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A Bayesian Approach for Autoregressive Models in Longitudinal Data Analysis: An Application to Type 2 Diabetes Drug Comparison

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ABSTRACT

The study of drug treatment remains to be an important issue to deal with high prevalence of type 2 diabetes. In this study, an auto regressive time-series framework into longitudinal data has been incorporated. The auto regressive covariance structure models have been applied on type 2 diabetes patient's data set to study the effect of drug treatment. The simulation results suggest that the estimate of covariate based on the Markov Chain Monte Carlo (MCMC) methods are consistent compared to the estimates obtained by mixed effect models and meta analysis. The study reveals that treatment of metformin with pioglitazone for twelve months reduce the Fasting Blood Sugar (FBS) level compared to pioglitazone with gliclazide combination.

Key words: WinBUGS , lag, correlation, survival analysis, time series, mixed effect models

INTRODUCTION

The forces of diabetes are extensive burden in terms of premature mortality and morbidity. Venkat *et al.* (2003) has predicted that the life expectancy of people with diabetes reduced by 10 years compared to others. Wild *et al.* (2004) shows that the prevalence of diabetes worldwide will be 4.4% by 2030. According to the International Diabetes Federation, the number of diabetes cases will be around 69.9 million by 2025 in India. At present, the prevalence of diabetes enhance from 2 to 6% in rural south India (Ramachandran *et al.*, 2004). The type 2 diabetes becomes harmful by insulin production of pancreatic ß-cell dysfunction and insulin action through reduction of insulin resistance and plasma homocysteine achieves higher level among the patients (Laghari *et al.*, 2009).

By 2025, the total number of type 2 diabetes patients will be around 380 million in world population (Sicree *et al.*, 2006) and 51 million in Indian population (Unwin *et al.*, 2009). They also have called India as the "diabetic capital of the world". Ramachandran *et al.* (1997) have observed that the South Indian population goes along with high familial aggregation of diabetes.

In last two decades, the longitudinal data analysis gives the opportunity to detain the time-varying nature of the drug effect intervention (Hedeker and Gibbons, 2006, 1994). The longitudinal data modeling with distribution free assumption involves the over-dispersion problem. In some situation, the assumption on the response observation can be unrealistic. Recently, Rao *et al.* (2011) have applied the stochastic model to know the blood glucose levels in type 2 diabetes mellitus. Fitzmaurice and Lipsitz (1995) and Brown and Prescott (1999) have introduced the Bayesian method to estimate drug treatment effect in longitudinal data. Fotouhi (2008) has extended it in repeatedcount observation to deal with over dispersion problem in epileptic data. Zeger and Karim (1991) have encountered the problem of estimation through maximum likelihood

approach in presences of random effect for generalized linear modeling. They have used the likelihood approach by integrating over the random effects. The uses of random effects allow the longitudinal data to work with Autoregressive (AR) process. The Bayesian approach provides several advantages by Markov Chain Monte Carlo (MCMC) in-place of conventional Maximum Likelihood Estimation (MLE). Robert and Casella (2004) have explained how to obtain sample for the parameters through MCMC.

The investigations on the effect of drug treatment on diabetes patients have become an increasing and important aspect in medical researches (Panikar *et al.*, 2007; Schernthaner *et al.*, 2004; Fineman *et al.*, 2003). Saud and Shahjahan (2001) have comared the different dosage of oral hypoglycemic drugs in type 2 diabetes mellitus to reduce the obesity. Meybodi *et al.* (2008) have concluded that the aminotransferase in type 2 diabetes patients is 1.6 times higher than general population. However, it has not yet been observed that how much pioglitazone with gliclazide becomes more effective in comparison to metformin with pioglitazone. Study on effects of combined drug treatment and its complications have not yet been observed, particularly on South Indian population.

This study compares the drug treatment effects between combination of metformin with pioglitazone and pioglitazone with gliclazide for type 2 diabetes patients using the secondary data of clinical trial on south Indian patients. To deal with autoregressive problems, 1st order AR random effects model has been applied through the Bayesian approach in the longitudinal data.

