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On the Performance of a Class of Generalized Linear Mixed Model on Some Psychiatric Patients' Data

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Abstract: A generalized linear mixed model (GLMM) is an extension to the generalized linear mixed (GLM) in which the linear predictor contains random effects in addition to the usual fixed effects. They also inherit from GLMs the idea of extending linear mixed models to non-normal data. There are several applications of various types of generalized linear mixed models (GLMMs) to various fields, especially in the areas of health and biological sciences. In this our study Poisson logistic mixed regression model (a class of GLMM) was adopted to investigate the performance of the above mentioned method on some psychiatric patients' data. A clinical trial of ninety (90) mentally disordered patients was examined in this work. Patients suffering from some level of psychiatric disorder were randomized to receive either Amitryphylline or Benzhexol in addition to other therapy. This work is motivated by Thall and Vail, which investigated the performance of the Poisson logistic mixed model on some epileptics' data. The two types of therapy have little effect on the patients, but the interaction (between treatments and visits) has a substantial impact on the patients. The number of seizures is reduced by visits, and a combination of visits and medicines decreases the number of seizures. The fact that the treatments are insignificant suggests that mental disorders are mostly treatable with currently available medications. These drugs only 'manage' them for a short period of time.

Keywords: GLMMs, Poisson, Regression, Psychiatric, Amitryphylline and Benzhexol

1. Introduction

Many mixed models for continuous normal outcomes have been extensively developed since the paper of Laird and Waire [11] but Agresti [1], described a variety of its applications in categorical data analysis. Also some important sources such as Fahrmeir and Tutz [6] as well as McCulloch and Searle [13], provide a great wealth of statistical materials on GLMMs. Because they are natural outgrowth of both linear mixed models and generalized linear models, they are of wide applicability and practical importance (Breslow and Clayton [4]).

Clayton [5], described its applicability to biostatistics and highlighted the importance of binary outcome to health, social and behavioral sciences.

A random intercept model was proposed to a clustered binary data (of cardiac abnormalities in children born to HIV-infected parents) set by Wang and Louis [18], The marginal model was said to have a logistic form and the only acknowledged limitation was that it allows only a single random effect that varies from cluster to cluster. This model was modified to allow flexible correlation structure among the random intercepts. This modified model, was used to analyze data from a longitudinal design to monitor cardiac abnormalities in children born to HIV-infected women. This highlight the important application of GLMMs in medicine.

Venables and Dichmont [17], provided an overview of the modeling process using generalized linear models (GLMs), generalized additive models (GAMs) and generalized linear mixed models (GLMMs), especially as they are applied within fisheries research. The essential aspect of model interpretation and construction were discussed so as to achieve its correct application. They started with the simplest models and showed the progression from GLMs to either GAMs or GLMMs as topics relevant to fisheries science such as transformation options, link functions, adding model

flexibility through splines, and using random and fixed effects were emphasized. Various aspects of these models, their variants, and their relative benefits to fisheries research were presented in this source.

Although, the use of generalized linear models (GLMs) in actuarial statistics received a lot of attention over the last decade, starting from the actuarial illustrations in the standard text by McCullagh and Nelder [12]. Traditional GLMs however, model a sample of independent random variables but since actuaries very often have repeated measurements or longitudinal data (i.e. repeated measurements over time), the GLMs become inappropriate for fitting such data. However, Antonio et al [2], considered statistical techniques to model such data within the framework of GLMs and made use of generalized linear mixed models (which model a transformation of the mean as a linear function of both fixed and random effects). The likelihood and Bayesian approaches to GLMMs were explained and the models were illustrated by considering classical credibility models and more general regression models for non-life ratemaking in the context of GLMMs with details on computation and implementation carried out in SAS and WinBugs.

Moreover, Klinker [10], also applied generalized linear mixed models to ratemaking in actuarial science, by introducing credibility-like shrinkage towards the mean in a GLM setting.

The application of GLMMs to insurance was also seen in Garrido and Zhou [7]. Although, GLMs are gaining popularity as a statistical analytic method for insurance data but was extended to study the limited fluctuation credibility of GLMMs estimators and it was established that credibility depends on sample size, the distribution of covariates and the link function. This article also provided a mechanism to obtain confidence intervals for the GLM and GLMM estimators.

