Outlier Detection in $2 \times 2$ Crossover Design using Bayesian Framework
(Pengesanan Titik Terpencil dalam $2 \times 2$ Reka Bentuk Pindah Silang Menggunakan Rangka Kerja Bayesian)

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ABSTRACT
We consider the problem of outlier detection method in $2 \times 2$ crossover design via Bayesian framework. We study the problem of outlier detection in bivariate data fitted using generalized linear model in Bayesian framework used by Nawama. We adapt their work into a $2 \times 2$ crossover design. In Bayesian framework, we assume that the random subject effect and the errors to be generated from normal distributions. However, the outlying subjects come from normal distribution with different variance. Due to the complexity of the resulting joint posterior distribution, we obtain the information on the posterior distribution from samples by using Markov Chain Monte Carlo sampling. We use two real data sets to illustrate the implementation of the method.

Keywords: Bayesian; crossover design; Markov Chain Monte Carlo; outlier

INTRODUCTION
In a standard $2\times2$ crossover design, we assume that there are two different groups of subjects. Each group receives two treatments in a different order and the trial is to last for two treatment periods, with the order of treatments reversed in the second period. A common problem in crossover trials is the occurrence of extremely large or small observations. These extraordinary observations are called outliers and they may influence the conclusion drawn from the data set. An outlier is a data point which is significantly different from the remaining data (Aggarwal 2013). Hawkins (1980) formally defined the concept of outlier as an observation which deviates so much from the other observations as to arouse suspicions that it was generated by a different mechanism.

Chow and Tse (1990) proposed two procedures based on Cook’s likelihood distance and the estimated distance for the detection of outliers in crossover studies. Liu and Weng (1991) carried out procedures based on Hotelling $T^2$ statistics and residuals for the same purpose. Wang and Chow (2003) presented a general test procedure based on a mean-shift model. Furthermore, Ramsay and Elkum (2005) compared different outlier detection methods proposed by Chow and Tse (1990) and Liu and Weng (1991) via simulation study. They concluded that the estimated distance test performs better than other tests. Most recently, Karasoy and Daghan (2012) applied these existing methods to a real data set in order to investigate outliers. In crossover studies, Enachescu and Enachescu (2009) initially used principal components for the identification of outliers. Meanwhile, Singh et al. (2014) provided details regarding a studentized residual test and the Lund test for identification of outlier subjects. It is therefore important that methods of identifying outliers in $2 \times 2$ crossover design are developed for proper handling of the data in studies.

Lim et al. (2016) carried out two outlier detection procedures based on residuals in non-Bayesian framework. Under a simplified model of $2 \times 2$ crossover design, we present a classical calculation of studentized residual and propose a new studentized residual using median absolute deviation to identify possible outliers. The performances of both procedures are compared via simulation. With the availability of data set provided by the University of Malaya Medical Centre (UMMC), the results showed that the procedure using performs better in detecting outliers. In this study, we extend our previous works and consider the problem of outlier detection method in $2 \times 2$ crossover design via Bayesian framework. We study the problem of...
outlier detection in bivariate data fitted using generalized linear model (GLM) in Bayesian framework presented by Nawama et al. (2015) and Unnikrishnan (2010). We follow closely their works but adapt them into a 2×2 crossover design. In Bayesian framework, we assume that the random subject effect and the errors to be generated from normal distributions. However, the outlying subjects come from normal distribution with different variance. Due to the complexity of the resulting joint posterior distribution, we obtain the information on the posterior distribution from samples by using Markov Chain Monte Carlo (MCMC) sampling. The paper is organized as follows: The concept of standard 2×2 crossover design is described in the next section; two real data sets and the application and implementation of the outlier detection using Bayesian approach to these data set are discussed in detail in the following sections where we consider the case of single outlier; the conclusions are given in the final section.

