Application of Non-Linear Mixed Model for Efficacy Endpoint Analysis in Dermatology Clinical Trials

Presented By

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Agenda

- Introduction
- Linear vs Non-Linear
- SAS-PROC NLMIXED
- Endpoints in Dermatology (Mock Shell → Program → Output)
- Summary
- Limitations

Introduction

- Data involving nonlinear, sparse grouped data are common in the health sciences, especially in drug trials.

- Nonlinear mixed-effects (NLME) modeling provides a good solution for modeling sparse data and in which both fixed and random effects enter non linearly.

- Nonlinear mixed-effects models have received a great deal of attention in the statistical literature in recent years because of the flexibility they offer in handling the unbalanced repeated-measures data.

Linear Regression

Linear regression requires a linear model. But what does that really mean?

A model is linear when each term is either a constant or the product of a parameter and a predictor variable. A linear equation is constructed by adding the results for each term. This constrains the equation to just one basic form:

Response = constant + $parameter_1$ * $predictor_1$ + ... + $parameter_k$ * $predictor_k$ + error

$Y = b_o + b_1X_1 + b_2X_2 + ... + b_kX_k + e$

Linear Regression Cont…

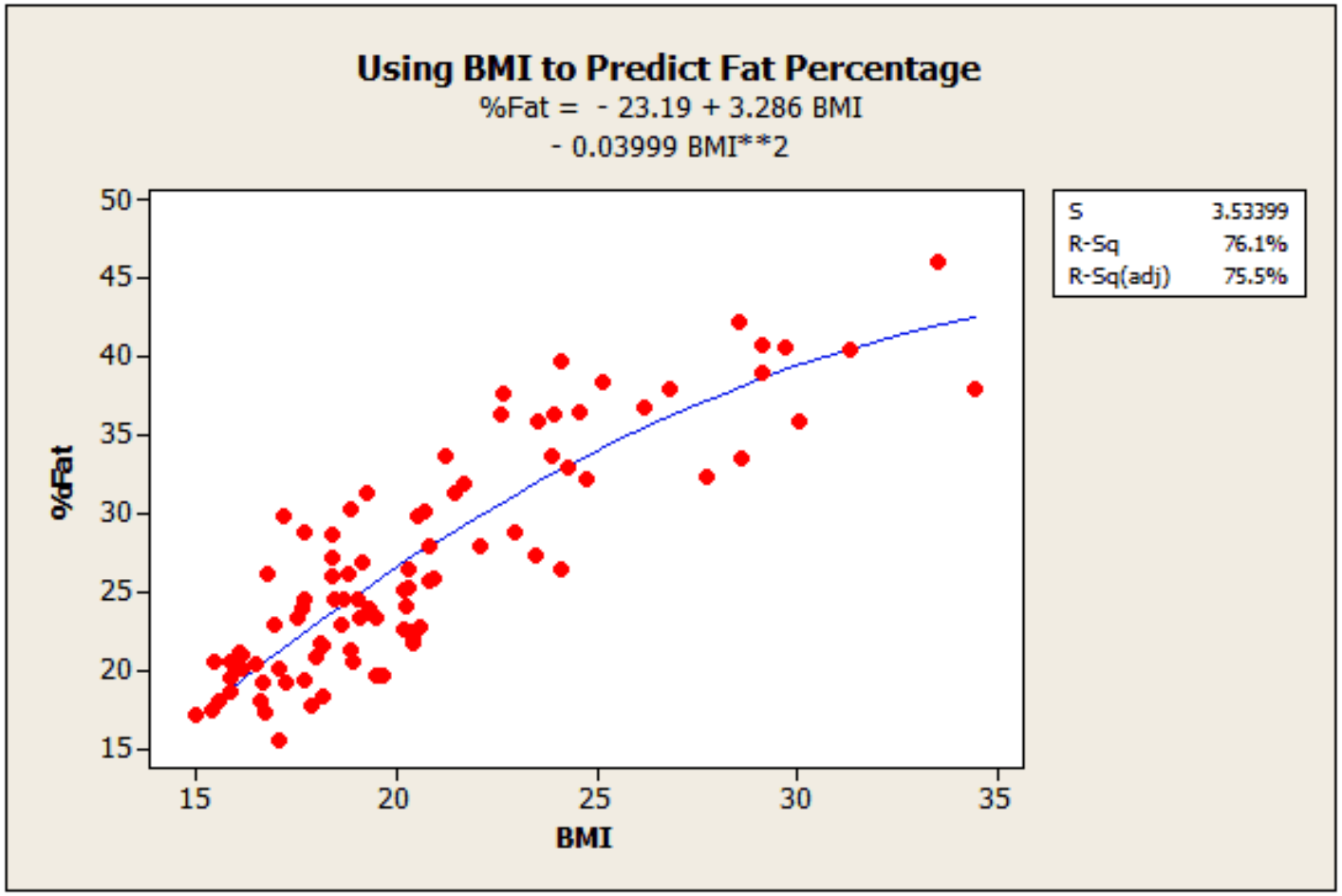
In statistics, a regression equation (or function) is linear when it is linear in the parameters. While the equation must be linear in the parameters, you can transform the predictor variables in ways that produce curvature. For instance, you can include a squared variable to produce a U-shaped curve.