AUTOREGRESSIVE MODELING

The autoregressive covariance model is based on autocorrelation coefficient ρ and variances response τ^2 (Weiss, 2005). If Y_{ij} and Y_{il} are the representative of two responses in time point j and l of the ith individual, then the covariance of the responses can be represent by:

$$\sigma_{il} = \tau^2 \rho^{|t_j - t_l|} \tag{1}$$

σ_{ij} is the covariance between two time of responses j and 1. In case of same time of response the covariance of two observations becomes, $\sigma_{il} = \tau^2$.

In theory, ρ can be negative when the data set is not balanced but in longitudinal data analysis practice negative correlations are rarely encountered. So our assumption is $0 < \rho < 1$.

In this problem, the data point has been combined to $t_i = (1,2,3)$, with the ith individuals' responses covariance matrix:

$$\text{Var}(Y_i) = \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} \rho^2$$

Bayesian approach for AR (1) longitudinal models: Humphreys (1960), Heise (1969) and Werts *et al.* (1971) have proposed the autoregressive model with a variable of additive function. The simple autoregressive model is:

$$Y_{it} = \beta + \rho_{t,t-1} Y_{i,t-1} + \varepsilon_{it} \tag{2}$$

where, $E(\varepsilon_{it})=0$ for the ith individual tth observation.

Heckman (1981) has used the lagged effect of Y_t on Y_{t-1}, Y_{t-2} by the rank function. In case of binary response the logistic model is useful with likelihood function.

Beck *et al.* (2001) has introduced the AR (1) dependence model by:

$$Y_t = \rho Y_{t-1} + \beta X_t + \varepsilon_t \text{ for } \rho \in [-1,1] \tag{3}$$

where, X_t is the latent variable attached to the response Y_t and ρ is the correlation between latent and response variable. The response variable Y_t has been taken with 0,1 for the tth time observation.

Beck *et al.* (2001) has proposed to use $Y_t \sim N(0,1) I(a_t,b_t)$ where $-\infty \le a_t \le 0$ and $0 \le b_t \le \infty$.

Bollen and Curran (2004) have considered the growth model by:

$$Y_{it} = \beta_1 + \beta_{i2t} + \phi Y_{i,t-1} + \varepsilon_{it} \tag{4}$$

where, ϕ is the lag effect with response.

Jhonson and Hoeting (2003) have incorporated the autoregressive model into the area of survival analysis. Ojo *et al.* (2008) have performed and preferred the autoregressive model by linearity test on simulated data in time series framework. Maddala (2001) has applied the Bayesian algorithm in time series frame for firm investigation data analysis. In this study, the drug effect has been compared with auto regressive model through Bayesian approach.

Model specification: The AR model with Bayesian approach is sensitive compared to MLE. Here, the error term ε_{it} has been assumed to follow autoregressive process. The model is:

$$Y_{it} = \beta_1 + \beta_2 V_{i,t-1} + \beta_3 C_{i,t-1} + \varepsilon_{it} \tag{5}$$

$$\varepsilon_{it} = \rho \varepsilon_{i,t-1} + Y_{it} \tag{6}$$

where, V_{i1} and C_{i1} are the covariates of interest, respectively and $Y_{it} \sim N(0, \tau-1)$ is the unstructured white noise (Maddala, 2001). This model can be extended to the form:

$$Y_{it} = \rho Y_{i,t-1} + \beta_1(1-\rho) + \beta_2(V_{i,t} - \rho V_{i,t-1}) + \beta_3(C_{i,t} - \rho C_{i,t-1}) + \varepsilon_{it} \tag{7}$$

The model in Eq. 6 allows to work with stationary error ε by the uniform prior of the AR.

The parameter ρ is assumed to follow U (-1, 1). The model for the first visit (t=1) may be written as:

$$Y_{i1} = \beta_1 + \beta_2 V_{i1} + \beta_3 C_{i1} + \varepsilon_{i1} \tag{8}$$

$$\varepsilon_{i1} \sim N(0, 1/\tau_1) \tag{9}$$

where, $\tau_1 = (1\text{-}\rho)\ \tau\beta_1$ is assumed to follow N (0, 1). The model in Eq. 7 has been reformed, to allow the non-stationary error process, where ρ is assumed to follow N (0,1) by:

$$Y_{i1} = \beta_1\ (1\text{-}\rho) + \beta_2 V_{i1} + \beta_3 C_{i1} + \varepsilon_i \tag{10}$$

where, ϵ_i is the random effect with variance τ_μ. The variance τ_μ is assumed to follow Gamma (1,0.001).