The explosions of research on GLMMs in the last decade has generated considerable uncertainty for practitioners in ecology and evolution. Despite the availability of accurate techniques for estimating GLMM parameters in simple cases, complex GLMMs are challenging to fit and statistical inference such as hypothesis testing remains difficult since most of the data sets in ecology and evolution often fall outside the scope of the methods taught in introductory statistics and as such, Bolker et al [3], gave a review of application of GLMMs in ecology and evolution, estimation, inference and best data analysis procedure.

Utilization of Generalized Linear Mixed Models (GLMM) in invasion biology has increased exponentially during the last 5-10 years. As stated earlier, GLMMs are useful tools that can handle data with various distributions as well as spatial or temporal dependence which are involved in many study designs.

Thiele and Markussen [16], gave a review of the current state-of-the-art of GLMM with special focus on applications in invasion biology and addressed the frequently encountered practical problems, such as failure of convergence, and put some emphasis on validation of model assumptions. They also pointed towards possibilities of analysing zero-heavy data using combined GLMM through the use of certain examples and pointed out that modelers should be conscious of the estimation of random-effects rather than random variation in accounting for non-independence of observations due to study designs especially in studies relating to genetic variation of invasive species.

In general, a feature of random effect logistic regression models (a class of GLMMs) for longitudinal binary data is that the marginal functional form when integrated over the distribution of the random effects, is no longer of logistic form.

The performance of the binary logistic mixed model has been investigated in the popular Salamander Mating data (published in McCullagh and Nelder [12]) in various sources such as Karim and Zeger [9], Breslow and Clayton [4], Shun [14], as well as Halid and Adeleke [12, 9, 4, 14, 8] to mention a few, through the development of different estimation techniques.

This work is motivated by Thall and Vail [15], which investigated the performance of the Poisson logistic mixed model on some epileptics data.

2. Materials and Methods

A clinical trial of 90 mentally disordered patients was examined in this work. Patients suffering from some level of psychiatric disorder were randomized to receive either Amitryphylline or Benzhexol in addition to other therapy. At each of the four successive clinic visits, the number of psychiatric ‘breakdown’ rate occurring over the previous two weeks was reported. Each patient was subsequently crossed over to the other treatment but only the four precrossover responses were considered in an eight-week baseline period, segmented into four two-week treatment periods in which patients received either Amitryphylline or Benzhexol. The covariates in the model are psychiatric baseline ‘breakdown’ rate, logarithm of patients’ ages (in years), the binary indicator treatment for the drugs administered (Amitryphylline or Benzhexol) and the clinic visits. The cross design and count nature of the data give rise to the Poisson logistic mixed model.

The Poisson logistic mixed model, a class of GLMM was therefore fitted to the data of mentally disordered patients. This data was collected from the records Department of Neuro-Psychiatric Hospital Aro, Abeokuta, Ogun State, Nigeria. The data is therefore similar to that in Thall and Vail [15], which involves some epileptics.

The execution was carried out using GLIMMIX PROCEDURE of SAS 9.4. With successive weekly count of 90 mentally disordered patients.

3. The Generalized Linear Mixed Model

The basic formulation of a single-level GLMM is that the response y_i vector for a given group i, conditional on

random effects α_i, is distributed as independent random variables with distribution in the exponential family. That is, the conditional distribution of the data y_i, given the random effects α_i, is a member of the exponential family of distribution such as binary, binomial, Poisson, gamma, beta or chi-square distribution.

The most important cases of practical interest are the Binomial and Poisson distributions.

The GLMMs are specified through the following ways:

1. Formulate the linear predictor, including fixed and random effects
2. Choose a link function
3. Choose the distribution of the response, conditional on the random effects, from the exponential family

Given α_i the conditional density of y_i in canonical form is

$$f(y_i \mid \alpha_i) = \prod_{j=1}^{n_i} \exp\{(y_{ij}\theta_{ij} - d(\theta_{ij}))/a(\phi) + c(y_{ij},\phi)\}$$

$$= \exp\{(y_i'\theta_i - d(\theta_i)'1)/a(\phi) + c(y_i,\phi)'1\} \quad (1)$$

For appropriate functions $a(.)$, $d(.)$ and $c(.)$

The random effects are assumed to be independently distributed on $N(0, G(\alpha))$.

The model is further determined through the specification of an invertible link function $g(.)$ relating the conditional expectation of y_i given α, non-linearly

$$\mu_i = E(y_i \mid \alpha) \quad (2)$$

to a set of covariates and the fixed and random effects (linear predictor).