$$Y = b_o + b_1X_1 + b_2X_1^2 + e$$

This model is still linear in the parameters even though the predictor variable is squared. You can also use log and inverse functional forms that are linear in the parameters to produce different types of curves.

Linear Regression - Example

Here is an example of a linear regression model that uses a squared term to fit the curved relationship between BMI and body fat percentage.



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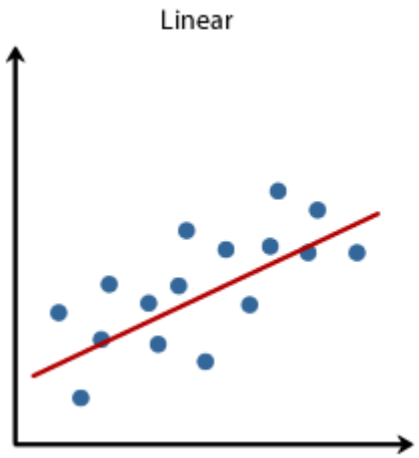
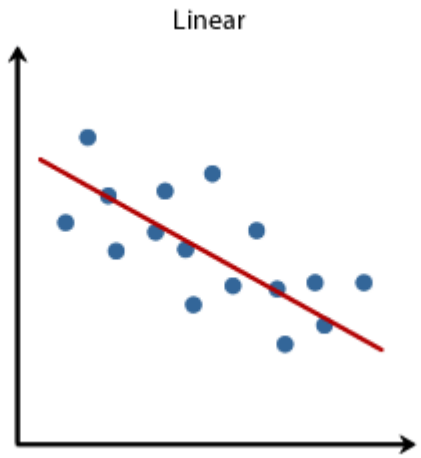
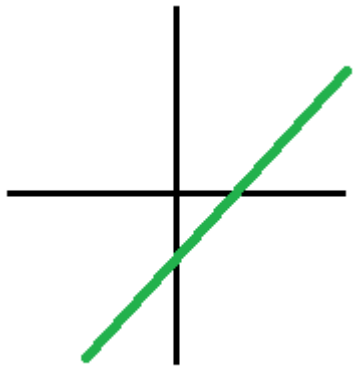
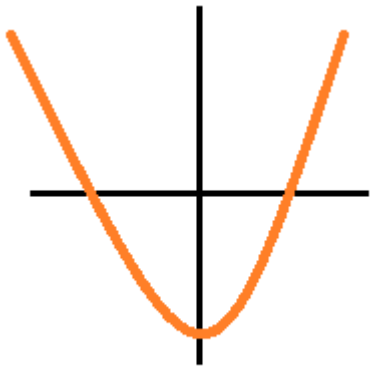
Linear vs Non-Linear

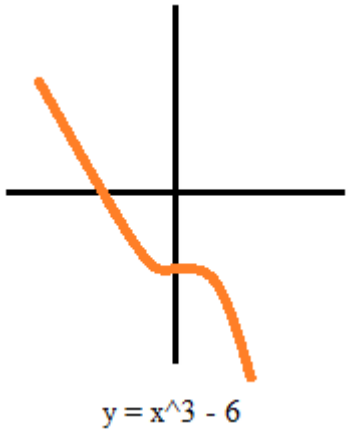
In simple terms “Linear functions are lines and non-linear functions are other shapes like parabolas”