THE 2 × 2 CROSSOVER DESIGN

Let \( Y_{ikj} \) be the response of the \( j \)th subject in sequence \( i \) during period \( k \) under the \( d[i,j] \)th treatment, where \( i,j = 1,2; m_i \) is the size of group with treatment \( d[i,j] \) and \( k = 1,2,\ldots, m_i \). From Jones and Kenward (1989), the full model is

\[
Y_{ikj} = \mu + p_j + \tau_{d[i,j]} + S_{ik} + e_{ijk}
\]  

(1)

where \( \mu \) is the overall mean; \( p_j \) the fixed effect of the \( j \)th period; \( \tau_{d[i,j]} \) the fixed effect of the treatment administered in period \( j \) of sequence \( i \); \( S_{ik} \) is the fixed effect of the carryover of the treatment administered in period \( j - 1 \) of sequence \( i \) where \( \lambda_{i[j]} = 0 \); \( S_{ik} \) is the random effect of the \( \theta \) subject; and \( e_{ijk} \) the random error. The variance components \( \{S_{ik}\} \) and \( \{e_{ijk}\} \) are assumed to be independent and normally distributed with mean 0 and variances \( \sigma^2_s \) and \( \sigma^2_e \), respectively.

DATA DESCRIPTION

There are two data sets considered for this study: Clayton and Leslie’s data (1981) and kinesiology data. For the first data set, Clayton and Leslie (1981) considered the blood concentration-time curve (AUC) data from two erythromycin formulations in a bioavailability study. In their study, a standard 2×2 crossover experiment was conducted with 18 subjects to compare a new erythromycin formulations in a bioavailability study. As no sequence was conducted with 18 subjects to compare a new erythromycin base). As no sequence formulation (erythromycin base). As no sequence was conducted with 18 subjects to compare a new erythromycin formulations in a bioavailability study.

THE MODEL

Under the full model (1), for case without outliers, the expected value of \( y_{ijk} \) is

\[
E(y_{ijk}) = E(\mu + p_j + \tau_{d[i,j]} + S_{ik} + e_{ijk}) = \mu + p_j + \tau_{d[i,j]} + \lambda_{d[i,j-1]}
\]

while the variance of \( y_{ijk} \) is

\[
Var(y_{ijk}) = Var(\mu + p_j + \lambda_{d[i,j-1]} + S_{ik} + e_{ijk}) = Var(S_{ik}) + Var(e_{ijk}) = \sigma^2_s + \sigma^2_e.
\]

Hence,

\[
y_{ijk} \sim N(\mu + p_j + \tau_{d[i,j]} + \lambda_{d[i,j-1]}, \sigma^2_s + \sigma^2_e).
\]

On the other hand, for the case with outliers, the variance component \( \{S_{ik}\} \) is assumed to be independent and normally distributed with mean 0 and variances \( \delta^2 \sigma^2_s \). Therefore,

\[
y_{ijk} \sim N(\mu + p_j + \tau_{d[i,j]} + \lambda_{d[i,j-1]}, \delta^2 \sigma^2_s + \sigma^2_e).
\]

Assume that a random sample size \( n = \sum m_i \) of is obtained with a number of suspected outliers. Define \( Y_{ijk} = (Y_{111}, Y_{112}, \ldots, Y_{h(k)}) \). Let \( v^k \) be the set of all outlying observations, where \( h \) denotes the number of outliers. We consider the model with/without outliers such that

\[
f(y_{ijk}|p_j, \tau_{d[i,j]} \lambda_{d[i,j-1]}, \delta) = \frac{1}{\Gamma(\gamma^2 \sigma^2_s + \sigma^2_e)^{1/2}} \exp \left\{ -\frac{1}{2\gamma^2 \sigma^2_s + \sigma^2_e} (y_{ijk} - \mu - p_j - \tau_{d[i,j]} - \lambda_{d[i,j-1], v^k})^2 \right\}
\]

(2)
Using the Bayesian approach, we consider normal
prior distributions for the overall mean, \( \mu \), the period
effect, \( p_j \), the treatment effect, \( \tau_{d[i,j]} \) and the carryover
effect, \( \lambda_{d[i,j-1]} \), as suggested by Chen and Huang (2015).
For the parameter \( \delta \), Unnikrishnan (2010) assume that this
extra variance component of the outlying observations is
bounded above by a known constant \( \delta_{\text{max}} \), so that \( 1 < \delta < \delta_{\text{max}} < \infty \) and therefore Uniform(1, \( \delta_{\text{max}} \)) prior is assigned
to it. According to the suggestions in Unnikrishnan (2010),
we shall assume that any distinct -tuples are equally likely
to be outliers and prior for \( \nu^h \) assigns equal probability of
In other words, we assume that

\[
\begin{align*}
\mu & \sim N(\mu_0, \sigma_\mu^2) \\
p_j & \sim N(\mu_p, \sigma_{p_j}^2), \quad j = 1, 2 \\
\tau_{d[i,b]} & \sim N(\mu_\tau, \sigma_{\tau}^2), \quad i = 1, 2; \quad j = 1, 2 \\
\lambda_{d[i,j-1]} & \sim N(\mu_\lambda, \sigma_\lambda^2) \\
\delta & \sim \text{Uniform}(1, \delta_{\text{max}})
\end{align*}
\]

