

1. The general linear mixed model and the linear mixed model hypothesis

It is common to define the general linear mixed model as a statement about only the observations for independent sampling unit $i \in \{1, \dots, N\}$ (Muller and Stewart, 2006, section 6.7). Let p_i be the number of outcomes for independent sampling unit i , and let $j \in \{1, 2, \dots, p_i\}$ index outcomes. For example, if there are 6 repeated measures of BMI for a person in the study, we would have $p_i = 6$. Let y_{ij} indicate the j^{th} outcome (dependent) variable for independent sampling unit i . For independent sampling unit i , define the $(p_i \times 1)$ vector of outcomes by \mathbf{y}_i , where

$$\mathbf{y}_i = \begin{bmatrix} y_{i1} \\ y_{i2} \\ \vdots \\ y_{ip_i} \end{bmatrix}. \quad (1)$$

Here, we define the total number of outcome observations by

$$n = \sum_{i=1}^N p_i. \quad (2)$$

The mixed model includes fixed-effect predictors \mathbf{X}_i (fixed and known) and random-effect predictors \mathbf{Z}_i (fixed and known):

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{d}_i + \mathbf{e}_i. \quad (3)$$

Here $\boldsymbol{\beta}$ contains unknown fixed-effect parameters which represent slopes and intercepts, \mathbf{X}_i includes intercepts and predictors, \mathbf{Z}_i is the participant-specific matrix of random effects, \mathbf{d}_i is the participant specific matrix of random slopes and intercepts, and \mathbf{e}_i is the participant-specific matrix of errors. By assumption, both \mathbf{d}_i and \mathbf{e}_i are independently normally distributed, with mean zero. The distributions are

$$\begin{bmatrix} \mathbf{d}_i \\ \mathbf{e}_i \end{bmatrix} \sim \mathcal{N}_{r+p_i} \left(\begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \begin{bmatrix} \boldsymbol{\Sigma}_d & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\Sigma}_{e_i} \end{bmatrix} \right), \quad (4)$$

which implies $E(\mathbf{y}_i) = \mathbf{X}_i \boldsymbol{\beta}$ and $\mathcal{V}(\mathbf{y}_i) = \boldsymbol{\Sigma}_i = \mathbf{Z}_i \boldsymbol{\Sigma}_d \mathbf{Z}_i' + \boldsymbol{\Sigma}_{e_i}$.

For the entire study sample, construct stacked matrices, so that

$$\mathbf{y} = \begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \\ \vdots \\ \mathbf{y}_N \end{bmatrix}, \quad (5)$$

$$\mathbf{X} = \begin{bmatrix} \mathbf{X}_1 \\ \mathbf{X}_2 \\ \vdots \\ \mathbf{X}_N \end{bmatrix}, \quad (6)$$

$$\mathbf{Z} = \begin{bmatrix} \mathbf{Z}_1 \\ \mathbf{Z}_2 \\ \vdots \\ \mathbf{Z}_N \end{bmatrix}, \quad (7)$$

$$\mathbf{d} = \begin{bmatrix} \mathbf{d}_1 \\ \mathbf{d}_2 \\ \vdots \\ \mathbf{d}_N \end{bmatrix}, \quad (8)$$

and

$$\mathbf{e} = \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \\ \vdots \\ \mathbf{e}_N \end{bmatrix}, \quad (9)$$

The general linear mixed model is given by

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{d} + \mathbf{e}. \quad (10)$$

A general linear mixed model hypothesis about fixed effects can be written in terms of $\boldsymbol{\theta} = \mathbf{C}\boldsymbol{\beta}$ as

$$H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0. \quad (11)$$

2. The three models: a simplified version

2.1 Definitions and notation

We start with thinking about the data for one participant in the study. The paired data for person i looks like this, where y_{ij} is the outcome for person i at time point j , and x_{ij} is the predictor for person i at time point j . To make the dataset labels short, write PID for participant ID, write \mathbf{y} for the outcome, \mathbf{a} for age in years, and \mathbf{x} for the predictor. For the purposes of this explanation, we assume four time points, and ignore covariates.

