

SuperMix

MIXED EFFECTS MODELS



SuperMix.

User's Guide

Version 1.0

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SuperMix Preface



Preface

SuperMix combines the functionality of four mixed-effects programs, MIXREG, MIXOR, MIXNO, and MIXPREG, into a single application to provide estimates for mixed-effects regression models. These models can be used for the analysis of unbalanced longitudinal data, where each individual may be measured at a different number of occasions, even at different timepoints. They can also be used for clustered data, where the mixed-effects model does not assume that each observation is independent, but does assume that data within clusters are dependent to some degree.

SuperMix uses a maximum marginal likelihood solution, based on a Fisher-scoring algorithm for continuous, ordinal, and nominal data; and a Newton-Raphson iterative solution for count data.

SuperMix also features data management capabilities and, in the PRO version, graphical output.

How to use this manual

(body text)

Exploring the SuperMix work area

(body text)

Getting Started

System requirements

To run SuperMix you must have certain hardware and software installed on your computer. The minimum requirements are:

- Windows 95, 98, Me, NT 4.0(SP4), 2000, or XP.
- 30 Mb of available hard disk space.
- VGA 256-color display or better.
- A CD-ROM drive.
- A Windows compatible printer to print results. SuperMix supports both color and monochrome printers.

Installation

SuperMix is installed on your computer using the program SETUP.EXE. If you are installing a software upgrade, it is important that you install SuperMix in the same directory as your original installation. In most cases, this is probably the SuperMix directory in C:\Program Files. However, if you had chosen to install your previous version of SuperMix elsewhere, make note of its location on your hard drive before you begin installing the new version.

The installation program will attempt to find a previously installed version of SuperMix, but if it is unsuccessful you must specify the location of your existing copy. It is not necessary to remove the previous version of SuperMix; the installation program will automatically replace the required files without altering any of your data.

Windows NT, 2000, and XP users

The SuperMix installation program must work with system files that are only accessible to users with administrator rights. If your account does not have administrator access rights, you will be warned of this and the installation program will not proceed. To

gain administrator rights, you can either log on to the Administrator account (if you have the password) or ask for assistance from your computer support technician.

To install SuperMix:

1. Close all currently running Windows applications.
2. If the installation process does not begin automatically, locate and run SETUP.EXE from the root directory of your computer's CD drive.
3. Follow the prompts.

Quick tour

(body text)

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I - SuperMix Primer



Linear mixed-effects modeling: an applied introduction

Introduction

- ▶ History of mixed-effects modeling
- ▶ Different names used to describe mixed-effects models
- ▶ Review of standard ordinary least squares (OLS).
- ▶ Interpretation of intercept and slope parameters.
- ▶ Graphical display of regression lines for different groups

Sample survey methods

- ▶ Clustered data
- ▶ Longitudinal data
- ▶ Consequence of violating independence assumptions in OLS regression models

Mixed-effects modeling

- ▶ What is a multilevel analysis
- ▶ Why do a multilevel analysis
- ▶ The goals of mixed-effects modeling
 - ▶ Estimation of correct standard errors
 - ▶ Parsimony in number of parameters to be estimated

A random-effects model for clustered data

- ▶ The within-clusters model
- ▶ The between-clusters model
- ▶ Distributional assumptions
- ▶ Interpretation of model parameters
- ▶ The intra-class correlation coefficient
- ▶ Illustrative example
 - ▶ Background and description of data
 - ▶ Graphical display and interpretation of regression lines
 - ▶ Discussion of results

Mixed-effects modeling of longitudinal data

- ▶ Advantages of mixed-effects models over repeated measures MANOVA
- ▶ Random-effects growth modeling
- ▶ Unconditional growth models
 - ▶ Fixed and random effects
 - ▶ Linear and nonlinear trajectories
- ▶ Conditional growth models
 - ▶ A single predictor of growth
 - ▶ Two or more predictors of growth
- ▶ Conditional growth models with time-varying covariates
- ▶ Illustrative example
 - ▶ Background and description of data
 - ▶ Graphical display of growth trajectories
 - ▶ Discussion and interpretation of results

Special topics

- ▶ Group- and grand-mean centering
 - ▶ When to use centering
 - ▶ Interpretation of model parameters

- Empirical Bayes estimates of regression coefficients
 - What is an empirical Bayes estimate
 - Empirical Bayes estimates of subject trends
 - Confidence intervals
 - Illustrative example
- Standard errors and fit statistics
- Handling of missing data and case weights
- Extensions to 3-level models