(3)

where the hyperparameters \( \mu_0, \sigma_\mu^2, \mu_p, \sigma_{p_j}^2, \mu_\tau, \sigma_{\tau}^2, \mu_\lambda, \sigma_\lambda^2, \delta_{\text{max}}, N, h \) are all pre-specified. Then, the joint likelihood
function is given by

\[
L(y|\mu, p, \tau, \lambda, \delta, \nu^h) = \prod_{i=1}^{2} \prod_{j=1}^{2} \prod_{k \in \nu^h} \left[ 2\pi(\sigma_\delta^2 + \sigma_\nu^2) \right]^{-\frac{1}{2}} \exp \left[ -\frac{1}{2(\sigma_\delta^2 + \sigma_\nu^2)} \left( y_{ijk} - \mu - p_j - \tau_{d[i,j]} - \lambda_{d[i,j-1]} \right)^2 \right]
\]

(4)

Consequently, from the result obtain in (3) and (4),
the full joint posterior distribution for the parameters \( \mu, p, \tau, \lambda, \delta, \nu^h \) is given by

\[
\begin{align*}
f(\mu, p; \nu^h) & = \prod_{i=1}^{2} \prod_{j=1}^{2} \prod_{k \in \nu^h} \left[ 2\pi(\sigma_\delta^2 + \sigma_\nu^2) \right]^{-\frac{1}{2}} \exp \left[ -\frac{1}{2(\sigma_\delta^2 + \sigma_\nu^2)} \left( y_{ijk} - \mu - p_j - \tau_{d[i,j]} - \lambda_{d[i,j-1]} \right)^2 \right]
\end{align*}
\]

(5)

Since this posterior distribution is intractable,
sampling is carried out using the MCMC sampling method,
in particular using Metropolis-Hastings (MH) algorithm (Tierney 1994).

SAMPLING METHODS OF THE PARAMETERS
Note that model (2) involves multiple parameters that are
structured hierarchically such that the dependency of the
parameters is reflected in the joint probability distribution.
The conditional posterior distributions of the parameters are
intractable and therefore we use the MH algorithm for
sampling purposes. The sampling methods for each of the
parameters \( \mu, p, \tau, \lambda, \delta, \nu^h \) are given in detail as below.

PARAMETER \( \delta \)
Based on the full joint posterior distribution (5), the conditional posterior distribution for parameter given is

\[
f(\delta|\mu, p, \tau, \lambda, \nu^h) = \frac{1}{\delta_{\text{max}} - 1} \left( \frac{N!}{(N-k)!k!} \right)
\]

(6)

Here we propose to use a proposal density for \( \delta_{\text{prop}} \) as

\[
g(\delta) = \frac{1}{\delta_{\text{max}} - 1}
\]

so that \( \delta_{\text{prop}} \) has a uniform \( (1, \delta_{\text{max}}) \) distribution. Using the MH algorithm, candidate point \( \delta_{\text{prop}} \) is accepted with probability
The full formula of the acceptance probability above is easily obtained by substituting the relevant functions into this equation.

**PARAMETER $p$**

Based on the full joint posterior distribution (5), the conditional posterior distribution for parameter $p_j$, $j = 1, 2$, given $\mu, \tau, \lambda, \delta, v^i$ is given by

$$f(p_j | \mu, \tau, \lambda, \delta, v^i, p)$$

$$= \frac{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}$$

$$= \frac{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}$$

We use the function $\omega_k$ as defined in equation (7) so that

$$f(p_j | \mu, \tau, \lambda, \delta, v^i, p)$$

$$= \frac{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}{\prod_{i \neq j} \int_{\mathbb{R}} f_{p_{ij}}(\theta | \mu, \tau, \lambda, \delta, v^i, p) f_{\theta | \mu, \tau, \lambda, \delta, v^i}(\theta | \mu, \tau, \lambda, \delta, v^i, p) d\theta}$$

