)},\tau^{(2)})\end{aligned} \tag{3.13}$$

$$\propto \left[\frac{MN(\mu^{(1)},\tau^{2(1)})+\sum_{k\neq i}\delta_{\psi_k^{(1)}}}{M+m-1}\right]\left[\frac{MN(\mu^{(2)},\tau^{2(2)})+\sum_{k\neq i}\delta_{\beta_k^{(2)}}}{M+m-1}\right]$$
$$\times N_2(\beta_i^{(1)}X_i^{(1)},\beta_i^{(2)}X_i^{(2)},\sigma_i^{2(1)},\sigma_i^{2(2)},\rho_i) \tag{3.14}$$

$$= \left(\frac{M}{M+m-1}\right)^2 N(\mu^{(1)}, \tau^{2(1)}) N(\mu^{(2)}, \tau^{2(2)}) N_2(\beta_i^{(1)} X_i^{(1)}, \beta_i^{(2)} X_i^{(2)}, \sigma_i^{2(1)}, \sigma_i^{2(2)}, \rho_i)$$

$$+ \frac{M}{(M+m-1)^2} \sum_{k \neq i} \delta_{\beta_k^{(2)}} N_2(\beta_i^{(1)} X_i^{(1)}, \beta_k^{(2)} X_k^{(2)}, \sigma_i^{(1)^2}, \sigma_i^{(2)^2}, \rho_i) N(\mu^{(1)}, \tau^{(1)^2})$$

$$+ \frac{M}{(M+m-1)^2} \sum_{k \neq i} \delta_{\beta_k^{(1)}} N_2(\beta_k^{(1)} X_k^{(1)}, \beta_i^{(2)} X_i^{(2)}, \sigma_i^{(1)^2}, \sigma_i^{(2)^2}, \rho_i) N(\mu^{(2)}, \tau^{(1)^2})$$

$$+ \left(\frac{M}{M+m-1}\right)^2 \sum_{k \neq i} \sum_{h \neq i} \delta_{\beta_k^{(1)}} \delta_{\beta_k^{(2)}} N_2(\beta_k^{(1)} X_k^{(1)}, \beta_h^{(2)} X_h^{(2)}, \sigma_i^{(1)^2}, \sigma_i^{(2)^2}, \rho_i)$$

Now we compute the first term of the above equation separately.

$$I = \left(\frac{M}{M+m-1}\right)^2 N(\mu^{(1)}, \tau^{2(1)}) N(\mu^{(2)}, \tau^{2(2)}) N_2(\beta_i^{(1)} X_i^{(1)}, \beta_i^{(2)} X_i^{(2)}, \sigma_i^{2(1)}, \sigma_i^{2(2)}, \rho_i)$$

$$= \left(\tfrac{M}{M+m-1}\right)^2 \tfrac{1}{4\pi^2 \sqrt{(1-\rho_i^2)} \sigma_i^{(1)} \sigma_i^{(2)} \tau^{(1)} \tau^{(2)}} \exp\left[\tfrac{-\left(\beta_i^{(1)} - \mu^{(1)}\right)^2}{2\tau^{2(1)}} - \tfrac{\left(\beta_i^{(2)} - \mu^{(2)}\right)^2}{2\tau^{2(2)}} \right]$$
$$\times \exp\left[-\tfrac{1}{2(1-\rho_i^2)} \left\{ \left(\tfrac{D_i^{(1)} - \beta_i^{(1)} X_i^{(1)}}{\sigma_i^{(1)}} \right)^2 + \left(\tfrac{D_i^{(2)} - \beta_i^{(2)} X_i^{(2)}}{\sigma_i^{(2)}} \right)^2 \right\} \right]$$
$$\times \exp\left[-\tfrac{1}{2(1-\rho_i^2)} \left\{ -2\rho_i \left(\tfrac{D_i^{(1)} - \beta_i^{(1)} X_i^{(1)}}{\sigma_i^{(1)}} \right) \left(\tfrac{D_i^{(2)} - \beta_i^{(2)} X_i^{(2)}}{\sigma_i^{(2)}} \right) \right\} \right] \tag{3.15}$$

