

Review

GENERALIZED LINEAR MIXED MODELS. ITS APPLICATION IN PLANT BREEDING

Revisión bibliográfica

Los modelos lineales generalizados mixtos. Su aplicación en el mejoramiento de plantas

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ABSTRACT. Frequently, in agricultural research, experimental data do not satisfy the assumptions of general linear models, making the recommended transformations very few effective. Generalized Linear Mixed Models (GLMMs) provide a way of analysis for those data that are correlated and that does not necessarily require that the evaluated variable be normally distributed and but to a distribution of the exponential family (Gamma, Poisson, Binomial among others). The objective of this review was to present the applications of generalized linear mixed models in breeding programs. This model has been focused fundamentally in three directions in plant breeding programs: in the prediction of family behavior, in the estimation of variance components and in multi-environment trials. GLMM estimation procedures make it possible to reduce biases when data is incomplete, unbalanced or adjust scattered data and also allow modeling the structure of errors in data from longitudinal measurements. There are several commercial and free programs such as: the GLIMMIX and GENMOD procedure of the SAS package and the lme4 of the R package that enable the use of The Generalized Linear Mixed Models for most current applications in plant genetics.

RESUMEN. Con frecuencia, en las investigaciones agrícolas los datos experimentales no satisfacen las premisas de los modelos lineales generales y las transformaciones recomendadas tienen poca efectividad. Los Modelos Lineales Generalizados Mixtos (GLMMs, Generalized Linear Mixed Models) proporcionan una vía de análisis para aquellos datos que se encuentran correlacionados y no requiere necesariamente que la variable evaluada se distribuya normalmente, sino a una distribución de la familia exponencial (Gamma, Poisson, Binomial, entre otras). El objetivo de esta revisión fue presentar las aplicaciones de los modelos lineales generalizados mixtos en los programas de mejoramiento genético. Este modelo ha estado enfocado fundamentalmente en tres direcciones en los programas de mejoramiento en plantas: en la predicción del comportamiento familiar, en la estimación de los componentes de varianza y en los ensayos multiambientes. Los procedimientos de estimación de los GLMMs posibilitan reducir los sesgos cuando los datos están incompletos, desbalanceados o ajustar datos dispersos y permiten además modelar la estructura de los errores en datos provenientes de mediciones longitudinales. Existen varios programas comerciales y libres tales como: el procedimiento GLIMMIX y GENMOD del paquete SAS y el lme4 del paquete R, que posibilitan el uso de los Modelos Lineales Generalizados Mixtos para la mayoría de las aplicaciones actuales en la genética de plantas.

Key words: plant breeding, quantitative genetics

Palabras clave: fitomejoramiento, genética cuantitativa

INTRODUCTION

Traditional linear models emerge in the 20th century and are based on estimates by the Minimum

Squares method such as Analysis of Variance (ANOVA), Analysis of Covariance (ANACOVA), Analysis of Multivariate Variance (MANOVA) and partial correlation. In general, they use continuous response variables and one or several independent variables, which can be classification variables

that divide the observations into different groups or continuous variables. The objective of these models can be the comparison of groups or treatments (test of hypothesis) or the prediction of a response (dependent variable) from the dependent variables (1). The premises of the ANOVA based

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on a traditional linear model are assumed, sometimes without strict compliance, on the basis that if the number of observations is high, the data can be adjusted to normal.

Sometimes, it is not correct to assume a normal distribution. For example, if it is counts or proportions that are discrete variables; when the mean of the data has a limited range, as in binary data (0.1) and the linear predictor of the mean is not limited to that range. In addition, classical linear models, whether ANOVA or regression, assume that the variance of the error is constant between observations; however, there are data for which the variance of the observations increases with the value of the mean (1).

A very frequent case in genetic studies is the analysis of correlated data from repeated measurements in the same individuals, either in time or space. There are contexts where it is not possible to use classical linear models for the analysis of variances, because when performing measurements repeated over time in the same experimental units, the assumptions of independence, normality, homoscedasticity and linearity required for their use are ignored.