Here we propose to use a proposal density for $p_j$ as

$$g(p_j) = \left(2\pi\sigma_p^2\right)^{-\frac{1}{2}} \exp\left[-\frac{(p_j - \mu_j)^2}{2\sigma_p^2}\right].$$

Therefore, by using MH algorithm, for parameter $p$, we update $p_1$ first and followed by $p_2$, where for each $p_j$, the acceptance probability for candidate point $p_{prop}$ can be obtained by replacing the corresponding functions in (6).

**PARAMETER $\tau$**

Based on the full joint posterior distribution (5), the conditional posterior distribution for parameter $\tau_{ij}$, $i, j = 1, 2$, given $\mu, \tau, \lambda, \delta, v^i$ is given by

$$f(\tau_{ij} | \mu, \tau, \lambda, \delta, v^i, \tau)$$

Here we choose the proposal density for $\mu_{prop}$ as

$$g(\mu) = \left(2\pi\sigma_{\mu}^2\right)^{-\frac{1}{2}} \exp\left[-\frac{(\mu - \mu_0)^2}{2\sigma_{\mu}^2}\right].$$

so that $\mu_{prop}$ has a $N(\mu_0, \sigma_{\mu}^2)$ distribution. Using the MH algorithm, the acceptance probability for candidate point $\mu_{prop}$ then can be obtained by replacing the corresponding functions in (6).
We use the function $\omega_t$ as defined in equation (7) so that
\[
\frac{f}{d(i,j)}(\tau d(i,j) | \mu, p, \lambda, \delta, v, \tau) = \prod_{i=1}^{\infty} \prod_{j=1}^{\infty} \prod_{k \in V} \left[ \frac{(2\pi(\sigma_t^2 + \sigma_k^2))^{\frac{1}{2}}}{2^{\sigma_t^2 + \sigma_k^2}} \exp \left( -\frac{1}{2(\sigma_t^2 + \sigma_k^2)} \left( y_{ik} - \mu - p_j - \tau d_{i,j} - \lambda d_{i,j} \right)^2 \right) \right] 
\]
Here we propose to use a proposal density for $\lambda d_{i,j}$ as
\[
g d_{i,j}(\lambda d_{i,j}) = \left( \frac{\lambda d_{i,j}}{2\sigma_t^2 + \sigma_k^2} \right)^{\frac{-1}{2}} \exp \left( -\frac{1}{2(\sigma_t^2 + \sigma_k^2)} \left( y_{ik} - \mu - p_j - \tau d_{i,j} - \lambda d_{i,j} \right)^2 \right) \]
We use the function $\omega_t$ as defined in equation (7) so that
\[
\frac{f}{d(i,j)}(\lambda d_{i,j} | \mu, p, \tau, \delta, v, \lambda) = \prod_{i=1}^{\infty} \prod_{j=1}^{\infty} \prod_{k \in V} \left[ \frac{(2\pi(\sigma_t^2 + \sigma_k^2))^{\frac{1}{2}}}{2^{\sigma_t^2 + \sigma_k^2}} \exp \left( -\frac{1}{2(\sigma_t^2 + \sigma_k^2)} \left( y_{ik} - \mu - p_j - \tau d_{i,j} - \lambda d_{i,j} \right)^2 \right) \right] 
\]
Here we propose to use a proposal density for $\lambda d_{i,j}$ as
\[
g d_{i,j}(\lambda d_{i,j}) = \left( \frac{\lambda d_{i,j}}{2\sigma_t^2 + \sigma_k^2} \right)^{\frac{-1}{2}} \exp \left( -\frac{1}{2(\sigma_t^2 + \sigma_k^2)} \left( y_{ik} - \mu - p_j - \tau d_{i,j} - \lambda d_{i,j} \right)^2 \right) \]
Therefore, by using MH algorithm, for parameter $\lambda$, we have $\lambda_{i,j} = \lambda_{20}$ and update $\lambda_{i,j}$ one by one, where for each $\lambda_{i,j}$, the acceptance probability for candidate point $\lambda_{i,j} \text{prop}$ can be obtained by replacing the corresponding functions in (6).