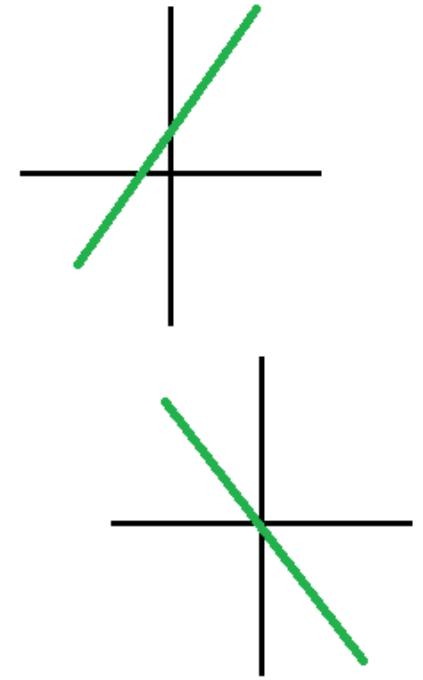


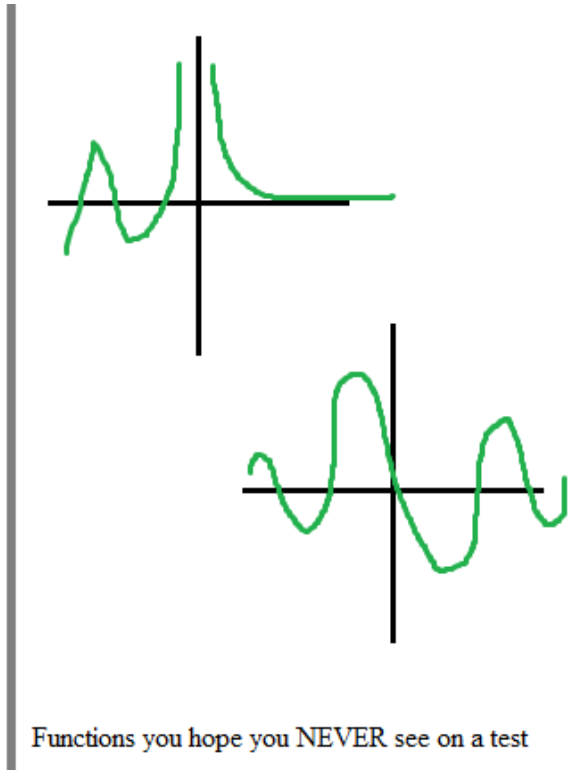












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The Difference

- A linear model is one in which the independent variable/s is/are multiplied together with the parameters.

- A non-linear model has exponents, logarithms, or other complicated functions of the independent variable and parameters.

- A linear regression model is linear in the parameters. That is, there is only one parameter in each term of the model and each parameter is a multiplicative constant on the independent variable(s) of that term.

$$Y = \beta_0 + \beta_1 X + \beta_2 X^2 + \varepsilon$$

$$Y = \beta_0 + \beta_1 \ln(X) + \varepsilon$$

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \varepsilon$$

Linear Models

The Difference cont…

- A nonlinear model is nonlinear in the parameters. Nonlinear, in this sense, means that the mathematical relationship between the variables and parameters is not required to have a linear form.

$$Y = \beta_1 e^{-\beta_2 X} + \varepsilon$$

$$Y = \beta_1 + (\beta_2 - \beta_1) e^{-\beta_3 X} + \varepsilon$$

$$Y = \frac{(\beta_1 X)}{(\beta_2 + X)} + \varepsilon$$

Nonlinear Models

- When fitting a linear model, the general form of the model is known. It is only necessary to identify the dependent and independent variables and the terms to include in the model.

- For a nonlinear model, the form of the model must be specified, the parameters to be estimated identified, and starting values for those parameters must be provided.

Non-Linear Model

General form of NLR model:

$$Y_i = F(\boldsymbol{x_i}, \boldsymbol{\Theta}) + e_i,$$

where i = 1, …, n is the number of measurement, Y_i are responses, $\boldsymbol{x_i}$ is the vector $(x_{i1}, \ldots, x_{ik})$ of measurements of k independent variables, $\boldsymbol{\Theta}$ is the parameter vector $(\Theta_1, \ldots, \Theta_p)$, and e_i are random errors, usually assumed to have mean 0 and constant variance.