Mixed effect model: The treatment effect on Fasting Blood Sugar (FBS) has been obtained through the mixed effect models. The relationship between pre and post-treatment values has been assumed to be same among the patients. It is general tendency that patients with relatively high FBS before the study are likely to be in high FBS at the end of the study compared to others. Mixed effect models are useful for the relationship between a response variable and covariates in data that are grouped by treatment. The model can be expressed as:

$$Y_{it} = \beta_1 + \beta_2\mu_1 + \beta_3\mu_2 + \beta_4 t_j + e_{ij} \quad \text{or}$$

$$Y_{it} = \beta_1\ (\text{Intercept}) + \beta_2{}^* \text{PPBS} + \beta_3\ ^*\text{serum cereatinine} + \beta_4\ ^* \text{treatment effect} + e_{ij} \tag{11}$$

where, j = drug 1 or drug 2. Y_{it} = observation for treatment t of the ith patients.
t_j is the effect of drug j and e_{ij} is the error for drug j on the ith patients.
μ_1, μ_2 has been replaced by the mean value of post parandial (PPBS) and serum creatinine of the tth visit.

Analysis: Diabetes data
Experimental: The secondary data have been obtained from a clinical trial of twelve months randomized controlled trial to compare the effects of drug treatment on type 2 diabetes patients in south Indian population. A total of 100 patients have been selected to participate in the study, 50 in each group viz. (1) A combination of metformin with pioglitazone and (2) A combination of pioglitazone with gliclazide. At the end of the study 18 patients have lost to complete their all follow up visits. The response of interest, FBS samples are collected from patients after an overnight fast in each visit. To overcome the biased estimate of the treatment effect, the 'last value carried forward' approach has been used to substitute the lost value of the dropout patient. Other types of drug products (than those mentioned) have been prohibited during the entire trial.

Analyzing data from a longitudinal trial: The response of interest FBS has been considered in a normal range of 100-125 mg dL^{-1} (Ch 3, Codario, 2005), where high values indicate severe diabetes status. A patient with type 2 diabetes has completed a clinical trial may typically expect to be the FBS value around 100 mg dL^{-1}.

The patients have been observed at base-line (t=1), at months 3 and 12 (t=2,3) of the study. The covariates are the drug groups, serum creatinine and PPBS. The FBS observations across the follow-up period are shown in Fig. 1. It shows that reductions of FBS among the patients due to metformin with pioglitazone are faster in comparison to pioglitazone with gliclazide. In 1st month's visits, the gap between mean FBS value of metformin with pioglitazone and pioglitazone with gliclazide has been increased after 12th month's visits. Subjects who have received the pioglitazone with gliclazide during the follow-up period are in higher FBS from the study initiation to study end than subject with metformin with pioglitazone of type 2 diabetes.
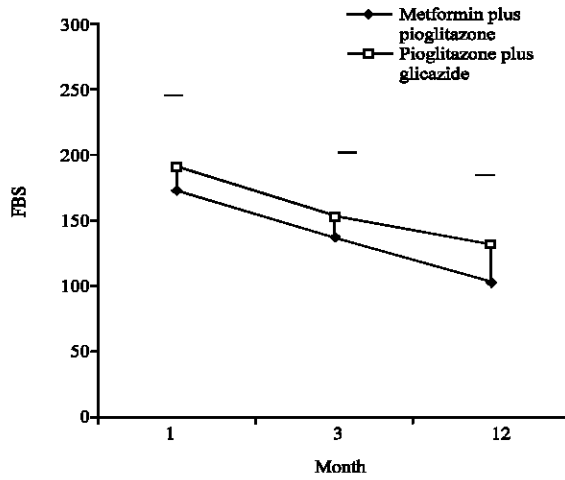
Fig. 1: Mean FBS changes over the study periods, FBS: Fasting blood sugar

