# Improved longitudinal data analysis:
# A Piecewise linear mixed effect modelling approach

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Supriya , Cytel Statistical Software and Services Pvt Ltd, India


## Abstract

Mixed effects models for repeated measures are extensively used in clinical trials. It provides a comprehensive way to analyze longitudinal continuous endpoints of clinical trials.

In many applications, we observe irregular rates of changes (rapid fluctuations in the rate of change) during the study period. Nonlinear trends of this type may not be well approximated by polynomials of any order. Piecewise linear mixed effects models offer an attractive alternative to commonly used spline regression because the coefficients obtained from fitting the model have meaningful substantive interpretation. One way to represent polynomial curves of this type is to have a sequence of connected line segments that produces a piecewise linear pattern. Piecewise linear mixed effects model consists of piecewise linear trends with different slopes in different segments but joined together at fixed times (knots).

The concept of piecewise linear mixed effects model will be discussed in detail. The results will be interpreted using an example.


## Introduction

- Piecewise linear mixed effects model is an extension of the standard linear mixed effects model, incorporating piecewise (or segmented) regression.
- It is used when the relationship between the independent and dependent variables changes at certain points ( breakpoints or knots) and these changes are modeled using linear segments rather than a single straight line.
- The basic idea is , divide the time axis into a series of segments considering a model that consists of piecewise linear trends with different slopes in different segments but joined together at fixed times (knots)

**Piecewise linear mixed effects model**

$$y_i=\beta_0+\beta_1 x_i+\beta_2(x_i-c)+u_i+e_i$$

- **yi :** The outcome for the ith observation
- **xi** : The independent variable
- **β0**: The intercept term
- **β1xi**: Slope before the breakpoint c
- **β2(xi−c)**: Slope after the breakpoint c
- **ui :** The random effect associated with the ith observation or group
- **ei** : The residual error term for the ith observation

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## Example

Consider an example where the response variable is measured at different timepoints

- PATID: Identification variable of each subject
- AVAL: Continuous response variable
- time represents the analysis visits number in years
- Age is the baseline age
- timespl1 is the spline variable created using following SAS code

Time spline equals 0 when time is less than or equal to k. time spline equals (time – k) given time is greater than k .
We assume that each subject has a two-piece linear spline with a knot at 1 year (Month 12)

```
data example;
  set example;
  k = 1;
  if time <= k then timespl1 = 0;
  if time > k then timespl1 = time - k;
run;
```

| Obs | PATID | AVAL | AGE | AVISIT | time |
|---|---|---|---|---|---|
| 1 | 123 | 26.982428445 | 17 | BASELINE | 0 |
| 2 | 123 | 38.623907209 | 17 | MONTH 12 | 1 |
| 3 | 123 | 50.002318107 | 17 | MONTH 24 | 2 |
| 4 | 123 | 58.884699824 | 17 | MONTH 36 | 3 |
| 5 | 123 | 69.176049463 | 17 | MONTH 48 | 4 |
| 6 | 123 | 71.668182864 | 17 | MONTH 60 | 5 |
| 7 | 123 | 70.398824745 | 17 | MONTH 72 | 6 |
| 8 | 123 | 59.862023218 | 17 | MONTH 84 | 7 |

```
proc mixed data=<dataset name> method=reml;
  class usubjid t;
  model aval=time timespl1 age time*age timespl1*age/solution outpm=pred cl ddfm=kr;
  random intercept/subject=usubjid type=un;
  estimate 'before 1 year' time 1 timespl1 0 time*age &mn. timespl1*age 0/cl;
  estimate 'after 1 year' time 1 timespl1 1 time*age &mn. timespl1*age &mn./cl;
run;
```

here &mn. is a macro variable with Average Baseline age.

| Estimates | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Label | Estimate | Standard Error | DF | t Value | Pr > \|t\| | Alpha | Lower | Upper |
| before 1 year | 21.2696 | 4.9721 | 56.3 | 4.28 | <.0001 | 0.05 | 11.3106 | 31.2286 |
| after 1 year | 0.3952 | 0.9078 | 57.2 | 0.44 | 0.6649 | 0.05 | -1.4224 | 2.2129 |

**Interpretation:**

The value before 1 year is significantly positive (around 21.27 on average), and we are 95% confident that the true value lies between 11.31 and 31.23.

The value after 1 year is close to 0, and since the confidence interval includes 0, the result is not statistically significant. We cannot conclude that there is a meaningful effect after 1 year.

## Conclusions

- Piecewise linear mixed effect model is a powerful statistical tool for analyzing the longitudinal data where a significant change in trend occurs at a specific time point (Knots)
- Piecewise linear mixed effects model can capture non- linear trends by fitting separate linear regressions for different critical periods (Knots), providing a more accurate representation of data compared to simple linear model
- Quadratic and higher-order polynomial models can be used to model longitudinal data, However the interpretation of coefficients would be difficult.

## References


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## Contact Information


Name: Supriya
Company: Cytel Statistical Software and Services Pvt.Ltd., India
Address: “Atharva”, Yedthady, Brahmavara Taluk, Udupi District
Karnataka- 576210
Phone: 8550084348
E-mail: Supriya@cytel.com