SAS Procedure

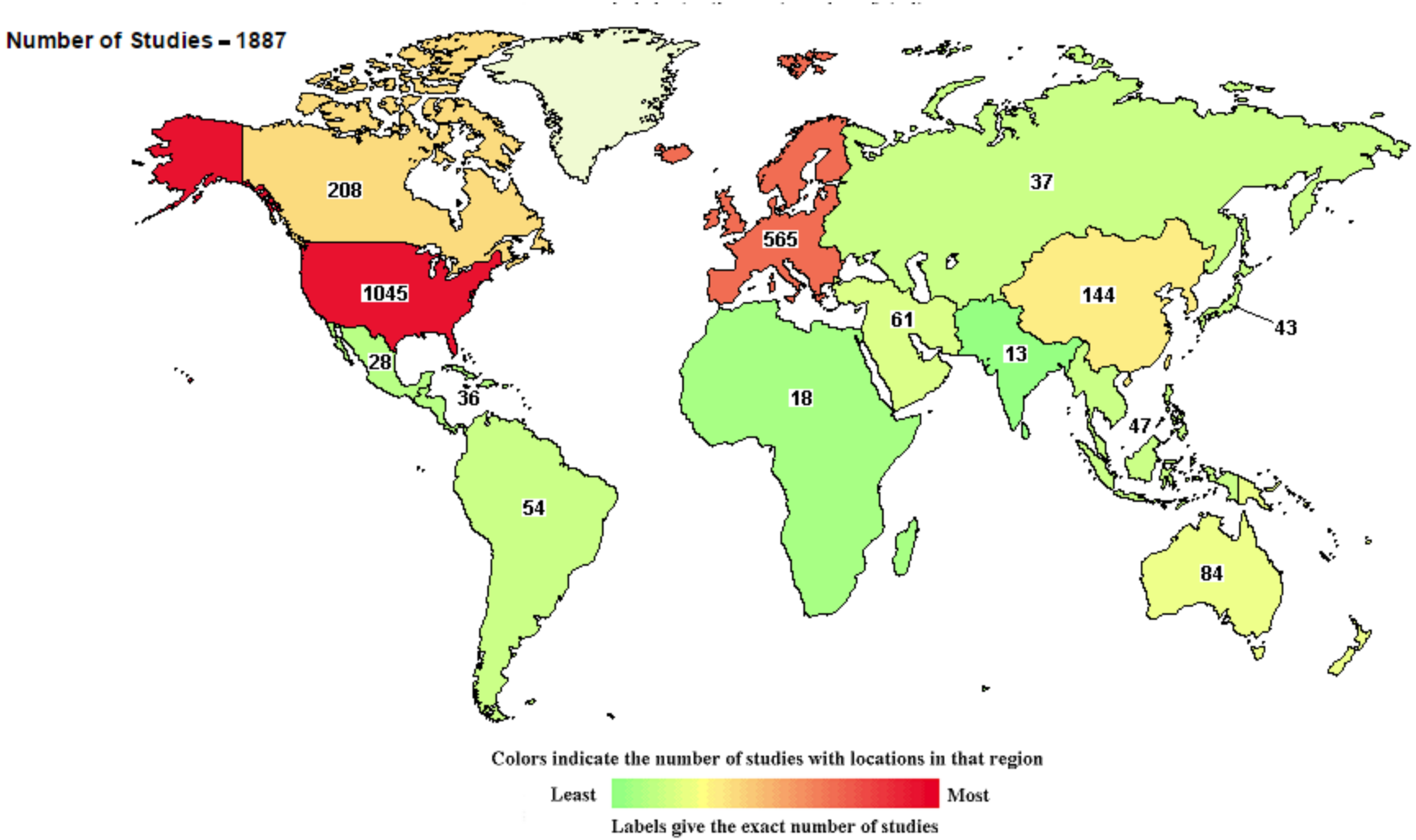
General Syntax

```
PROC NLMIXED < options > ;
    ARRAY array specification ;
    BOUNDS boundary constraints ;
    BY variables ;
    CONTRAST 'label' expression < ,expression >< options > ;
    ESTIMATE 'label' expression < options > ;
    ID names ;
    MODEL model specification ;
    PARMS parameters and starting values ;
    PREDICT expression OUT=SAS-data-set < options > ;
    RANDOM random effects specification ;
    REPLICATE variable ;
    Program statements ;
```