Now with some algebraic computations we have:

$$I = \left(\frac{M}{M+m-1}\right)^2 \frac{1}{4\pi^2 \sqrt{(1-\rho_i^2)} \sigma_i^{(1)} \sigma_i^{(2)} \tau^{(1)} \tau^{(2)}}$$

$$\times \exp\left[-\frac{1}{2(1-\rho_i^2)} \left\{ B_i^{-2(1)} \left(\beta_i^{(1)} - A_i^{(1)}\right)^2 + B_i^{-2(2)} \left(\beta_i^{(2)} - A_i^{(2)}\right)^2 \right\} \right]$$

$$\times \exp\left[-\frac{1}{2(1-\rho_i^2)} \left\{ -2\rho_i B_i^{-(1)} B_i^{-(2)} \left(\beta_i^{(1)} - A_i^{(1)}\right) \left(\beta_i^{(2)} - A_i^{(2)}\right) \right\} \right]$$

$$\times \exp\left[-\frac{\left(D_i^{(1)} - \mu^{(1)} X_i^{(1)}\right)}{2\left[(1-\rho_i^2)\sigma_i^{2(1)} + \tau^{2(1)} X_i^{2(1)}\right]} - \frac{\left(D_i^{(2)} - \mu^{(2)} X_i^{(2)}\right)}{2\left[(1-\rho_i^2)\sigma_i^{2(2)} + \tau^{2(2)} X_i^{2(2)}\right]} + R \right]$$

$$I = C^{(1,2)} N_{-,-}^{(\mu^{(1)}, \mu^{(2)})}(A^{(1)}, A^{(2)}, B^{2(1)}, B^{2(2)}, \rho_i) \qquad \diamondsuit$$

For generating $(\mu^{(1)}, \mu^{(2)}, \tau^{(1)^2}, \tau^{(2)^2})$ form $\pi_D(\mu^{(1)}, \mu^{(2)}, \tau^{(1)}, \tau^{(2)} | \boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$ note that:

$$\pi_D(\mu^{(1)}, \mu^{(2)}, \tau^{2(1)}, \tau^{2(2)} | \boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)}) = \pi(\mu^{(1)}, \mu^{(2)}, \tau^{2(1)}, \tau^{2(2)} | \boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$$

$$= \pi(\mu^{(1)}, \tau^{(1)}|\boldsymbol{\beta}^{(1)})\pi(\mu^{(2)}, \tau^{(2)}|\boldsymbol{\beta}^{(2)})$$

Which have no known closed form, so as Burr and Doss (2005) and Ohlsen et al.(2006) we will use of Sethuraman construction in order to making sure that these posterior distribution have closed form.

Suppose $m^{(j)^*}$ be numbers of distinct values of $\beta_i^{(j)}$ and define $\overline{\boldsymbol{\beta}^{(j)}}^* = \frac{1}{m^{(j)*}} \sum^{dist} \beta_i^{(j)}$, where 'dist' in sum shows that the sum is taken only on distinct values. So the posterior distributions will be of the form of prior distributions with updated parameters $a^{(j)'}, b^{(j)'}, c^{(j)'}$ and $d^{(j)'}$ where:

$$a^{(j)'} = a^{(j)} + \frac{m^{(j)^*}}{2}$$

$$b^{(j)'} = b^{(j)} + \frac{1}{2}\sum^{dist}(\beta_i^{(j)} - \overline{\boldsymbol{\beta}^{(j)}}^*)^2 + \frac{m^{(j)^*}(\overline{\boldsymbol{\beta}^{(j)}}^* - c^{(j)})^2}{2(1 + m^{(j)^*}d^{(j)})}$$

$$c^{(j)'} = \frac{c^{(j)} + m^{(j)^*}d^{(j)}\overline{\boldsymbol{\beta}^{(j)}}^*}{1 + m^{(j)^*}d^{(j)}}$$