PID	\mathbf{y}	\mathbf{a}	\mathbf{x}
1	y_{i1}	1	x_{i1}
1	y_{i2}	2	x_{i2}
1	y_{i3}	3	x_{i3}
1	y_{i4}	4	x_{i4}

(12)

2.2 Fixed effect predictor matrix for the all-times-before model

The fixed effect predictor matrix for participant i is

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & x_{i1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & x_{i1} & x_{i2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & x_{i1} & x_{i2} & x_{i3} \end{bmatrix}, \quad (13)$$

with $\boldsymbol{\beta}$

$$\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \\ \beta_6 \\ \beta_7 \\ \beta_8 \\ \beta_9 \\ \beta_{10} \end{bmatrix}. \quad (14)$$

2.3 Fixed effect predictor matrix for the immediately-before model

The fixed effect predictor matrix for participant i is

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & x_{i1} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & x_{i2} & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & x_{i3} \end{bmatrix}. \quad (15)$$

The contrast matrix to test the difference between all-times-before model and the immediately before model is

$$\mathbf{C} = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}, \quad (16)$$

which tests

$$H_0 : \beta_5 = 0 \quad \beta_8 = 0 \quad \beta_9 = 0. \quad (17)$$

If these coefficients are zero, the all-times-before model reduces to the immediately-before model.

2.4 Fixed effect predictor matrix for the differential-sensitive-period model

The fixed effect predictor matrix for participant i is

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & x_{i1} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & x_{i1} & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & x_{i1} \end{bmatrix}. \quad (18)$$

The contrast matrix to test the difference between all-times-before model and the differential-sensitive period model is

$$\mathbf{C} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}, \quad (19)$$

which tests

$$H_0 : \beta_6 = 0 \quad \beta_9 = 0 \quad \beta_{10} = 0. \quad (20)$$

If these coefficients are zero, the all-times-before model reduces to the differential sensitive period model.

The fixed-effect predictor model for the differential sensitive period is as follows

$$\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \\ \beta_7 \\ \beta_8 \end{bmatrix}. \quad (21)$$

2.5 Fixed effect predictor matrix for the stable-sensitive-period model

The fixed effect predictor matrix for participant i is

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 \\ 1 & x_{i1} \\ 1 & x_{i1} \\ 1 & x_{i1} \end{bmatrix}. \quad (22)$$

The contrast matrix to test the difference between the differential-sensitive period model and the stable-sensitive period model is

$$\mathbf{C} = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & -1 \end{bmatrix}, \quad (23)$$

which tests

$$H_0 : \beta_5 - \beta_7 = 0 \quad \beta_5 - \beta_8 = 0 \quad (24)$$

If these hypotheses are true, the differential sensitive period model reduces to the stable sensitive period model.

3. Organizing the dataset for the models

3.1 Data set-up for all-times-before model

Reformat the data for person i so it looks like this, where x_j is the predictor value for the participant at age j .

PID	y	a	x	x_1	x_2	x_3	x_4
1	y_{i1}	1	x_{i1}	x_{i1}	x_{i2}	x_{i3}	x_{i4}
1	y_{i2}	2	x_{i2}	x_{i1}	x_{i2}	x_{i3}	x_{i4}
1	y_{i3}	3	x_{i3}	x_{i1}	x_{i2}	x_{i3}	x_{i4}
1	y_{i4}	4	x_{i4}	x_{i1}	x_{i2}	x_{i3}	x_{i4}

(25)

The goal is reformat the predictor matrix to define the all-times-before model. For this purpose, define indicator variables. Let

$$b_1 = \begin{cases} 0 & \text{age} \leq 1 \\ 1 & \text{otherwise} . \end{cases} \quad (26)$$

Let

$$b_2 = \begin{cases} 0 & \text{age} \leq 2 \\ 1 & \text{otherwise} . \end{cases} \quad (27)$$

In general, define

$$b_j = \begin{cases} 0 & \text{age} \leq j \\ 1 & \text{otherwise} . \end{cases} \quad (28)$$

We do not define an indicator variable b_4 , because we are getting set up for a model which uses only predictors measured before the outcome.

PID	y	a	x	b_1	b_2	b_3	b_4
1	y_{i1}	1	x_{i1}	0	0	0	0
1	y_{i2}	2	x_{i2}	1	0	0	0
1	y_{i3}	3	x_{i3}	1	1	0	0
1	y_{i4}	4	x_{i4}	1	1	1	0

(29)

Form $i_1 = b_1 * x_1$, $i_2 = b_2 * x_2$, and so forth.