Core Syntax

- Proc NLMIXED <Options>
- Bounds <Boundary constraints>
- Parms <Parameters and starting values>
- Model <Model specification>
- Random <Random effect specification>
- Predict <Expression OUT=SAS-data-set < options > >
- Estimate <'label' expression < options >>

Clinical trials in Dermatology



Source:http://ClinicalTrials.gov

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Endpoint Types in Dermatology

Categorical: Analysis of Proportions of subjects who achieve a Physician Global Assessment score of 0 or 1 and a minimum 2-grade improvement from baseline to each study visit.

Analysis Proposed: A Repeated Measure Factorial Logistic Regression for the dichotomous endpoint.

Model Specification:

$$\pi_{ij} = \left(\frac{exp(\beta_0 + \beta_1 Dose_i + \beta_2 Freq_i + \beta_3 Dose_i \times Freq_i + \gamma_i)}{1 + exp(\beta_0 + \beta_1 Dose_i + \beta_2 Freq_i + \beta_3 Dose_i \times Freq_i + \gamma_i)}\right)\left(\frac{1 - exp(kt_j)}{1 - exp(kd)}\right)$$

$$y_{ij} \sim Bernoulli(\pi_{ij})$$

$$\gamma_i \sim Normal(0, \sigma_S^2)$$

where $Dose_i$ and $Freq_i$ are the dose and frequency for the ith subject and t_j is the time in days for the jth visit; d is fixed to be 84 days and γ_i is a random subject effect. For the primary analysis, the parameters $\beta_0 - \beta_3$ and k will be considered fixed and the model will be fit using a nonlinear mixed modelling algorithm such as SAS Proc NLMIXED. In order to help ensure the convergence of the model fitting algorithm the covariates dose and frequency may be standardized, or the covariate frequency may be removed from the model.

Table Mock

Analysis of Proportion of Subjects Who Achieve a Physician Global Assessment (PGA) Score of 0 or 1 and Minimum 2-Grade Improvement from Baseline to Each Study Visit – mITT

Visit	Statistic	Trt A 0.5% QD (N=xx)	Trt A 0.5% BID (N=xx)	Trt A 1% QD (N=xx)	Trt A 1% BID (N=xx)	Vehicle QD (N=xx)	Vehicle BID (N=xx)
Week 1	n	xx	xx	xx	xx	xx	xx
	Responder [1]	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Estimate (SE)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	80% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	Difference vs Vehicle (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)		
Week 2	n	xx	xx	xx	xx	xx	xx
	Responder [1]	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Estimate (SE)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	80% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	Difference vs Vehicle (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)		
Etc..							

SE = Standard Error; CI = Confidence Interval

[1] Responder = Subject who achieves a Physician Global Assessment (PGA) Score of 0 or 1 and Minimum 2-Grade Improvement from Baseline

Note: Analysis was performed by a repeated measures factorial logistic regression with Integrated two-component prediction (ITP) model with covariates for dose (0% for vehicle, 0.5% and 1%), frequency of administration (once or twice daily), and study day as well as a dose by frequency interaction term.

n = number of subject with available data at the specified visit.

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SAS Code

```
/*------non linear mixed logistic regression model-------*/
ods listing close;
ods output AdditionalEstimates = estimates0;
proc nlmixed data=data0 qpoints=90;
    parms ebata0= -2.5 ebata1=3.1 ebeta2=1 ebeta3=1 ek1=-.01 es2u=0.042;
    bounds es2u > 0;

    week1_itp=(1-exp(7*ek1))/(1-exp(84*ek1));
    week2_itp=(1-exp(14*ek1))/(1-exp(84*ek1));
    week4_itp=(1-exp(28*ek1))/(1-exp(84*ek1));
    week8_itp=(1-exp(56*ek1))/(1-exp(84*ek1));
    week12_itp=(1-exp(84*ek1))/(1-exp(84*ek1));

    term1=ebeta0 + ebeta1*0.5 + ebeta2*1 + ebeta3*0.5*1; *0.5% QD;
    term2=ebeta0 + ebeta1*0.5 + ebeta2*2 + ebeta3*0.5*2; *0.5% BID;

    term3=ebeta0 + ebeta1*1 + ebeta2*1 + ebeta3*1*1;    *1% QD;
    term4=ebeta0 + ebeta1*1 + ebeta2*2 + ebeta3*1*2;    *1% BID;

    term5=ebeta0 + ebeta2*1;  *Vehicle QD;
    term6=ebeta0 + ebeta2*2;  *Vehicle BID;
```

