Analysis of Dynamic Pupil with Generalized Linear Mixed Models

Marcela A. D'Urso Villar*
Facultad de Medicina, Tucumán, Argentina – durso.marcela@gmail.com
Ana M. Sfer
Facultad de Ciencias Exactas y Tecnología, Tucumán, Argentina– asfer@herrera.unt.edu.ar
Bárbara Silva
Facultad de Ciencias Exactas y Tecnología, Tucumán, Argentina – bsilva@herrera.unt.edu.ar
Elisa Colombo
Facultad de Ciencias Exactas y Tecnología, Tucumán, Argentina – ecolombo@herrera.unt.edu.ar

Abstract

Pupil size is one of the adaptation mechanisms used by the visual system when the perceived luminance changes occur. The study of the effects of multiple glares in the visual system during night driving route has been of interest in our environment. This prompted researchers from the Institute of Lighting of Tucuman University, Argentina, to study the dynamics of pupil diameter under certain conditions. In the study the measurements of pupil diameter (Dpmax), were carried out on 10 young subjects and 10 older adults, considering three levels of luminance. At each level of luminance, the same subject was evaluated 30 times. Generalized linear mixed model (GLMM) was used, since Dpmax follows an Exponential distribution and it is longitudinal study. The GLMM provide a tool to model data where assumptions about the response such as independence, linearity, constant variance, and normality are questionable. They have attracted considerable attention, with the development of routines such as lme4 R and SAS macro GLIMMIX during the last ten years. These models combine the features of generalized linear models and mixed models. The descriptive analysis of the data was performed using STATA 11 software; and inferential analysis with the software R. The estimates were made by maximum likelihood with Laplace approximations. The fit indicates that both age and luminance levels are significant. The average value of Dpmax is 27% lower in adults for a given luminance and time, and decreases approximately 4% from a low level to high level of luminance, for a given age and time. Besides, the average value of Dpmax is lower when the number of glare grows. The GLMM models allow answering the research question, taking into account the within-subject dependence of the observed values. They allow quantifying the contribution of the explanatory variables and do not require the response observed to follow a Normal distribution. In addition, not less important, is that the mixed models in the area of lighting technology were introduced. This may be an improvement in future designs of experiments, since the mixed models allow experiments with fewer subjects, ensuring reliable estimations

Keywords: pupil diameter**;** luminance; correlation within subject, random effect.

1. Introduction

Pupil size and its dynamics in specific situations are important to analyze the performance of the visual system and its optical and neuroretinal behavior. In particular the study of the effects of multiple glares in the visual system during night driving route has been of interest in our environment. The researcher is interested to study the dynamics of pupil diameter under certain conditions in people of different ages. Researcher holds the hypothesis that as the flash or glare occurs, the pupil diameter decreases and does not recover its initial value. This decrease continues until a stable level.

Further, the researcher says that the pupil diameter depends on the age and level of glare. In the study the measurements of pupil diameter (Dpmax), were carried out on 10 young subjects and 10 older adults, considering three levels of luminance. At each level of luminance, the same subject was evaluated 30 times. Mixed models are widely used in the analysis of longitudinal data. They have been studied as an extension of the classical regression model for cross-sectional data by introducing random effects. These effects facilitate specific-individual inference, and incorporate for correlation between repeated measures within each subject since each subject shares the same random effects. Besides, the mixed model taking into account the within-subject dependence of the observed values, quantifies the contribution of the explanatory variables.

Thus, the mixed models are increasingly useful for the design of experiments, where it is expensive to get subjects to demonstrate research hypotheses.

The aim of this paper is to explain the behavior of the pupil diameter over time, according to age and level of luminance, using a mixed model.

It is important to note that in longitudinal studies there are two sources of variation, one within subject and other between subjects. The mixed effects model proposed incorporates both sources of variation, where the random effect due to the subject represents the deviation of individual longitudinal path from the average longitudinal path.