That is,

$$g(\mu_i) = X_i\beta_i + Z_i\alpha_i = \eta_i$$

and

$$\mu_i = h(\eta_i) = g^{-1}(X_i\beta_i + Z_i\alpha_i) \quad (3)$$

where β denotes the vector of fixed effects and α the vector of random effects, X_i and Z_i are (known) fixed and random effects regression matrices and

$$h = g^{-1}$$

is the inverse link function.

We will assume the canonical link function for the exponential family,
in which case $\theta_i = \eta_i$.

It then follows that the joint density of (y_i, α_i) is given by

$$f(y_i,\alpha_i) = \exp\{[y_i'(X_i\beta + Z_i\alpha_i) - d(X_i\beta + Z_i\alpha_i)'1]/a(\phi)$$

$$+ c(y_i,\phi)'1 - b_i G(\alpha)^{-1}\alpha_i/2\}/[(2\pi)^{q/2} \mid G(\alpha)\mid^{1/2}] \quad (4)$$

where q denotes the number of random effects (the length of α_i).

As with any mixed-effects models, because the random effects are non-observable quantities, likelihood estimation must rely on the marginal density of y_i, which is obtained by integrating the joint likelihood function with respect to α_i. For the GLMM, this integral does not have a closed form expression and approximations are required for computationally feasible estimation.

Recall that the extension of GLMs with random effects is called GLMM (McCulloch and Searle [13]). The conditional independence assumption of the response variable, given the random effects, plays an important role in the formulation of GLMM.

3.1. The Particular Case of the Poisson Logistic Mixed Model

The Poisson distribution is often used to model responses that are counts. Suppose that, given the random effects α_i the counts $y_1,...,y_n$ are conditionally independent such that $y_i \mid \alpha \sim Poisson\ (\lambda_i)$
where,

$$\log(\lambda_i) = X_i\beta_i + Z_i\alpha_i \quad (5)$$

and X_i, Z_i are as in definition of GLMM.

Again it is a special case of GLMM, in which the (conditional) exponential family is Poisson and the link function is

$$g(\mu) = \log(\mu) \quad (6)$$

The dispersion parameter ϕ in the case is again equal to 1.

3.2. Modeling the Data of Psychiatrics with the Poisson Logistic Mixed Model

From the Poisson Logistic Mixed Model, the model can be written below:

$$\log(P_{ij}) = \mu + \alpha_i + \beta_j + (\alpha\beta_{ij})\ \ i = 1,...,4,\ j = 1,2 \quad (7)$$

$$P_{ij} = \begin{cases} P(Y_{ij}) = 0, for\ \text{Amitryphylline treatment} \\ P(Y_{ij}) = 1, for\ \text{Benzhexol treatment} \end{cases}$$

μ=grandmean
α_i=visits
β_j=treatmenteffect
$\alpha\beta_{(ij)}$= is the effects of interaction between visits and treatment.