Table 1: Posterior means, standard deviations and 95% HPD intervals for the AR (1) model parameters type 2 diabetes patients

Parameter	Mean	SD	95% HPD interval highest posterior density	
			2.5%	97.5%
Model1β_1(Intercept)	39.20	13.77	22.83	55.71
β_2 (PPBS)	0.49	2.89	0.43	0.54
β_3 (Serum creatinine)	-0.10	0.001	-0.09	-0.101
β_4 (DRUG)	-2.51	4.22	-10.36	4.65
τ (random effect variances)	0.0011	0.00	0.00009	0.0014
ρ (Correlation coefficient)	0.08	0.07	0.04	0.22
Model2				
β_1 (intercept)	37.48	13.68	23.54	59.05
β_2 (PPBS)	0.49	0.00	0.48	0.49
β_3 (Drug)	-1.97	4.616	1.26	5.78
τ (random effect variances)	0.0009	0.0001	0.0007	0.0009
ρ (Correlation coefficient)	0.082	0.073	0.05	0.22

The model 1 and model 2 in Eq. 8 and 10 are reformed to Eq. 12 and 13, respectively. The model 2 is the reduced model that has been obtained from model 1. The posterior mean has been obtained through MCMC in WINBUG. The same likelihood function has been used to obtain the posterior mean in two auto regressive models. In this model, ρ has been assumed to follow normal distribution with mean 0 and variance 1, τ_μ follows normal distribution with mean 1 and variance 0.001 and β_1 with a flat prior of normal distribution with mean 0 and variance 1. The models are given by:

$$FBS = \beta_1 \text{ (Intercept)} + \beta_2 *PPBS + \beta_3 *serum\ creatinine + \beta_4 *DRUG \qquad (12)$$

$$FBS = \beta_1 \text{ (Intercept)} + \beta_2 *PPBS + \beta_3 *DRUG \qquad (13)$$

The posterior means, standard deviations and 95% Highest Probability Density (HPD) interval estimates have been generated from model 1 and 2 and are given in Table 1.

Table 2: Estimation of the parameters generated from meta analysis and mixed effect modeling

Parameter	Mean	p-value
Mixed Effect		
β_2 (PPBS)	5.65*	<0.001
β_3 (serum creatinine)	4.97*	0.0292
β_3 (Drug effect)		0.7387
Meta Analysis		
β_2 (PPBS)	0.21*	<0.001

* P-value is significant with <0.001

RESULTS

In order to select the sample of two independent chains of 20,000 iterations, each run has been obtained to a burn-in period of 5000 iterations to allow the normal proposal distribution to finish the adapting. The chains are appeared to converge well before the end of the burn-in period. The posterior estimates of the regression parameters (from a two-chain run of 5000 iterations with 1000 burn-in) are not same.

The obtained models are like:

Model 1: FBS=39.20+0.49*PPBS-0.10*serum creatinine -2.51*DRUG
Model 2: FBS=37.48+0.49*PPBS-1.97*DRUG

In model 1 the coefficients β_2 and β_3 have means (HPD interval) of 0.49 (0.43,0.54) and -0.10 (-0.09,-0.101), respectively. The posterior mean of autoregressive coefficient ρ is 0.08 with 95% HPD interval (0.04, 0.22). In model 2 the two chain of posterior means (Highest Posterior Density) has been completed by β_2 and β_3 at 0.49 (0.48, 0.49),-1.97 (1.26, 5.78) with a 95% HPD interval on ρ value by 0.08 (0.05, 0.22). The results of mixed effect model and meta analysis are given in Table 2. The coefficients of mixed models are β_2 and β_3 have the value 4.97 and 5.65, respectively. In case of meta analysis, the β_2 coefficient value is 0.21.The level of PPBS and serum creatinine are significantly associated with FBS value. The posterior mean of the PPBS coefficients generated from model 1 and model 2 are 39.2 and 37.48, respectively. The regression estimates in model 1 and model 2 are quite similar. The results of mixed effect models suggest that PPBS and serum creatinine significantly associated with FBS value. The results of Model 1 and 2 are suggested that serum creatinine is negatively associated with FBS. The combined drug metformin with pioglitazone is positively associated to reduce the FBS value.