Mixed-effects modeling for categorical outcome variables: an applied introduction

Introduction

- Types of categorical variables considered
- Dichotomous outcomes: logistic regression
- Ordinal outcomes: proportional odds and partial odds models
- Nominal outcomes: nominal logistic regression

Definition and use of link functions

- Logit link function
- Cumulative logit link function
- Probit link function
- Complementary log-log link function

Basic models

- Random intercept logistic model
- Random intercept and trend model
- Mixed-effects representation of basic models

Basic concepts

- Meaning and interpretation of observed and fitted proportions
- Meaning and interpretation of observed and fitted odds
- Meaning and interpretation of observed and fitted log odds
- Meaning and interpretation of observed and fitted logits
- Model fit of observed marginal proportions

Illustrative example: Dichotomous logistic regression

- Background and description of data
- Graphical displays
- Discussion and interpretation of results

Illustrative example: Nominal logistic regression

- Background and description of data
- Graphical displays
- Discussion and interpretation of results

Illustrative example: Partial odds model for an ordinal outcome variable

- Background and description of data
- Graphical displays
- Discussion and interpretation of results

II - SuperMix Program



Working with SuperMix

Steps needed to get underway:

1. Import data.
2. Set the model definitions correctly.
3. Run the analysis.

SuperMix models

Dependent variable form:

- ▶ Continuous
- ▶ Ordered
- ▶ Nominal
- ▶ Count

Continuous

Continuous data

Data that is ordered with a constant scale, with or without a natural zero.

MIXREG is a program which provides estimates for a mixed-effects regression model (MRM) including autocorrelated errors. This model can be used for the analysis of unbalanced longitudinal data, where each individual may be measured at a different number of occasions, even at different timepoints. Autocorrelated errors of a general form or following an AR(1), MA(1), or ARMA(1) are allowable.

This model can also be used for the analysis of clustered data, where the mixed-effects model does not assume that each

observation is independent, but does assume that data within clusters are dependent to some degree. The degree of this dependency is estimated along with estimates of the usual model parameters, thus adjusting these effects for the dependency resulting from the clustering of the data.

This model uses a maximum marginal likelihood estimation, utilizing both the EM algorithm and a Fisher-scoring solution. For the scoring solution, the covariance matrix of the random effects is expressed in its Gaussian decomposition, and the diagonal matrix reparameterized using the exponential transformation. Estimation of the individual random effects is accomplished using an empirical Bayes approach.

Ordered

Ordinal data

Data that follows some order or continuum, but whose values are generally arbitrary. Ex. degree of toxicity on a scale of 1 to 5.

MIXOR is a program that provides estimates for mixed-effects ordinal (and binary) regression models. This model can be used for the analysis of clustered or longitudinal (i.e., 2-level) outcome data. Several response functions are available:

- probit
- logistic
- log-log
- complementary log-log

For clustered data, the mixed-effects model does not assume that each observation is independent, but does assume that data within clusters are dependent to some degree. The degree of this dependency is estimated along with estimates of the usual model parameters, thus adjusting these effects for the dependency resulting from the clustering of the data. Similarly, for longitudinal data, the mixed-effects approach can allow for individual-varying intercepts and slopes across time, and can estimate the degree to which these time-related terms vary. Model covariates can be either time-varying or time-invariant.

MIXOR uses a maximum marginal likelihood solution, specifically implementing a Fisher-scoring algorithm; as a result, standard errors are provided for all model terms. Numerical integration is used to integrate over the distribution of random effects. At present, two possibilities are possible for the random-effects distribution, namely normal distribution and uniform distribution.

For models with one random effect specified or scalar random effect multiplication, the program produces empirical Bayes estimates of the random effects for each level-2 unit. These can be found in the file MIXOR.RES after running the program. The information in MIXOR.RES is, in order:

- level-2 ID
- number of level-1 observations
- empirical Bayes estimate (the mean of the posterior distribution)
- precision associated with the empirical Bayes estimate (the standard deviation of the posterior distribution)

Also, for all analyses, two additional files are produced upon program completion. MIXOR.EST which contains all parameter estimates, and MIXOR.VAR which contains the asymptotic variance-covariance matrix of the parameter estimates.

For basic MIXOR usage, as described in the manual published in *Computer Methods and Programs in Biomedicine* (1996), vol 49:157-176, the user only needs to select options on the first four index cards, Configuration, Variables, Starting Values, and Missing Values. Simply leave the Advanced index card with its default values.