$$d^{(j)'} = \frac{1}{m^{(j)^*} + d^{(j)^{-1}}}.$$

4. The Gibbs Sampling

Our proposal Gibbs sampler has two steps, and is as follows:
Step 1: Update $(\boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$. For $i = 1, ..., m$ we generate successively $(\beta_i^{(1)}, \beta_i^{(2)})$ given the current values of $(\beta_j^{(1)}, \beta_j^{(2)})$, $j \neq i$, $(\mu^{(1)}, \mu^{(2)})$, $(\tau^{(1)}, \tau^{(2)})$ and the data.
Step 2: Update $(\mu^{(1)}, \mu^{(2)}, \tau^{(1)}, \tau^{(2)})$. To generate $(\mu^{(1)}, \mu^{(2)}, \tau^{(1)}, \tau^{(2)})$ given $(\boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$, we perform two steps:
a: generate $(\mu^{(1)}, \mu^{(2)})$ from its marginal conditional distribution given $(\boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$.
b: generate $(\tau^{(1)}, \tau^{(2)})$ from its conditional distribution given $(\mu^{(1)}, \mu^{(2)})$, $(\boldsymbol{\beta}^{(1)}, \boldsymbol{\beta}^{(2)})$.

5. Simulation Study

In this section we implement presented model on simulated data using a R codec which is available by request from second authors. For this purpose we will study two scenarios. In the first scenario each centers contains two population that have joint distribution as:

$$N_2\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 4 & 3 \\ 3 & 9 \end{pmatrix}\right)$$

Table 1: Estimate, MSE and Confidence Interval of $\psi^{(1)}$ and $\psi^{(2)}$

		$\psi^{(1)}$	$\psi^{(2)}$
$Estimate$	$scenario\ \ one$	-0.0498	-0.0085
	$scenario\ \ two$	-0.0569	2.0597
MSE	$scenario\ \ one$	0.0164	0.0766
	$scenario\ \ two$	0.900	0.3230
$Confidence\ \ interval$	$scenario\ \ one$	$(-1.7587, 1.5816)$	$(-1.3903, 1.4869)$
	$scenario\ \ two$	$(-0.8906, 0.7272)$	$(1.4169, 2.7724)$

In the second scenario, each center contain two population too, where means of these two populations are not equal, the joint distribution for this scenario is as:

$$N_2\left(\begin{pmatrix} 0 \\ 2 \end{pmatrix}, \begin{pmatrix} \sqrt{2} & 0.5\sqrt{2} \\ 0.5\sqrt{2} & 1 \end{pmatrix}\right)$$

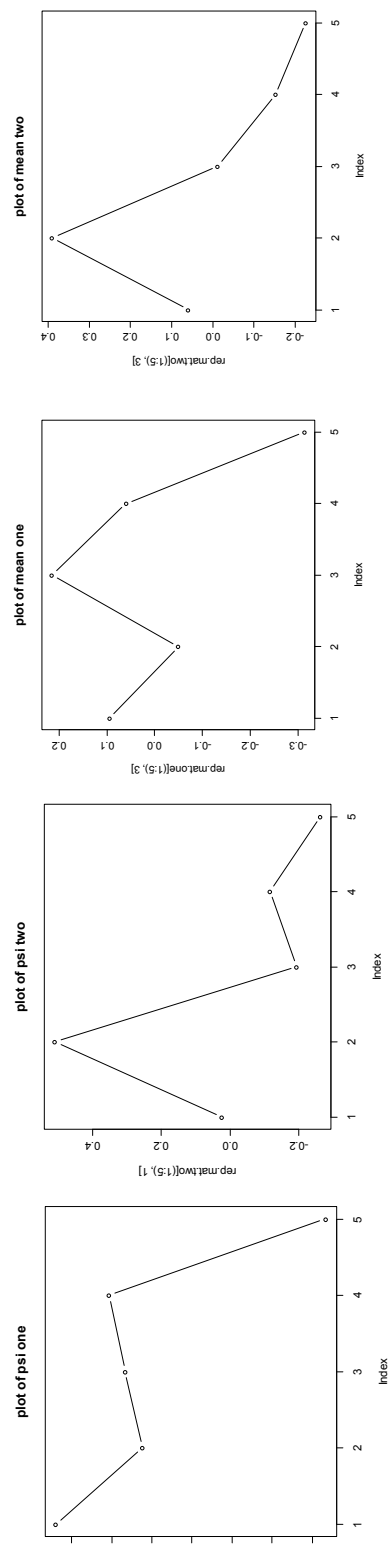
In each scenario we use of 10 center. And do this 15 times, and saw that the algorithm became a little diverge after 5 iteration, so we use of the first 5 iterations and report the mean of these iterations for estimated parametrs.