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SAS Code cont….

```
   eta = (ebeta0 + ebeta1*dose + ebeta2*freq + ebeta3*dose*freq + gamma);
   mu = (exp(eta) / (1 + exp (eta)))*((1-exp(ady*ek1))/(1-exp(84*ek1)));
   model response ~ binary (mu);
   random gamma ~ normal(0,es2u) subject=usubjid;

   predict gamma out=gamma_pred;
   predict mu out=mu_pred;

**Estimates and 80 % CI ;
   estimate 'Week 1 0.5% QD' ((exp(term1)) / (1 + exp (term1)))*week1_itp*100 ALPHA=0.2;
   estimate 'Week 1 1% QD' ((exp(term3)) / (1 + exp (term3)))*week1_itp*100 ALPHA=0.2;
   estimate 'Week 1 0% QD' ((exp(term5)) / (1 + exp (term5)))*week1_itp*100 ALPHA=0.2;

   estimate 'Week 1 0.5% BID' ((exp(term2)) / (1 + exp (term2)))*week1_itp*100 ALPHA=0.2;
   estimate 'Week 1 1% BID' ((exp(term4)) / (1 + exp (term4)))*week1_itp*100 ALPHA=0.2;
   estimate 'Week 1 0% BID' ((exp(term6)) / (1 + exp (term6)))*week1_itp*100 ALPHA=0.2;

**Estimates and 95% CI ;
   estimate 'Week 1 0.5% QD' ((exp(term1)) / (1 + exp (term1)))*week1_itp*100 ALPHA=0.05;
   estimate 'Week 1 1% QD' ((exp(term3)) / (1 + exp (term3)))*week1_itp*100 ALPHA=0.05;
   estimate 'Week 1 0% QD' ((exp(term5)) / (1 + exp (term5)))*week1_itp*100 ALPHA=0.05;

   estimate 'Week 1 0.5% BID' ((exp(term2)) / (1 + exp (term2)))*week1_itp*100 ALPHA=0.05;
   estimate 'Week 1 1% BID' ((exp(term4)) / (1 + exp (term4)))*week1_itp*100 ALPHA=0.05;
   estimate 'Week 1 0% BID' ((exp(term6)) / (1 + exp (term6)))*week1_itp*100 ALPHA=0.05;
```

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SAS Code cont….

```
** Difference between Active and Vehicle;
    /*difference at week 1*/

    estimate 'Diff 0.5% QD vs Vehicle QD'     ((exp(term1) / (1 + exp(term1))) - (exp(term5) / (1 + exp(term5))))*week1_itp*100;

    estimate 'Diff 0.5% BID vs Vehicle BID'   ((exp(term2) / (1 + exp(term2))) - (exp(term6) / (1 + exp(term6))))*week1_itp*100;


    estimate 'Diff 1% QD vs Vehicle QD'      ((exp(term3) / (1 + exp(term3))) - (exp(term5) / (1 + exp(term5))))*week1_itp*100;

    estimate 'Diff 1% BID vs Vehicle BID'    ((exp(term4) / (1 + exp(term4))) - (exp(term6) / (1 + exp(term6))))*week1_itp*100;

run;
```

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Output

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Analysis of Proportion of Subjects Who Achieve a Physician Global Assessment (PGA) Score of 0 or 1 and Minimum 2-Grade Improvement from Baseline to Each Study Visit - mITT