The transformations of scale of the data, constitutes an alternative to achieve the fulfillment of the premises of the parametric analysis; however, although they improve the adjustment of the variable, they do not always achieve compliance with them. This situation limits the application of classical models, so it is necessary to determine which analytical strategy is most appropriate. If repeated measures in an individual belong to different correlated characteristics, then multivariate

analyses, such as MANOVA, are used. If the repeated evaluations are of the same characteristic or levels within one of the sources of variation, they are sometimes assumed incorrectly, with normal distribution and analyzed by means of an ANOVA, identifying the individuals and the evaluative moment. However, the correct thing is not to suppose normality and obtain greater efficiency by means of generalized estimation equations (2).

Most of the genetic tests used in plant breeding include fixed factors (controllable by the researcher), as well as random factors that vary in their nature in the selection environments during the stages of the improvement program (3). These limitations have contributed to the emergence of mixed models, such as generalized linear models (GLM, Generalized Linear Models), and provide variations to the traditional linear model (LM, Linear Model), allowing it to be applied to a wider range of data.

On the other hand, generally the data that are collected in the agricultural investigations do not satisfy the premises of the general linear models; therefore, the mixed generalized linear models provide a way of analysis that does not necessarily require normal distribution of the variables, enabling them to be adjusted to an exponential family distribution (4).

Based on this background and considering the importance of these methods at present, the objective of this review is to present the applications of mixed generalized linear models in breeding programs.

Classification

The types of models currently available can be grouped by the type of the response variable or dependent variable, which can be distributed according to a normal distribution (General Linear Model) or another type (Generalized Linear Models) (Table 1).

THE LINEAR MIXED MODELS

The mixed model analyzes are applied particularly to investigations involving factors with few levels, which can be controlled by researchers (fixed); as well as factors with levels that are beyond the control of the researcher (random) (3).

Mixed linear models are a generalization of general linear models and are used when (5):

The effects are random: where the set of values of a categorical predictor variable are seen not as the complete set, but as a random sample of all values

Hierarchical effects: where predictor variables are measured at more than one level.

Repeated measures: where observations are correlated independently.

The general form of a mixed linear model is:

$$Y = Xb + Zu + e$$

where:

Y is the response vector (data), **X** and **Z** are known design matrices, **b** is a vector of fixed parameters, **u** (random effects) and **e** (error) are unobservable random vectors. The mathematical expectations of **u** and **e** are assumed equal to zero (6).

Table 1. Types of models depending on the type of variable, characteristics and procedure to be used with the SAS program

Type of model	Characteristics	PROC-SAS
Modelos Lineales Generales (GLM, <i>General Linear Models</i>)	Fixed effects Normal distribution. Estimation by Least Squares (LS) Continuous dependent variable Continuous or discrete independent variable	ANOVA, ANACOVA, Regression analysis, MANOVA
Modelos Lineales Generales Mixtos (<i>General Linear Mixed Models</i>)	Fixed and random effects Normal distribution. Estimation by maximum likelihood (MV), REML, MIVQUEO (for its acronym in English) Does not require a linkage function Continuous dependent variable Continuous or discrete independent variable	MIXED-SAS: supports correlated data and inconstant variability. HPMIXED-SAS
Modelos Lineales Generalizados Mixtos (GLMM, <i>Generalized Linear Mixed Models</i>)	Exponential family distributions Least-squares estimation of fixed and random effects Requires a non-linear linkage function Continuous or discrete dependent variable Continuous or discrete independent variable	GENMOD: fixed effects GLIMMIX: fixed and random effects. Supports correlated, variability, inconstant, unbalanced or incomplete data

The algorithm of the mixed models allows calculating the best non-biased linear estimator (BLUE, *Best Linear Non-biased Estimate*) of fixed effects and the best non-biased linear predictor (BLUP, *Best Linear Non-biased Predictor*) of the random effects. The BLUP represents the conditional expectation of the random effects given to the observed data, and it is also a Bayesian estimator. The BLUP of a linear combination of fixed and random effects is the linear combination of the fixed-effect BLUE and the random-effects BLUP (7).

Theoretically, the BLUPs have the least mean squares of the prediction error among all the linear non-biased predictors, providing the assumed model and that the parameters of the model are known (8). For the estimation of genetic parameters, the geneticists resorted to maximum likelihood (ML - *Maximum Likelihood*) and assumed normality in the experimental data. To provide a solution to the bias of the maximum likelihood estimator of the residual variance, the method known as "Restricted" (REML, Maximum Likelihood) was proposed (9).