We carry out our model, using simulated data. The estimates, MSE's and confidence intervals of $\boldsymbol{\psi^{(1)}}$ and $\boldsymbol{\psi^{(2)}}$and $mean\ \ of\ \ F^{(1)}$ and $F^{(2)}$ computed and come in the Tables (1) and (2), also plots of estimates in iterations plot and come as Figure (1), for computing these quantities we run the Gibbs sampler 1500 times and burn out the first 500 run. So in Figure (1) each point show the estimated value of one of parameters in one iteration of method.

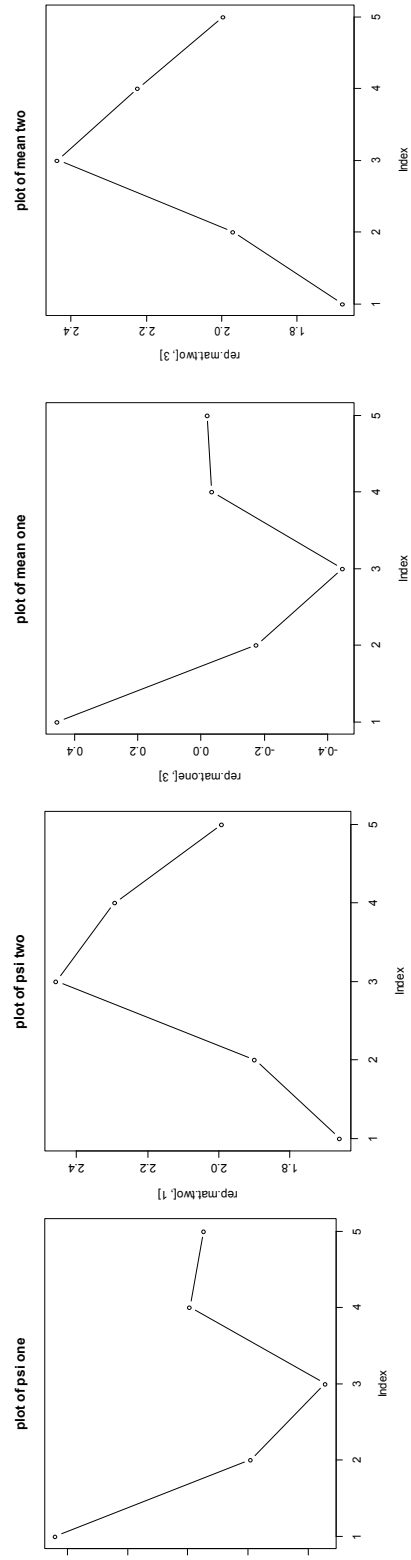
Table 2: Estimate, MSE and Confidence Interval of mean of $F^{(1)}$ and mean of $F^{(2)}$

		$mean\ \ of\ \ F^{(1)}$	$mean\ \ of\ \ F^{(2)}$
$Estimate$	$scenario\ \ one$	0.0009	0.0119
	$scenario\ \ two$	-0.0445	2.0610
MSE	$scenario\ \ one$	0.0268	0.0815
	$scenario\ \ two$	0.0754	0.2860
$Confidence\ \ interval$	$scenario\ \ one$	$(-2.8012, 1.7000)$	$(-1.7202, 1.7342)$
	$scenario\ \ two$	$(-0.9927, 0.8752)$	$(1.2926, 2.8284)$