2. Metodology

The experiment was carried out in Department of Lighting at Tucumán University, during 2012. The study included 20 subjects, 10 young (20-30 years) and 10 adults (50-60 years). The subjects had not disease or visual deficiency. Each subject was undergone to 30 flashes, every 5 seconds and for 0.5 seconds, of a glare source (60 lux at 10º from the line of sight). Glare or flash were similar to those that a driver receives at night. There were considered 3 luminance level, these levels, according to the researcher, can be considered independent. The measured variables were: luminance level (0.1, 0.2 and 0.5 cd/m^2), age (young adult), maximum and minimum pupil diameter (mm), latency time (msec) and speed pupil diameter fall after a glare occurs (mm / sec). In this paper we only refer to maximum pupil diameter (Dpmax), versus time, age and the luminance level.

It was decided to model the variable Dpmax using generalized linear mixed model (GLMM), since on the one hand, the researcher conducted an empirical adjustment of variable Dpmax and determined that it follows an exponential shape (Silva et al 2012). On the other hand this is a longitudinal study that incorporates correlation between observations of the response variable. STATA 11 software and lme4 package of the software R were used. The first software is used for descriptive analysis and the second one for inferential analysis.

The GLMM are an extension of Generalized Linear Models (GLM) obtained by introducing random effects in the model. The random effects account for correlation between repeated measures within each subject and the variation between subjects. A GLMM it is assumed that the correlation between repeated observations arise within each subject since they share the same random effect (subject) but are assumed to be conditionally independent given the random effect.

The lme4 package for R provides functions to fit and analyze linear mixed models, generalized linear mixed models and nonlinear mixed models. In each of these names, the term “mixed” or, more fully, “mixed effects”, denotes a model that incorporates both fixed and random effects terms in a linear predictor expression from which the conditional mean of the response can be evaluated. It uses the function lmer() for linear mixed models and glmer() for generalized linear mixed models.

The default methods for fit a linear mixed model is "REML" indicating that the model should be fit by maximizing the restricted log-likelihood. The alternative is "ML" indicating that the log-likelihood should be maximized.(This method is sometimes called "full" maximum likelihood.) For a generalized linear mixed model the criterion is always the log-likelihood but this criterion does not have a closed form expression and must be approximated. The default approximation is "PQL" or penalized quasi-likelihood. Alternatives are "Laplace" or "AGQ" indicating the Laplacian and adaptive Gaussian quadrature approximations respectively. The "PQL" method is fastest but least accurate. The "Laplace" method is intermediate in speed and accuracy. The "AGQ" method is the most accurate but can be considerably slower than the others.

The development of general software for fitting mixed models remains an active area of research with many open problems. Consequently, the lme4 package has evolved since it was first released, and continues to improve as we learn more about mixed models.

3. Results

Figure 3.1 shows the variable Dpmax depending on time, by subject and luminance level. It can be seen that Dpmax varies over time, with age and with the luminance level. Dpmax has, in general, higher values with lower dispersion to young subjects. Also, it can be seen that Dpmax trajectories have an exponential shape over time, and the intercept depends on the subject.