Visit	Statistic	Trt A 0.5% QD (N=38)	Trt A 0.5% BID (N=32)	Trt A 1% QD (N=28)	Trt A 1% BID (N=39)	Vehicle QD (N=27)	Vehicle BID (N=32)
Week 1	n	37	31	26	38	26	32
	Responder [1]	0	0	1 (4%)	1 (3%)	0	0
	Estimate (SE)	0.0 (0.00)	0.0 (0.00)	0.0 (0.12)	0.0 (0.04)	2.0 (7.77)	0.3 (1.33)
	95% CI	-0.0, 0.0	-0.0, 0.0	-0.2, 0.3	-0.1, 0.1	-13.4, 17.3	-2.3, 2.9
	80% CI	-0.0, 0.0	-0.0, 0.0	-0.1, 0.2	-0.0, 0.1	-8.0, 12.0	-1.4, 2.0
	Difference vs Vehicle (95% CI)	-2.0 (-17.3, 13.4)	-0.3 (-2.9, 2.3)	-1.9 (-17.2, 13.3)	-0.3 (-2.9, 2.3)		
Week 2	n	36	27	26	36	25	31
	Responder [1]	2 (6%)	0	4 (15%)	2 (6%)	1 (4%)	2 (6%)
	Estimate (SE)	0.0 (0.01)	0.0 (0.01)	0.1 (0.23)	0.0 (0.08)	3.7 (14.55)	0.6 (2.49)
	95% CI	-0.0, 0.0	-0.0, 0.0	-0.4, 0.5	-0.1, 0.2	-25.0, 32.4	-4.3, 5.5
	80% CI	-0.0, 0.0	-0.0, 0.0	-0.2, 0.3	-0.1, 0.1	-15.0, 22.4	-2.6, 3.8
	Difference vs Vehicle (95% CI)	-3.7 (-32.4, 25.0)	-0.6 (-5.5, 4.4)	-3.6 (-32.2, 25.0)	-0.5 (-5.4, 4.4)		

Etc..

SE = Standard Error; CI = Confidence Interval
[1] Responder = Subject who achieves a Physician Global Assessment (PGA) Score of 0 or 1 and Minimum 2-Grade Improvement from Baseline
Note: Analysis was performed by a repeated measures factorial logistic regression with Integrated two-component prediction (ITP) model with covariates for dose (0% for vehicle, 0.5% and 1%), frequency of administration (once or twice daily), and study day as well as a dose by frequency interaction term.
n = number of subject with available data at the specified visit.

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Endpoint Types in Dermatology

Continuous: Analysis of mean change in weekly average of Itch/Pruritus (Numeric Rating Scale) from Baseline to each study visit.

Analysis Proposed: A Repeated Measures E-Max model with Integrated Two - Component Prediction (ITP) time component.

Model Specification:

$$y_{ij} = \left(E_o + \frac{Emax_i \times dose_i}{ED_{50} + dose_i} + \gamma_i\right)\left(\frac{1-e^{kt_j}}{1-e^{kd}}\right)$$

$$\gamma_i \sim Normal(0, \sigma^2)$$

$$Emax_i = \beta_1 + \beta_2 \times freq_i = \begin{cases} \beta_1, if\ QD\ (freq_i = 0) \\ \beta_1 + \beta_2, if\ BID\ (freq_i = 1) \end{cases}$$

where $dose_i$ and $freq_i$ are the dose and frequency for the i^{th} subject and t_j is the time in days for the jth visit; d is fixed to be the maximum study day of week 12 visit among all subjects in the population and γ_i is a random subject effect. The parameters E_0, Emax, ED_{50}, β_1, β_2 and k will be considered fixed and the model will be fit using a nonlinear mixed modelling algorithm such as SAS Proc NLMIXED.

Table Mock

Analysis of Mean change in weekly average of Itch/Pruritus (Numeric Rating Scale) from baseline to Each Study Visit – mITT

Visit	Statistic	Trt A 0.5% QD (N=xx)	Trt A 0.5% BID (N=xx)	Trt A 1% QD (N=xx)	Trt A 1% BID (N=xx)	Vehicle QD (N=xx)	Vehicle BID (N=xx)
	E0 [SE]: x.x [x.xx] ED50 [SE]: x.x [x.xx] Emax QD [SE]: x.x [x.xx] Emax BID [SE]: x.x [x.xx]						
Week 1	n	xx	xx	xx	xx	xx	xx
	Estimate (SE)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	80% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Etc..							