The methodology of mixed models allows to correctly and efficiently analyze the data of experiments with repeated measures by modeling the covariance structure, which considers the correlations between repeated measures and the presence of heterogeneous variances. Not considering the correlation between subjects with the use of fixed effects or mixed models with very simple covariance structures, could cause the type I error rate to increase for the fixed effects test of the model. However, a very complicated model would affect the power and efficiency of the test for fixed effects (10).

APPLICATIONS OF MIXED LINEAR MODELS

The application of mixed models in breeding programs in plants has been focused in three directions (11):

- ◆ Predicting family behavior
- ◆ The estimation of variance components
- ◆ Multi-environment tests

PREDICTION OF FAMILY BEHAVIOR

The mixed models based on prediction (BLUP) have been used in different plant species such as: soybean (12), corn (13), kiwi (14), potato (15), cane (16); with the objective of selecting individuals and families that present the characteristics desired by the researcher, to be recommended in future research.

There is evidence to show that a combination of family and individual selection is more effective than a single family selection (17). The selection of individuals within each family goes through a process of visual evaluation, which leads to it being more difficult to obtain it at the individual level (18,19). The use of the simulated individual BLUP methodology (BLUPIS, *BLUP individual simulated*) allows indicating a number of individuals to be selected visually by family, total number of clones or number of families to contribute with selected individuals (20).

In order to determine the number of individuals selected per family in sugarcane (16), the best non-biased predictors

at the individual level (BLUPIS) were estimated. These authors considered in their experiment as fixed effects, the experimental effects, which include the general average and as random effects the additive effects of the genotype of the individuals, the specific capacity of combination and the effect of the blocks. From the analysis of the results, they determined that the families that were formed by group two were those that should be recommended in the cane improvement program in Brazil, for having varieties optimally adapted to Brazilian savanna conditions.

Similarly, in another study they used the methodology of mixed models to predict the genotypic effects of each family and the genotypic values of each individual within each family (21).

These authors considered in their mixed model, the general average, as fixed effects and the genotypic effect of each family, as random. The optimal number of genotypes was selected in the best families, obtaining a high efficiency of the BLUPIS method.

ESTIMATION OF VARIANCE COMPONENTS

The amount of genotype variation is measured and expressed by the variance. The phenotypic variance is broken down into genetic variance and environmental variance. In turn, the genetic variance is decomposed into additive variance, dominance and epistatic interaction (22). The partition of the variance into components allows estimating the relative importance of the phenotype determinants, in particular, the role of inheritance in relation to the environment.

The REML/BLUP method of mixed models allows estimating genetic parameters, BLUP and

predicting additive and genotypic genetic values (23). These authors selected the best sugar cane families for agroindustrial characters, based on the genetic values and additives obtained by this methodology. They also obtained high values of heritability for family selection and low and medium values for individual selection.

Other authors, using the REM/BLUP methodology, determined the families that had the expected production characteristics and the best individuals for each of them (24).

MULTI-ENVIRONMENT TESTS

The differential response of a given genotype or cultivar through different environments is known as Genotype-Environment Interaction (IGA, according its acronyms in Spanish) (GEI, Genotype-Environment Interaction).

The most important traits of cash crops are controlled by polygenes with various types of genetic effects that are affected by the environment. The use of the multiplicative operator to model the genotype x environment interaction has been proposed by several researchers (25-29).

Mixed linear-bilinear models are useful for modeling the genotype-environment interaction and estimating the variance-covariance matrices (30). A linear-bilinear model of mixed effect for G genotypes, S sites and R replicas is:

$$Y = Xb + Zr + Zg + Zge + e$$

Where: **X**, **Zr**, **Zg** and **Zge** are the design matrices for fixed effects, for random effects replicated within sites, genotypes, and interaction, respectively, and **e** is the waste vector. The vector **b** denotes the fixed effects of the sites, and the

vectors **r**, **g**, **ge** and **e** contain random effects of repetitions within the sites, genotypes, interaction and residues, respectively, and are assumed to be random and normally distributed with mean null vectors and variance-covariance matrices R, G, GE and E, respectively. These variance-covariance matrices have a simple structure of variance component (30).

The mixed regular ANOVA assumes that all terms of the genotype-environment interaction have the same variance and are independent; although some authors have used a mixed model that involves the diagonal of the G matrix with heterogeneous variances (by genotype) for the random terms of the interaction (31). Therefore, the model assumes that all the genotype-environment terms that involve a particular genotype have the same genotype-environment variance, and the genotype-environment variance components, such as the number of genotypes, will be as different. The REML variance components, assignable to each genotype, estimate the same parameters as the Shukla stability variance (32).