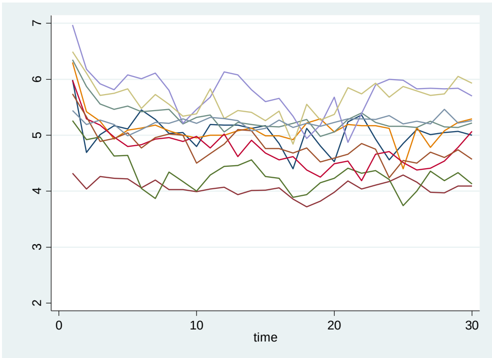
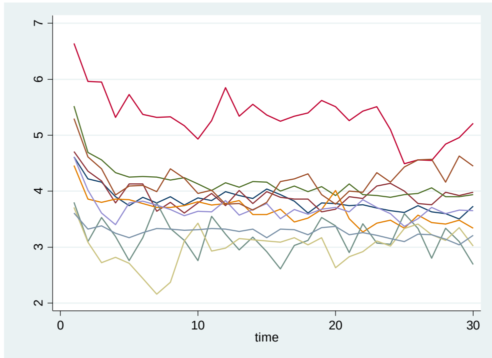
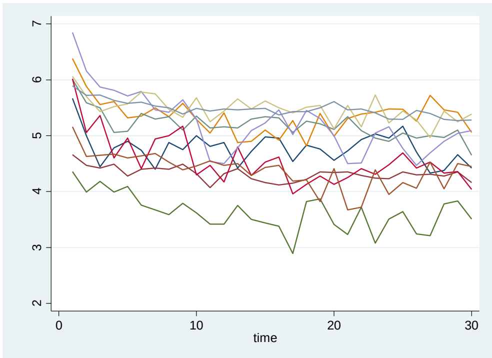
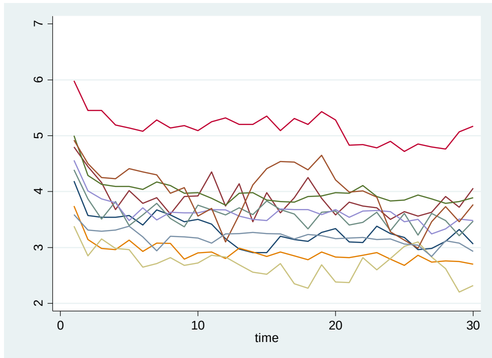
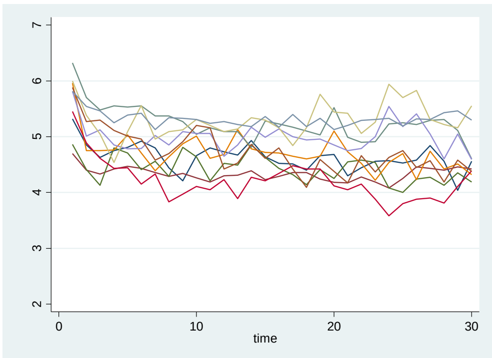
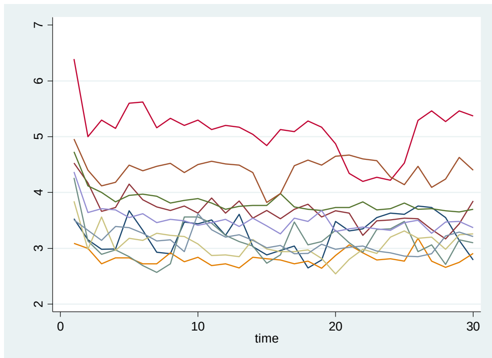
Luminance	Young	Adults
$0.1 cd/m^2$		
$0.2 cd/m^2$		
$0.5 cd/m^2$		

Figure 3.1: Dpmax versus time, by age and luminance level.

Generalized linear mixed model (GLMM) with random intercept is proposed, considering the research hypothesis, repeated observations and the exponential shape of the response.

The response observed Dpmax it can be represented as:

$$Dpmax_{ij} i = 1, 2, \dots, 20 \qquad j = 1, 2, \dots., 30$$

where, the subscript i represents the subject and the subscript j represents the repetitions (number of glare or flash). The observations of the response, given the random effect associated with the subject ($\mathrm{Dpmax_i/b_i}$) are independent and follow an exponential distribution with parameter λ , i.e.:

$$\forall i = 1,2, \dots 20 \qquad \mathrm{Dpmax_i/b_i} \;\sim\; \mathrm{E}(\lambda)$$

then the link function to consider is: g(x)=1/x. Thus the model is:

$$\forall i = 1,2, \dots, 20 \quad g[E(\mathbf{Dpmax_i}/b_i)] = X_i\boldsymbol{\beta} + \mathbf{Z_i}b_i$$

with $b_i \sim N(0, \sigma_i^2)$, **Dpmax** a vector 180x1, **X** a matrix 180x5, **β** a vector of fixed effect 5x1**, and Z** a vector design random effect 180x1.

Table 3.1 shows the result of setting GLMM with lme4 R package, using maximum likelihood (ML) with Laplace approximations.