Several new features have been implemented on the Advanced index card:

- Estimation of partial-proportional odds models
- Allowing for right-censoring of the ordinal outcome

- Allowing for different types of random-effect variance structure
- Allowing the random-effect variance structure to vary by level-2 or level-1 covariates.

Nominal

Nominal data

Unordered categorical data.
Ex. Brand A and Brand B.

MIXNO provides maximum marginal likelihood estimates for mixed-effects nominal logistic regression analysis. These models can be used for the analysis of correlated nominal response data, for example, data arising from a clustered design. For clustered data, the mixed-effects model assumes the data within clusters are dependent. The degree of dependency is jointly estimated with the usual model parameters, thus adjusting for dependence resulting from clustering of the data. MIXNO uses marginal maximum likelihood estimation, utilizing a Fischer-scoring solution. For the scoring solution, the Cholesky factor of the random-effects variance-covariance matrix is estimated, along with the effects of the model covariates.

Count

Count data

Data that describes independent occurrences.
Eg: number of hospitalization instances.

MIXPREG provides maximum marginal likelihood estimates for mixed-effects Poisson regression analysis. These models can be used for the analysis of correlated count data, for example, data arising from a clustered design. The degree of dependency is jointly estimated with the usual model parameters, thus adjusting for dependence resulting from clustering of the data. A Newton-Raphson iterative solution is used in the marginal maximum likelihood estimations. Specifically, the Cholesky factor of the random-effects variance-covariance matrix is estimated, along with the effects of the model covariates.

Defining a model

Model setups are defined using the following tabs:

- Configuration

- ▶ Variables
- ▶ Starting Values
- ▶ Missing Values
- ▶ Advanced

The SuperMix graphical interface

Before you can run an analysis, you must supply a data source for the model. SuperMix allows you to perform analyses from data residing in a spreadsheet. When setting up a new spreadsheet, you may either enter your data directly, or import an existing data file.

Creating SuperMix spreadsheets

SuperMix performs its analyses on data contained in a spreadsheet. When setting up a new spreadsheet, you may either enter your data directly, or import an existing data file.

To create a new SuperMix spreadsheet:

1. Select File > New. A blank sheet will appear.
2. Copy and paste or type your data into the sheet.

To open a SuperMix spreadsheet:

1. Select File > Open.
2. Locate the file in the directory structure. If necessary change the selection in the 'Files of Type' drop menu.
3. Click on Open.

Importing data files

You may import Excel spreadsheets or other data files for use in SuperMix. SuperMix will accept fixed-column and delimited file formats.

To import an Excel file:

1. Select File > Import Data File.
2. Locate the file in the directory structure.
3. Click on Open.
4. In the next window, select the worksheet name you wish to import. SuperMix can import single worksheets only.
5. Click on OK.

OR

Click on Cancel if you wish to stop the import.

To import a data file:

1. Select File > Import Data File.
2. Select 'All files' in the 'Files of Type' drop menu. Locate the file in the directory structure.
3. Click on Open.
4. In the next window, choose the correct data format: Fixed Column or Delimited.
5. If you have selected Delimited, choose the appropriate delimiter from the drop down menu.
6. Click on OK.

OR

Click on Cancel if you wish to stop the import.

If you are unsure whether your data file is Fixed Column or Delimited, open it in a text editor such as Notepad. Notice how the data appears-is it in obvious columns or in a big mass? Data that is not in obvious columns must be delimited. Note the character separating each record-this is the Delimiter.

Fixed column data

Data in which each column has a certain width.

Delimited data

Data whose values are separated by tabs, spaces, commas, or other characters.

Tip

You may resize the spreadsheet by clicking and dragging the edges or corners. Or, click in the upper righthand corner to maximize the window.

Saving SuperMix spreadsheets

To save a new SuperMix spreadsheet:

1. In an open spreadsheet, choose File > Save As.
2. In the Save As window, select the folder where you wish to save the spreadsheet.
3. In the File Name box, enter a name for the spreadsheet. Ensure that 'Save as type: Spread Sheets (.SS3)' is selected underneath.
4. Click on Save.

If you choose File > Save with an newly-created spreadsheet open, SuperMix will ask you to name the spreadsheet before saving.

To save an existing SuperMix spreadsheet:

With an open spreadsheet, choose File > Save.

To close a spreadsheet:

Choose File > Close. SuperMix will remain open.

To close all open files and exit SuperMix:

Choose File > Exit.

If you have not saved your open file(s), SuperMix will ask whether you wish to save your changes before exiting.