For scenario one all confidence intervals involves 0 so in one hand the number of study is enough, and on the other hand the means of two populations in each center are equal to 0.



a) Scenario one



b) Scenario two

Table 3: *Data from Clinical Trials on Efficacy of BCG Vaccine In The Prevention of Tuberculosis*

	Vaccinated		**Not Vaccinated**	
Trial	Disease	No Disease	Disease	No Disease
1	4	119	11	128
2	6	300	29	274
3	3	228	11	209
4	62	13536	248	12619
5	33	5036	47	5761
6	180	1361	372	1079
7	8	2537	10	619
8	505	87886	499	87892
9	29	7470	45	7232
10	17	1699	65	1600
11	186	50448	141	27197
12	5	2493	3	2338
13	27	16886	29	17825

In scenario two confidence intervals of $\psi^{(1)}$ and mean of $F^{(1)}$ involves 0. Although confidence interval of mean of $F^{(2)}$ doesn't contain 0 and so the number of studies aren't enough but confidence interval of $\psi^{(2)}$ contain 2; i.e. we came at the true decision.

6. A Real Example: The Efficacy of BCG Vaccine Against Tuberculosis

For illustrating above method we use of the meta-analysis data set given by Colditz et al. (1994) and Berkey et al.(1995) which is also reconsidered by Arends (2006). The data set concerns 13 trials on the efficacy of BCG vaccine against tuberculosis. In each trial a vaccinated group is compared with a non-vaccinated control group. The data consist of the sample size in each group and the number of cases of tuberculosis and is as Table (3):

As Arends (2006) mentioned, considering only the differences between the study arms may hide a lot information. Therefore, it is wise to consider the pair of outcomes of the two treatments. This is nicely done in the l'Abbe-plot

(1987), that gives a bivariate representation of the data by plotting the log odds in arm A versus the log odds in arm B. Arends (2006) showed the plot (Figure 4 of chapter3) for the data of this example with A the vaccinated arm and B the not vaccinated arm. As an example we carry out a bivariate meta-analysis with $\psi_i^{(1)}$ and $\psi_i^{(2)}$ the log odds of tuberculosis in the vaccinated and the not-vaccinated control arm, respectively. Since we didn't have the variance and covariance for centers, we use of estimated ones with Arends (2006) that obtained for pooled data, for each center. In This example our goal is obtaining estimates of $\psi^{(1)}$ and $\psi^{(2)}$ and to understand that if the number of studies in this data set is enough for making inference about efficacy of BCG vaccine against tuberculosis or not.

Note that because variances and covariances of each trail was so that cause the covariance matrix became singular, for estimating them and using in the first level of model, we use from a fixed effect approach.

For this purpose we run the Gibbs sampler 1500 times and burns the first 500 times. The results are reported in Tables (3) and (4).

Table 4: Estimate and Confidence interval of $\psi^{(1)}$ and $\psi^{(2)}$

	$\psi^{(1)}$	$\psi^{(2)}$
$Estimate$	-2.3602	-3.4447
$Confidence\ \ interval$	$(-2.7897, -2.0860)$	$(-3.6746, -3.2364)$

Table 5: Estimate and Confidence Interval of mean of $F^{(1)}$ and mean of $F^{(2)}$

	$mean\ \ of\ \ F^{(1)}$	$mean\ \ of\ \ F^{(2)}$
$Estimate$	-2.4649	-3.5837
$Confidence\ \ interval$	$(-3.0319, -2.0834)$	$(-4.3863, -3.1938)$

So with these results although we obtain estimates and confidence intervals for $\psi^{(1)}$ and $\psi^{(2)}$ but with respect to confidence intervals of $mean\ \ of\ \ F^{(1)}$ and $mean\ \ of\ \ F^{(2)}$ and this fact that last confidences don't contain 0, the number of studies aren't enough to making inference, and we need more studies.

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