Table 3.1: The GLMM output

Dependent variable: Dpmax

Family	Link	nAGQ
Gamma	inverse	1

Fixed effects

<table>
<tr><th></th><th>Estimate</th><th>Std. Error</th><th>t value</th><th>Pr(>|z|)</th></tr>
<tr><td>(Intercept)</td><td>0,19</td><td>0,02</td><td>11,82</td><td><0,0001</td></tr>
<tr><td>0.2 cd/m²</td><td>0,01</td><td>1,0E-03</td><td>9,19</td><td><0,0001</td></tr>
<tr><td>0.5 cd/m²</td><td>0,01</td><td>1,0E-03</td><td>11,39</td><td><0,0001</td></tr>
<tr><td>Adult</td><td>0,08</td><td>0,02</td><td>3,75</td><td>0,0002</td></tr>
<tr><td>time</td><td>7,3E-04</td><td>4,8E-05</td><td>15,16</td><td><0,0001</td></tr>
</table>

Parameters of the random effects

RndEff	Param	Var	SD
subject	(Intercept)	1,0E-04	0,01
Residual	NA	0,01	0,08

Dpmax - Adjusted means and standard errors for cat_lum and age

Inverse of the link function with random effect=0

LSD Fisher (Alfa=0,05)

Correction procedure of p-values: No

Cut lum	LinPred	S.E.	Mean	S.E.			
0.5 cd/m^2	0,25	0,01	3,94	0,16	A		
0.2 cd/m^2	0,25	0,01	3,97	0,16		B	
0.1 cd/m^2	0,24	0,01	4,12	0,18			C

Age	LinPred	S.E.	Mean	S.E.		
Adult	0,29	0,01	3,47	0,15	A	
Young	0,21	0,02	4,75	0,37		B

Means with the same letter are not significantly different (p > 0,05)

Table 3.1 shows that the fixed effects luminance, age and time are all statistically significant (p <0.001). The base category for luminance was 0.1cd/m^2 and young for age. With respect to the fixed effects, it can be said that:

– The Dpmax average for a given time and a given age, and a luminance equal to 0.1cd/m^2 is 4.12±0.18 mm; for a luminance equal to 0.2cd/m^2 is 3.97±0.16 mm and a luminance equal to 0.5cd/m^2 is 3.94±0.16 mm. Besides these means are statistically different.

– The Dpmax average for a given time and for a given luminance, for young subjects is 4.75 ± 0.37 mm, and for adults is 3.47±0.15 mm. Besides these means are statistically different.

– The Dpmax average for a given age and luminance level, changes significantly with time.

The Figure 3.2 shows the fitted path (dotted green line) on the observed trajectories by age and level of luminance equal to 0.1cd/m^2. The Dpmax fitted follows an exponential shape and is lower for adults at all times. Similar behavior was observed for the other levels of luminance.

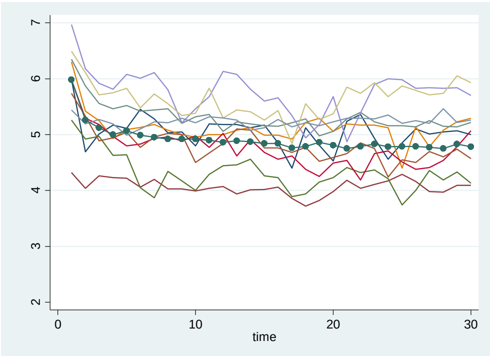
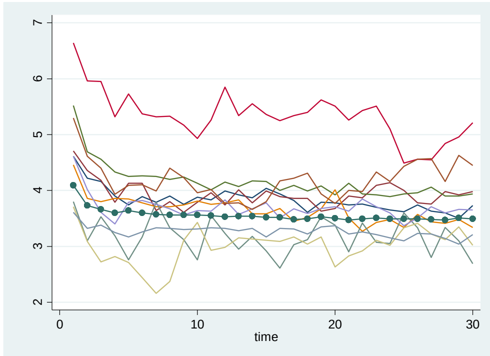
Luminance	Young	Adults
0.1cd/m^2		

Figure 3.2: Dpmax observed and fitted versus time for luminance 0.1 cd/m^2 by age

The Dpmax fitted for time 1, 15 and 30, for each age group and each luminance level are shown in Table 3.2. The Dpmax average decreases approximately 5% between 0.1 and 0.5cd/m^2 luminance levels in the youth group and 4% in the group of adults. Within the younger group Dpmax average decreases between 9% and 10% between time 1 and time 30. Within the group of adults this percentage is equal to 7%. At time 1 Dpmax average is approximately 28% lower in the group of adults in the three luminance levels. At time 30, the percentages are equal to 27% (luminance 0.1cd/m^2), 26% (luminance 0.2cd/m^2) and 25% (luminance 0.5cd/m^2).