Editing spreadsheets

Editing cells and cell contents

To edit cell contents:

1. Double-click the cell that contains the data you want to edit.
2. Make any changes to the cell contents.
3. To keep your changes, press ENTER. To cancel your changes, press ESC.

OR

1. Click on the cell that contains the data you want to edit.
2. Enter the changes in the text box above the spreadsheet.

To delete the contents of a cell:

When deleting a cell's contents, you may choose to delete the data in the cell, the formula applied to the cell, or both.

1. Select the cell.
2. Choose Edit > Clear **OR** right-click and choose Clear.
3. Choose Clear Cell to delete data and formulas.
OR Clear Data to delete the value in the cell while leaving the formula intact.
OR Clear Formula to delete the formula for that cell.

Tip

You may use the DELETE key to delete the contents of a cell. Select the cell(s) and press DELETE.

Inserting and deleting cells

To delete a cell:

1. Select the cell or range of cells.
2. Choose Edit > Delete Cell (shift up or left).
3. Choose Shift Up or Shift Left.
Shift Up causes all cells below the deleted cell(s) to shift upwards to fill the space. Shift Left causes all cells to the right of the deleted cell(s) to shift to the left to fill the space.

To insert a cell:

1. Select a cell or range of cells. Select the same number of cells as you wish to insert.
2. Choose Edit > Insert Cell (shift down or right).
3. Choose Shift Down or Shift Right.
Shift Down causes all cells below the inserted cell(s) to shift downwards to accommodate the new cell(s). Shift Right

causes all cells to the right of the inserted cell(s) to shift to the right to accommodate the new cell(s).

To move the contents of a cell to another cell:

When moving a cell's contents to another cell, you may choose to move only the value displayed in the cell, or the value and the formula that generated it (if you are using formulas).

To move the value only:

1. Select the cell.
2. Choose Edit > Cut
OR right-click and choose Cut
OR type Ctrl + X.
3. Click on the target cell and choose Edit > Paste (value only)
OR right-click and choose Paste (value only)
OR type Ctrl + V.

To move the value and formula of a cell:

1. Select the cell.
2. Choose Edit > Cut
OR right-click and choose Cut
OR type Ctrl + X.
3. Click on the target cell and choose Edit > Paste (with formula)
OR right-click and choose Paste (with formula)
OR type SHIFT + Ctrl + V.

Note that the content in the original cell will not be removed until you paste it elsewhere.

Controlling the number of decimal places shown

SuperMix controls the number of decimal places displayed in the data. You may set this number with Edit > Set Decimal Place.

You may have more than one decimal place setting in a single spreadsheet.

To change the number of decimal places shown:

1. Select the cell or group of cells.
2. Choose Edit > Set Decimal Place
OR
Right-click and choose Set Decimal Place.
3. Enter the number of places you would like. The default value for this setting is 2.

Please note:

- ▶ If data is entered with more decimal places than specified for that cell, the number will be truncated. If the number of decimal places is later increased, then zeros will be appended to the values.
- ▶ Once a number is entered, its precision will be maintained even if the number of decimal places is later reduced.
- ▶ Setting more decimal places than the data has will result in trailing zeros.

Editing column headers

To edit a column header:

1. Select the column whose heading you wish to change.
 2. Choose Edit > Change Header.
 3. Enter the text you wish to use for the header.
 4. Click on OK.
- OR**
1. Right-click in the column header.
 2. Choose Change Header from the popup menu.
 3. Enter the text you wish to use for the header.
 4. Click on OK.

Adjusting the size of columns and rows

Tip

To adjust the width of several columns at once, select multiple columns and drag the right edge of the rightmost column.

Tip

To adjust the height of several rows at once, select multiple rows and drag the lower edge of the bottom row.

To adjust column width:

1. Select the entire column by clicking in the column header.
2. Place the cursor at the header column edge. The cursor will change to a horizontal arrow with two vertical bars.
3. Drag the column edge to the desired width.

To adjust row height:

1. Select the entire row by clicking on the row number at the left.
2. Place the cursor on the bottom edge of the row. The cursor will change to a vertical arrow with two horizontal bars.
3. Drag the row edge to the desired height.

Inserting and deleting columns and rows

To insert a column:

1. Select a column.
2. Choose Edit > Insert Column. A blank column will be inserted to the left of your selected column.

To delete a column:

1. Select the column or range of columns.
2. Choose Edit > Delete Column. Columns to the right of the deleted column(s) will be shifted to the left.