PID	y	a	x	i_1	i_2	i_3
1	y_{i1}	1	x_{i1}	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	x_{i2}	0
1	y_{i4}	4	x_{i4}	x_{i1}	x_{i2}	x_{i3}

(30)

Define indicator variables for ages so that

$$a_j = \begin{cases} 1 & \text{age} = j \\ 0 & \text{otherwise} . \end{cases} \quad (31)$$

PID	y	a	x	$i1$	$i2$	$i3$	$a1$	$a2$	$a3$	$a4$
1	y_{i1}	1	x_{i1}	0	0	0	1	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	0	0	1	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	x_{i2}	0	0	0	1	0
1	y_{i4}	4	x_{i4}	x_{i1}	x_{i2}	x_{i3}	0	0	0	1

(32)

Form $h21 = a2*i1$, $h31 = a3*i1$, $h32 = a3*i2$, $h41 = a4*i1$, $h42 = a4*i2$, and $h43 = a4*i3$. The columns of the dataset have been re-sorted to show the sets of predictors for y_{i1} , y_{i2} and so on in order.

PID	y	a	x	$a1$	$a2$	$h21$	$a3$	$h31$	$h32$	$a4$	$h41$	$h42$	$h43$
1	y_{i1}	1	x_{i1}	1	0	0	0	0	0	0	0	0	0
1	y_{i2}	2	x_{i2}	0	1	x_{i1}	0	0	0	0	0	0	0
1	y_{i3}	3	x_{i3}	0	0	0	1	x_{i1}	x_{i2}	0	0	0	0
1	y_{i4}	4	x_{i4}	0	0	0	0	0	0	1	x_{i1}	x_{i2}	x_{i3}

(33)

The fixed effect predictor matrix for participant i is then

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & x_{i1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & x_{i1} & x_{i2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & x_{i1} & x_{i2} & x_{i3} & 0 \end{bmatrix} \quad (34)$$

3.2 Data set-up for immediately before model

Start with the data formatted as shown below.

PID	y	a	x	$i1$	$i2$	$i3$	$a1$	$a2$	$a3$	$a4$
1	y_{i1}	1	x_{i1}	0	0	0	1	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	0	0	1	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	x_{i2}	0	0	0	1	0
1	y_{i4}	4	x_{i4}	x_{i1}	x_{i2}	x_{i3}	0	0	0	1

(35)

Define variables $k21 = a2*i1$, $k32 = a2*i2$, $k42 = a4*i3$.

PID	y	a	x	$i1$	$i2$	$i3$	$a1$	$a2$	$a3$	$a4$	$k21$	$k32$	$k42$
1	y_{i1}	1	x_{i1}	0	0	0	1	0	0	0	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	0	0	1	0	0	x_{i1}	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	x_{i2}	0	0	0	1	0	0	x_{i2}	0
1	y_{i4}	4	x_{i4}	x_{i1}	x_{i2}	x_{i3}	0	0	0	1	0	0	x_{i3}

(36)

The fixed effect predictor matrix for participant i is then

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & x_{i1} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & x_{i2} & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & x_{i3} \end{bmatrix}. \quad (37)$$

3.3 Data set-up for differential sensitive periods model

Assume that the sensitive period is at age 1. Start with the data formatted as follows.

PID	y	a	x	$x1$	$a1$	$a2$	$a3$	$a4$
1	y_{i1}	1	x_{i1}	x_{i1}	1	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	1	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	0	0	1	0
1	y_{i4}	4	x_{i4}	x_{i1}	0	0	0	1

(38)

Compute $k21 = a2*x1$, $k31 = a3*x1$, and $k41 = a4*x1$.

PID	y	a	x	$x1$	$a1$	$a2$	$a3$	$a4$	$k21$	$k31$	$k41$
1	y_{i1}	1	x_{i1}	x_{i1}	1	0	0	0	0	0	0
1	y_{i2}	2	x_{i2}	x_{i1}	0	1	0	0	x_{i1}	0	0
1	y_{i3}	3	x_{i3}	x_{i1}	0	0	1	0	0	x_{i1}	0
1	y_{i4}	4	x_{i4}	x_{i1}	0	0	0	1	0	0	x_{i1}

(39)

The fixed effect predictor matrix for participant i is then

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & x_{i1} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & x_{i1} & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & x_{i1} \end{bmatrix}. \quad (40)$$

3.4 Data set-up for stable sensitive periods model

Again assuming that the sensitive period is period 1, start with the data formatted as below.