(7) can also be written as

$$\text{logit}(P_{ij}) = \mu + x_i + trt + x_i * trt \quad (8)$$

Table 1. *Data Of Some Psychiatric Patients.*

ID	TREATMENT	X1	X2	X3	X4	BASE LINE	AGE
271	0	1	1	2	3	180	60
270	0	1	2	3	3	120	38
265	0	3	1	4	1	400	32
410	0	3	2	8	4	420	65
234	0	3	1	1	4	132	22
302	0	1	3	1	1	300	46
602	0	1	1	1	2	420	71
650	0	1	1	1	2	100	24
759	0	1	1	2	1	100	36
827	0	1	1	1	2	121	20
930	0	1	1	1	2	122	45
650	0	1	1	1	1	200	33
200	0	3	2	1	3	400	20
241	0	3	1	1	1	222	26
127	0	1	2	2	1	120	32
195	0	2	1	2	3	120	70
141	0	3	1	1	3	200	27
158	0	1	1	3	1	123	46
493	0	2	1	2	1	111	37
496	0	7	1	2	3	120	44
541	0	1	1	1	1	100	52
166	0	1	1	1	2	213	30
373	0	3	2	1	2	480	35
113	0	1	1	1	2	113	28
650	0	1	1	1	2	240	70
308	0	1	1	1	1	100	32
488	0	3	2	1	3	240	50
510	0	3	1	1	1	100	35
725	0	1	2	2	1	100	29
938	0	2	1	2	3	240	28
960	0	3	1	1	3	321	60
511	0	1	1	3	1	100	31
525	0	2	1	2	1	100	37
475	0	7	1	2	3	124	30
804	0	1	1	1	1	100	56
259	0	1	1	1	2	480	45
221	0	1	1	1	2	360	39
409	0	3	2	1	2	240	64
598	0	1	1	1	1	480	35
963	0	2	1	2	3	120	60
979	0	2	1	2	3	200	31
932	0	2	1	2	3	240	36
886	0	1	1	2	1	180	43
500	1	1	8	3	2	300	25
388	1	1	2	1	1	120	29
346	1	3	3	1	1	144	60
376	1	2	1	2	1	120	28
579	1	1	1	1	3	221	48
708	1	1	3	3	1	300	20
863	1	1	2	1	1	213	33
492	1	1	3	3	1	120	26
401	1	1	4	1	2	121	40
402	1	1	1	2	1	333	35
969	1	3	1	1	1	121	17
952	1	2	1	1	1	500	71
181	1	2	1	1	1	212	50
284	1	2	3	1	2	101	28
248	1	1	1	2	1	333	52
366	1	1	1	1	2	168	60
800	1	2	2	1	1	211	48
792	1	1	1	2	1	300	20
826	1	1	3	1	1	100	41
997	1	1	1	1	2	240	32
847	1	1	1	2	2	360	44
622	1	1	1	2	1	121	40
748	1	1	2	2	4	421	30
754	1	1	4	2	3	120	25
580	1	2	1	2	2	200	40
186	1	1	1	1	1	360	51
386	1	1	1	2	1	240	26
566	1	1	1	1	2	120	36
383	1	4	1	3	1	200	22
558	1	1	1	1	3	360	26
551	1	1	1	1	2	240	12
292	1	1	1	1	1	121	30
923	1	1	1	1	1	240	11
545	1	2	1	1	3	200	14
419	1	1	1	1	2	110	27
245	1	1	6	1	2	480	23
824	1	1	1	1	2	121	21
250	1	3	1	1	2	222	16
533	1	2	3	8	1	101	18
127	1	1	2	1	3	382	33
254	1	1	2	1	1	123	17
298	1	2	3	8	1	123	14
470	1	1	2	1	3	331	39
744	1	1	2	1	1	481	21
742	1	1	2	1	1	111	14
830	1	1	2	1	2	144	23
290	1	1	2	1	2	390	30

Let Y_{ij} be the number of mental disordered count for subject i in interval j, where t_j is the length of interval j = 1,2,...,4. Here t_i = 8 and the other tj = 2. A reasonable model for this data would be to assume that the responses Y_{ij} have marginal Poisson distributions, but that the responses within an individual are correlated over time. An important aspect of this problem is that the observation length is 8 weeks for period 1 and 2 weeks for the next 4 periods. The standard way to incorporate the different length periods is to write the mean of the Poisson distribution in the form $E(Y_{ij}) = \mu^*_{ij} = \mu_{ij}t_i$ where μ_{ij} is the mean response per unit time (a week). This mean per unit time is directly comparable across different periods, so μ_{ij} is modeled as a function of predictor variables. With a log link $log(\mu^*_{ij}) = log(\mu_{ij}) + log(t_i)$, so a log-linear model for the mean response per unit time will lead to a log-linear model for the μ^*_{ij} with an offset term - the $log(t_i)$. The original data set (therapy) is in regression format with 1 record for each post-baseline count. The response is labeled y. The baseline count is included in each post-baseline record, in column baseline. Other columns in the data set are individual id, visit number (1-4), treatment (treatment with levels 0 for Amitryphylline and 1 for Benzhexol), and age at baseline.

After creating the data set to be analyzed, the means procedure was used to compute the mean number of mental retardation per observation period by treatment. The interval length was standardized and the raw and standardized means were printed with the standardized mean being log-transformed. The log of the sample mean per unit time provides information about how $log(\mu_{ij}) = log(\mu^*_{ij}) - log(t_i)$ might depend on time and treatment.