To insert a row:

1. Select a row.
2. Choose Edit > Insert Row. A blank row will be inserted above your selected row.

To delete a row:

1. Select the row or range of rows.
2. Choose Edit > Delete Row. Rows below the deleted row(s) will be shifted up.

Using formulas

A formula is an equation that performs operations on spreadsheet data. SuperMix allows the use of formulas provided they are in the right format.

Formulas can be made up of numerous functions and operators, as well as literal numbers and/or cell references.

Example: `NEG(SUM(E4:E10)*(B1+36))`

SuperMix formula operators and functions

The following operators may be used in formulas:

- + (addition)
- - (subtraction)
- ^ (exponentiation)
- * (multiplication)
- / (division)
- : (creates a range)
- # (wild card)

The following functions may be used in formulas.

Function	Definition
ABS(value)	Absolute value
ADD(value1, value2)	Addition
AVERAGE(value1, value2...)	Average
CEILING(value1, value2)	Ceiling
COMBIN(value1, value2)	Combination
EVEN(value)	Even
EXP(value)	Exponent base e
FLOOR(value1, value2)	Floor
IF(value1, value2, value3)	Comparison
INT(value)	Integer
INVERSE(value)	Inverse of the specified value
LN(value)	Natural log
LOG(value1, value2)	Logarithm
LOG10(value)	Base 10 logarithm
MAX(value1, value2)	Maximum value
MEDIAN(value1, value2...)	Median
MIN(value1, value2...)	Minimum value
MODE(value1, value2...)	Mode
NEG(value)	Negative value

ODD(value)	Odd integer
POWER(value1, value2)	Raises number to a power
PRODUCT(value1, value2...)	Product
RAND ()	Random number
RANK(Number, Ref, Order)	Ranks values
ROUND(value1, value2)	Round
ROUNDUP(value1, value2)	Round up
SIGN(value)	Sign of a number
SQRT(value)	Square root
SQUARE(value)	Square
STDEV(value1, value2...)	Standard deviation
STDEVP(value1, value2...)	Standard deviation for population
SUM(value1, value2...)	Summation
SUMSQ(value1, value2...)	Sum of the squares
VAR(value1, value2...)	Variance
VARP(value1, value2...)	Variance of population
XROOT(value1, value2...)	Root Y of value X

About cell references

Relative references

When you create a formula, references to cells or ranges are usually based on their position relative to the cell that contains the formula. This is known as a **relative** reference. When you copy a formula that uses relative references, SuperMix automatically adjusts the references in the pasted formula to refer to different cells relative to the position of the formula.

If you move or copy a formula, and the cells relative to the position of the formula are empty in the new location, the cell containing the formula will be empty as well.

Absolute references

If you don't want SuperMix to adjust references when you copy a formula to a different cell, use an **absolute** reference. For example, if your formula multiplies cell A5 with cell C1 (`=A5*C1`) and you copy the formula to another cell, SuperMix will adjust both references. You can create an absolute reference to cell C1 by placing a **dollar sign** (\$) before the parts of the reference that do not change. To create an absolute reference to cell C1, for example, add dollar signs to the formula as follows:

```
=A5*$C$1
```


III - SuperMix Examples



Practical applications and level-2 models with continuous outcome variables

Example 1: Description

Example 2: Description

Practical applications: level-2 models with categorical outcome variables

Example 1: Description

Example 2: Description

Practical applications and level-3 models with continuous outcome variables

Example 1: Description

Example 2: Description

Practical applications: level-3 models with categorical outcome variables

Example 1: Description

Example 2: Description

IV - SuperMix Syntax



Summary of Syntax

References

SuperMix

MIXED EFFECTS MODELS



Donald Hedeker



Robert D. Gibbons

This manual describes the programs for mixed-effects models, (also called multilevel, hierarchical, and random-effects models) developed by Don Hedeker and Robert Gibbons. These programs have been updated and merged into a single program.

- ◆ Easy to use graphical user interface: import data into the SuperMix spreadsheet, then build new models using menus and dialog boxes.
- ◆ Mixed-effects models for continuous outcome variables with auto-correlated residuals.
- ◆ Mixed-effects models for ordinal regression analysis, including non-proportional odds models and scaling effects.
- ◆ Mixed-effects models for Poisson regression analysis.
- ◆ Mixed-effects models for nominal logistic regression analysis.
- ◆ Mixed-effects models for grouped-time survival analysis.
- ◆ Accepts old definition files created by MIXREG, MIXOR, MIXNO, and MIXPREG.
- ◆ Two- and three-level models allowing for nested designs.
- ◆ Presentation quality graphics.

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