Table 3.2: Dpmax adjusted values for time 1, 15 and 30

Luminance	Age	T=1	T=15	T=30
0.1cd/m^2	Young	5.18	4.92	4.67
	Adult	3.7	3.56	3.43
0.3cd/m^2	Young	4.94	4.7	4.47
	Adult	3.57	3.45	3.32
0.5cd/m^2	Young	4.89	4.65	4.43
	Adult	3.54	3.42	3.3

According to the result of the Shapiro-Wilk test, p = 0.889, it can be concluded that the random effects follow a Normal distribution (Figure 3.3a). The residual plot is presented in Figure 3.3b and it is observed that they are randomly distributed around zero.

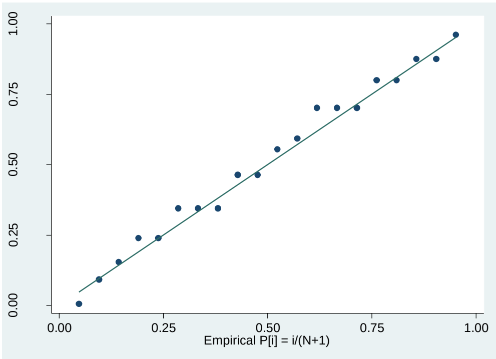
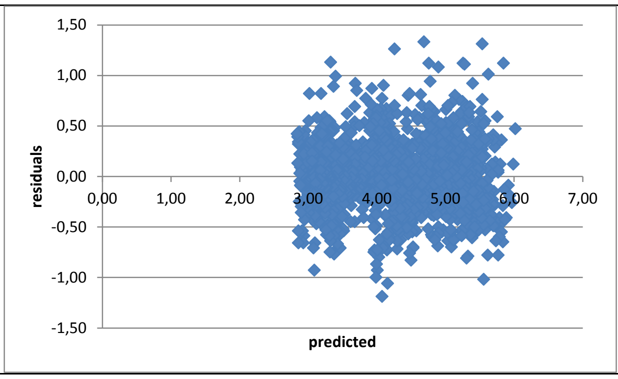
	
a) Q-Q plot	b) Residuals plot

Figure 3.3: Diagnostic plot of GLMM

4. Conclusions

The modeling process used in this work is relatively straightforward. As in any traditional approach, you need to identify the variable of interest or response and factors. The question is to realize the dependence between observations and to define as represent it in the model. You must observe, from the descriptive analysis, the need to introduce random effects. Also study the linearity and normality of the response.

This study is a longitudinal study where the correlation is clearly due to the subject. The observed trajectories indicated that the response is nonlinear and it was necessary to introduce a random intercept. The fit proposed confirmed the researcher´s hypothesis that the pupil diameter decreases with age, the level of glare received, and the number of flash; since that variables resulted statically significant. An individual aged between 50 and 60 years has a Dpmax average 27% lower than that of a subject of 20-30 years for the same luminance and number of flash. On average the value of Dpmax for luminance 0.5cd/m^2 is 4% lower than for the luminance of 0.1cd/m^2. The same goes for the luminance 0.3cd/m^2 and 0.1cd/m^2. The value of average Dpmax decreases when the number of flash grows.

GLMM models allow answering the research question, taking into account the within-subject dependence of the observed values. They allow quantifying the contribution of the explanatory variables and do not require the response observed to follow a Normal distribution. In addition, not less important, is that the mixed models in the area of lighting technology were introduced. This may be an improvement in future designs of experiments, since the mixed models allow experiments with fewer subjects, ensuring reliable estimations

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