4. Analysis and Discussion of Results

Table 2. *Outline of Baseline treatment and Visits.*

Treatment	Visit	log (μ_{ij})
Amitryphylline	Baseline	β_0
Amitryphylline	1-4	$\beta_0 + \beta_1$
Benzhexol	Baseline	$\beta_0 + \beta_2$
Benzhexol	1-4	$\beta_0 + \beta_1 + \beta_2 + \beta_3$

Thus, β_0 is the mean (on log scale) at baseline for the baseline treatment; β_2 is the difference in means at baseline between the treatment; β_1 is the change over time from baseline in treatment group, this is the main effect for time; β_3 is the effect of interaction between time and treatment. If β_3=0 then the difference between baseline and post-baseline is the same, and the difference between Amitryphylline and Benzhexol is independent of time.

Alternatively, if $\beta_3 < 0$ then the change from baseline in the treatment group is greater than the change from baseline in the group with reverse implication if β_3>0. Thus, a value of β_3<0 indicates a reduction in the expected change in the count from baseline associated with the treatment.

Table 3. *The raw correlation between the four visits.*

	visit 1	visit 2	visit 3	visit4
Visit 1	1			
Visit2	-0.1215801	1		
Visit 3	0.14807979	0.2095822	1	
Visit4	0.2703079	0.0001258	-0.02689774	1

The working correlation matrix shows that there is a perfect correlation between corresponding row r_i and column c_i only.

Table 4. *Table of empirical standard error estimates.*

Parameter Estimates Analysis						
Empirical Standard Error Estimates						
Parameter	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept	3.2656	0.0881	3.0930	3.4382	37.08	<.0001
x1	-3.4313	0.0920	-3.612	-3.251	-37.29	<.0001
Trt	0.0935	0.1153	-0.133	0.3195	0.81	0.4174
x1*trt	-0.0902	0.1320	-0.349	0.1686	-0.68	0.0001

The empirical standard error estimate table above, contains the parameter, standard error, confidence interval, and the Z score estimates.

It is clear from Table 4. that the visits have significant effect on the patients under study. It is also clear that the treatment does not have significant effect on the patients.

The interaction (between treatment and visits) have significant effect on the patients.

Table 5. *Table of model based standard error estimate.*

Parameter Estimates Analysis						
Model-Based Standard Error Estimates						
Parameter	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept	3.2656	0.0105	3.2449	3.2863	309.68	<.0001
x1	-3.4313	0.0475	-3.5243	-3.3382	-72.26	<.0001
Trt	0.0935	0.0142	0.0657	0.1213	6.59	0.4221
x1*trt	-0.0902	0.0652	-0.2179	0.0375	-1.38	0.0001
Scale	1.0000	.	.	.	.	.

The model-based standard error estimates in the table above contains the parameter, standard errors, confidence intervals, and the Z score estimates.

It is obvious that the visits have significant effect on the patients. It is also clear that the treatment does not have significant effect on the patients while interaction (between treatment and visits) have significant effect on the patients.

Table 6. *Summary Statistics for the two-week 'breakdown' counts.*

visit	Amitriphylline					Benzhexol				
	$\bar{y}$					$\bar{y}$				
	s^2	correlations				s^2	Correlations			
1	1.95					1.38				
	1.99	1				0.49	1			
2	1.23					1.91				
	0.23	0.016	1			1.95	-0.1188	1		
3	1.70					1.68				
	1.50	0.143	0.163	1		2.17	0.2005	0.255	1	
4	1.20					1.64				
	0.91	0.443	0.052	0.225	1	0.61	-0.21261	0.0885	-0.2104	1

The summary statistics for the visits within each group, the mean and variance at each visit is recorded, followed by the correlation for the first group (Amitryphylline) and the second group (Benzhexol).

From the above, it follows that the degree of association between the treatment and visits is higher in the first group than that of the second group.

5. Conclusion

The Poisson logistic mixed regression model (a class of GLMM) considered in this work adequately fitted the data of 90 psychiatric patients having put into consideration the patients' visits, treatments (drugs) and interaction between visits and treatments as the variates.

The patients' visits to the hospital was helpful for both groups of patients since the visits have significant effect on the patients. The two classes of treatment do not have significant effect on the patients whereas the interaction (between the treatments and visits) have significant effect on the patients.

The visits reduces the 'seizure' rate and a combination of visits and treatments also reduces the number of seizures. The fact that the treatments are insignificant further tells us that mental disorders are mostly incurable by existing drugs. They are only 'managed' for some period of time by these drugs.

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