DISCUSSION

In the present study, patients have been followed for a year to complete the clinical trial. The goal of the trial is to compare the drug combination of metformin with pioglitazone over a combination of pioglitazone with gliclazide to reduce the diabetes parameter like FBS for assess the treatment effect. In this problem, the first-order auto regressive structure has been applied on the longitudinal data setup. In any kind of data set there can be the infinite number of models to analyse it. The principle of model comparison is not to determine a 'accurate' model but to infer from the model, given a set of reasonable choices, is most 'useful' i.e., stand for an optimal equilibrium between accuracy and complexity. In other words, Bayesian model inference has nothing to say about 'accurate' models. All that it grants an inference about which is more to be expected in a given data set. These results are more similar in spirit to those reported by Pillai *et al.* (2007) in

meta analysis compared to the mixed model results. In terms of the standard error, the value obtained by model 1 and model 2 are quite similar compared to the mixed effect model. These, finding indicate that patients in high FBS seem to be with low serum creatinine level. However, on the other hand high FBS level patients are in the drug therapy group pioglitazone with gliclazide in comparison to metformin with pioglitazone.

Mixed effect model has been used to assess the FBS changes by analyzing the repeated response data of drug treatment effects. The model has been fitted using thenlme package in R and smallest Akaike's Information Criterion (AIC) is considered as the best fit model (Ngo and Brand, 1997).

Bailey and Turner (1996) have found that metformin lowers the fasting blood glucose levels. Pioglitazone reduce plasma glucose and insulin in patients with type 2 diabetes, implying a reduction in their insulin resistance (Gurnell *et al.*, 2003). Tan *et al.* (2005) have concluded that the patients with pioglitazone completed study with higher HBA1c level in comparison to gliclazide group. When monotherapy fails, treatment is need to changed in combined drug, or insulin therapy (Turner *et al.*, 1999). The combination of pioglitazone with metformin has been shown to be an effective alternative in comparison to monotheray (Charbonnel *et al.*, 2005). The present study indicates that there is significant association between the PPBS and FBS in type 2 diabetes patients in South Indian Populations. The results about the relation of FBS and PPBS are quite similar in mixed effect model and Bayesian approach. The results of analysis of the biochemical parameters in type 2 diabetes patients shows a significant association of FBS with total serum creatinine in the subjects suggesting a role for diagnoses of other biochemical parameter in clinical trial. High PPBS value is significantly associated with high FBS level in blood. The Decision Information Criterion (DIC) values in model 1 and model 2 are 4243, 4240, respectively. The smaller value of DIC has been confirmed that model 2 is appropriate compared to model 1.

The parametric Bayesian approach is useful for flexible inference on the treatment effect over time using an auto regressive correlation structure. It is useful to obtain consistent results compare to the mixed effect model and meta analysis. This computation has been performed in WinBUGS. Pillai *et al.* (2007) have considered a meta analysis of metformin drug effect on FBS from different clinical trial conducted all over the world. Unfortunately, in their results no measurements have found on the drug combination of gliclazide and pioglitazone. All these trials are involved with high number of sample size (patients) in order to apply the mixed effect model. The Bayesian approach with the help of WINBUGS generates computationally consistent results compared to the mixed effect model in R.

In this study, an auto regressive model has been applied in longitudinal data analysis. In time series data analysis, the auto regressive models are in extensive and wide record of use but their application in longitudinal data are very less. In this scenario, if the longitudinal data come with missing values, mistimed measurements and non-equidistant intervals between the measurement occasions, then it is become difficult to deal with auto regressive model. The 'last value carried forward' approach has been used to overcome the missing observation problem in the data set. To deal with the non-equidistant intervals problem the effect of treatment has been assumed to be in uniform over the years of observations. As a result, the standard deviations of β coefficients have been obtained through prior information. The standard deviations of β coefficient obtained through prior information are less in comparison to the mixed effect model.

CONCLUSION

The metformin with pioglitazone for twelve months is effective to reduce FBS level in comparison to gliclazide with pioglitazone.

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