The author compared the biplots obtained when placed on the m-th axis λ_{mj} , as genotypic values, in each multiplicative term, and the m-th element of the scaling EBLUP (x_i) as the value for the i-th environment, against the biplot traditional obtained from a fixed model (11). The biplots under both approaches were obtained for several complete files of variety trials. The different procedures to obtain the biplots in both approaches showed the same pattern of iteration. Data from field experiments of cane plants, from 2007 to 2009 (33) were

used to compare the prediction accuracy of several mixed models against the fixed models approach. Regular field trials involved 20 genotypes per trial. Each year, the experiments were conducted in several commercial farms (6). The experiment was conducted according to a design of completely randomized blocks with three replicas. The theoretical framework of the mixed linear models provided the possibility of a better adjustment of the data with respect to that which would have been obtained under the classical assumptions of variance homogeneity through tests and temporal and spatial independence of the observations, providing a smaller error standard for comparisons of means and, therefore, greater efficiency in the experiment. The change of model allowed to detect statistically significant differences between genotypes, not evidenced by the classical model, as well as to produce alterations in the relative position of hierarchy of their performances, which led to changes in the interpretation of the analyzed data. When evaluating the execution of genotypes in the presence of a small magnitude of genotype-environment variation under a fixed-model approach (with or without genotype-environment terms), a type-I error inflation could be expected (34).

In another study, a comparison of efficiency was made between the Eberhart-Russel (ER) methods, Principal Additive and Multiplicative Interaction Models (AMMI) and the mixed model (REML/BLUP) (35). These authors demonstrated that the mixed model has more sensitivity in the detection of the effects caused by the genotype-environment interaction than the other methods compared.

THE MIXED GENERALIZED LINEAR MODELS (GLMM)

The GLMs, most used nowadays are the Generalized Linear Models Mixed (GLMMs, Generalized Linear Mixed Models) that allow that the average of a population depends on a linear predictor through a function of link (link function) of non-linear type and that the probabilistic distribution of the response variable is any of the exponential family (Table II). In this way, the explanatory variables can be any combination of continuous variables, classification variables and their interactions. The estimation of parameters in these models is done through maximum likelihood procedures (36).

The Generalized Mixed Linear Models (GLMM, *Generalized, Linear Mixed Models*) offer new possibilities in these cases, since they make it possible to extend the classical linear models of fixed

effects, by including random effects and predictors BLUPs, for the analysis of data with distributions of the exponential family. In addition, they allow to process correlated data when using random effects and to estimate their components of variance associated with the model, in addition to the residual error. The estimation procedures used make it possible to reduce biases when the data are incomplete, unbalanced or to adjust dispersed data and also allow modeling the structure of errors in data from longitudinal measurements (37).

There are commercial and free programs such as: the GLIMMIX and GENMOD procedures of the SAS package and the lme4 of the R package that make possible the use of Mixed Generalized Linear Models (GLMMs) for most of the current applications in plant genetics. However, the mass of data from the molecular level and historical phenotypic information means that we are working on the development of tools capable of processing models with thousands of levels of fixed and random effects (38, 39).

Successful variants have been achieved that reduce the run time required for data of Poisson, Binomial and Conditional Gamma distributions by more than 90 % (40).

Table 2. Linking functions of the most widely used Generalized Linear Models (GLM) when using the SAS package

Models	Variable response	Distribution of the response variable	Link function SAS/Stat®9.1.)
Linear model traditional (LM)	Continue	Normal	Identity: $g(\mu) = \mu$
Logistic regression	Proportion	Binomial	Logit: $g(\mu) = \log(\mu/1-\mu)$
Poisson regression in linear Log model	Count	Poisson	Log: $g(\mu) = \log(\mu)$
Gamma model with Log link	Continuous positive	Gamma	Log: $g(\mu) = \log(\mu)$

CONCLUSIONS

Mixed models have been widely used in plant genetics studies, and generalized mixed models have allowed broadening the spectrum of work with those variables that by their nature do not conform to a normal distribution and their data are correlated. At present, its use requires highly complex computer programs, but they have great advantages over classical methods, since their estimation procedures reduce biases when data are incomplete, unbalanced or adjust dispersed data.

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