PID	y	a	x	x_1
1	y_{i1}	1	x_{i1}	x_{i1}
1	y_{i2}	2	x_{i2}	x_{i1}
1	y_{i3}	3	x_{i3}	x_{i1}
1	y_{i4}	4	x_{i4}	x_{i1}

(41)

As before, let

$$b_1 = \begin{cases} 0 & \text{age} \leq 1 \\ 1 & \text{otherwise,} \end{cases} \quad (42)$$

and define an intercept as a column where every value is 1. Form $i_1 = b_1 * x_1$, yielding a the dataset which follows

PID	y	a	x	intercept	x_1	b_1	i_1
1	y_{i1}	1	x_{i1}	1	x_{i1}	0	0
1	y_{i2}	2	x_{i2}	1	x_{i1}	1	x_{i1}
1	y_{i3}	3	x_{i3}	1	x_{i1}	1	x_{i1}
1	y_{i4}	4	x_{i4}	1	x_{i1}	1	x_{i1}

(43)

The fixed effect predictor matrix for participant i is then

$$\mathbf{X}_i = \begin{bmatrix} 1 & 0 \\ 1 & x_{i1} \\ 1 & x_{i1} \\ 1 & x_{i1} \end{bmatrix}. \quad (44)$$

4. Definitions and notation for the example study

Let $\mathbf{1}_N$ be an $(N \times 1)$ vector containing the entry 1 in every spot, and $\mathbf{0}_N$ similarly. Let $N = 191$ be the number of study participants. Let i index study participant, for $i \in \{1, 2, \dots, N\}$. Let j index outcome measurement within study participant, for $j \in \{1, 2, \dots, p_i\}$ indexing the number of measurements. Here, p_i is the number of outcome measures for study participant i . The total number of observations (i.e., the total number of repeated measured per person, summed over all the people in the study) is given by

$$n = \sum_{i=1}^N p_i. \quad (45)$$

The maximum number of observations per participant is 8, so $N_i \leq 8$. For participant i at measurement time j , let

$$\begin{aligned} a_{ij} &= \text{age (years) for participant } i \text{ at measurement time } j, \\ a_{ij}^2 &= \text{age}^2 \text{ (years) for participant } i \text{ at measurement time } j, \\ s_{i6} &= \text{income to needs ratio for participant } i \text{ at 6 months of age, and} \\ c_{i6} &= \text{predictor for participant } i \text{ at 6 months of age.} \end{aligned} \quad (46)$$

For study participant i , form vectors of predictors, so that, for example

$$\mathbf{a}_i = \begin{bmatrix} a_{i1} \\ a_{i2} \\ \vdots \\ a_{iN_i} \end{bmatrix}. \quad (47)$$

Let y_{ij} be the outcome measured on participant i for measurement j . The outcome vector for person i is given by

$$\begin{matrix} \mathbf{y}_i \\ (N_i \times 1) \end{matrix} = \begin{bmatrix} y_{i1} \\ y_{i2} \\ \vdots \\ y_{iN_i} \end{bmatrix}. \quad (48)$$

The population outcome vector stacks the participants-specific outcome vectors, so

$$\begin{matrix} \mathbf{y} \\ (N \times 1) \end{matrix} = \begin{bmatrix} y_{i1} \\ y_{i2} \\ \vdots \\ y_{in} \end{bmatrix}. \quad (49)$$

The population random effect matrix is

$$\mathbf{Z} = \begin{bmatrix} \mathbf{Z}_1 & & & \\ & \mathbf{Z}_2 & & \\ & & \ddots & \\ & & & \mathbf{Z}_n \end{bmatrix} \quad (50)$$

Immediately-before model Here, because \mathbf{X}_{IB} has 17 columns, we present \mathbf{X}'_{IB} , with columns containing 0 suppressed for clarity.

$$\begin{array}{r}
 \mathbf{X}' \\
 (17 \times N)
 \end{array}
 = \quad (53)$$

$$\left[\begin{array}{cccccccc}
 1 & & & & & & & \\
 & 1 & & & & & & \\
 & & 1 & & & & & \\
 & & & 1 & & & & \\
 & & & & 1 & & & \\
 & & & & & 1 & & \\
 & & & & & & 1 & \\
 & & & & & & & 1 \\
 & & c_6 & & & & & \\
 & & & c_{12} & & & & \\
 & & & & c_{24} & & & \\
 & & & & & c_{60} & & \\
 & & & & & & c_{78} & \\
 & & & & & & & c_{120} \\
 & & & & & & & & c_{132} \\
 a & a & a & a & a & a & a & a \\
 a^2 & a^2 & a^2 & a^2 & a^2 & a^2 & a^2 & a^2
 \end{array} \right]$$

All-times-before model: Here, because \mathbf{X}_b has 38 columns, we present \mathbf{X}'_b , with columns