**PARAMETER $\nu^v$**

Based on the full joint posterior distribution (5), the conditional posterior distribution for parameter $\nu^v$ given $\mu, p, \tau, \lambda, \delta$ is given by
\[
f(\nu^v | \mu, p, \tau, \lambda, \delta) = \prod_{i=1}^{\infty} \prod_{j=1}^{\infty} \prod_{k \in V} \left[ \frac{(2\pi(\sigma_t^2 + \sigma_k^2))^{\frac{1}{2}}}{2^{\sigma_t^2 + \sigma_k^2}} \exp \left( -\frac{1}{2(\sigma_t^2 + \sigma_k^2)} \left( y_{ik} - \mu - p_j - \tau d_{i,j} - \lambda d_{i,j} \right)^2 \right) \right] 
\]
For the case of $h = 1$, we let $v^i = v = \{v_i\}$. To find a new value of $v_i$, we select a unit at random from $v^i$, say $v^i \text{prop}$. If the proposal is accepted, then $v_i$ goes out and $v^i \text{prop}$ replace the value $v_i$ as the current outlier. Then, using MH algorithm, this state is accepted with probability
\[
\alpha(v_i, v^i \text{prop}) = \min \left\{ 1, \prod_{j=1}^{\infty} \prod_{k \in V} \frac{f(\nu^v | \mu, p, \tau, \lambda, \delta)}{f(\nu^v | \mu, p, \tau, \lambda, \delta)} \right\} 
\]

**RESULTS AND DISCUSSION**

The method as described in the previous section is now applied to Clayton and Leslie’s data (1981) and kinesiology
data. The values of \( \mu_0, \mu_\pi, \mu_\tau \) and \( \mu_\lambda \) equal to 0 while the values of \( \alpha_0, \alpha_\pi, \alpha_\tau, \alpha_\lambda \) and \( \sigma^2 \) equal to 1000; these values are suggested by Chen and Huang (2015), and \( \delta_{\text{max}} \) equals to 10.

Using Clayton and Leslie’s data (1981), we run the method for 1000 iterations, with a burn-in of 500. We are especially interested in estimating the probability of a subject being an outlier. The probability of subject \( i \) being an outlier in this model can be estimated using the proportion of iterations that \( v = \{i\} \). Figure 1 shows the estimated probability of being an outlier for subjects 1 to 18. Given that there is one outlier, subject 11 (blood concentration are 7.14 \( \mu \)g.h/mL and 9.83 \( \mu \)g.h/mL, respectively, in period 1 and period 2) has the highest probability of being an outlier with the probability of approximately 0.30. As can be seen, subject 11 (that is, subject 2 from group 2) have high value of blood concentration in period 2 compared to their means (3.51 \( \mu \)g.h/mL in group 1 and 4.72 \( \mu \)g.h/mL in group 2) indicating the subject 11 is candidate to be outliers. Note that subject 11 is one of the outlier, identified by the procedure using SR2 as described in Lim et al. (2016) with non-Bayesian framework.

The kinesiology data of peak oxygen consumption or \( VO_2 \) peak also is used as illustration in this section. However, only 74 subjects who completed the study (\( AB = 37, BA = 37 \)) are included for analyses. We run the method for 10000 iterations, with a burn-in of 5000. With the same interest as in the previous section, Figure 2 shows the estimated probability of being an outlier for subjects 1 to 74 using the proportion of iterations that \( v = \{i\} \). Given that there is one outlier, subject 50 has the highest probability of being an outlier with the probability of approximately 0.32. This is likely because for subject 50 (that is, subject 13 from group 2), the \( VO_2 \) is unusually large in the data set for period 1. Therefore, we may conclude that subject 13 from group 2 is likely an outlier. Note that subject 50 is one of the outliers identified by the procedures using SR1 and SR2 as described in Lim et al. (2016) with non-Bayesian framework.

**CONCLUSION**

In this chapter, we have considered the problem of detecting outlier using Bayesian approach in 2 \( \times \) 2 crossover design. We have shown that with the chosen prior distributions for the parameter, we can obtain the information from samples generated by MCMC sampling, in particular using the MH algorithm. When applied to both Clayton and Leslie’s data (1981) and kinesiology data, this method is able to detect an unusual large observation as being an outlier with the highest probability as compared to the other observations.
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