SE = Standard Error; CI = Confidence Interval
n = number of subjects with available data at the specified visit.
Analysis was performed by a repeated measures E-max model with integrated two-component prediction (ITP).

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SAS Code

```
*---------- E-max model with Integrated Two-Component Prediction----------;
/*To Store the max day of Week 12 period*/
proc sql noprint;
    select max(ady) into: d from data0 where avisitn=70; /*Week 12*/
quit;


proc sql noprint;
        %*** Define E0 as placebo effect;
        select min(chg) into: _ine0 from data0;

        %*** Initial EMAX as difference between maximum achievable response (at infinite dose) and baseline effect;
        select max(chg) into: _inemax from data0;

        %*** Initial ED50 as the dose that produces half maximal effect (E0 + Emax/2);
        select mean(dose) into: _ined50 from data0;

        %*** Standard error for chg;
        select std(chg) into: _err from data0;

        %*** EMAX by Dose Frequency;
        select max(chg) into: _inemax_bid from data0 where freq=2;
        select max(chg) into: _inemax_qd from data0 where freq=1;
quit;
```

SAS Code cont…

```
%let _inemaxdif=%sysevalf(&_inemax_bid. - &_inemax_qd.); /*Taking difference of EMAX of BID and QD */

%put "_inemaxdif: "&_inemaxdif.;

/*-----non linear mixed logistic model-------------------------*/

ods output ParameterEstimates = parameter0
           AdditionalEstimates=estimates0;
    proc nlmixed data=data0;
        PARMS E0=&_ine0. emax0=&_inemax. ED50=&_ined50. intersd=1 intrasd=1
        emaxdif=&_inemaxdif. ek1=-.01;

        week1_itp=(1-exp(7*ek1))/(1-exp(&d.*ek1));

        if freq eq 2 then emax=emax0+emaxdif;
        else emax=emax0;

        emaxpred=e0+sub1+((emax*dose)/(ed50+dose));

        prediction = emaxpred*((1-exp(ady*ek1))/(1-exp(&d*ek1)));

        MODEL chg~NORMAL(prediction,intrasd);
        RANDOM sub1 ~NORMAL(0, intersd) SUBJECT=usubjid;

        predict prediction out=y_pred;

        ESTIMATE "Emax QD" emax0;
        ESTIMATE "Emax BID" emax0+emaxdif;
```

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SAS Code cont…

```
%*** Estimates and its 80 % CI;

    estimate 'Week 1 0% QD'    (e0+((emax0*0)/(ed50+0)))* week1_itp ALPHA=0.2;
    estimate 'Week 1 0.5% QD'  (e0+((emax0*0.5)/(ed50+0.5)))* week1_itp ALPHA=0.2;
    estimate 'Week 1 1% QD'    (e0+((emax0*1)/(ed50+1)))* week1_itp ALPHA=0.2;

    estimate 'Week 1 0% BID'    (e0+(((emax0+emaxdif)*0)/(ed50+0)))* week1_itp ALPHA=0.2;
    estimate 'Week 1 0.5% BID'  (e0+(((emax0+emaxdif)*0.5))/(ed50+0.5))*week1_itp ALPHA=0.2;
    estimate 'Week 1 1% BID'    (e0+(((emax0+emaxdif)*1)/(ed50+1)))*week1_itp ALPHA=0.2;

%*** Estimates and its 95% CI;

    estimate 'Week 1 0% QD'    (e0+((emax0*0)/(ed50+0)))* week1_itp ALPHA=0.05;
    estimate 'Week 1 0.5% QD'  (e0+((emax0*0.5)/(ed50+0.5)))* week1_itp ALPHA=0.05;
    estimate 'Week 1 1% QD'    (e0+((emax0*1)/(ed50+1)))* week1_itp ALPHA=0.05;

    estimate 'Week 1 0% BID'    (e0+(((emax0+emaxdif)*0)/(ed50+0)))* week1_itp ALPHA=0.05;
    estimate 'Week 1 0.5% BID'  (e0+(((emax0+emaxdif)*0.5))/(ed50+0.5))*week1_itp ALPHA=0.05;
    estimate 'Week 1 1% BID'    (e0+(((emax0+emaxdif)*1)/(ed50+1)))*week1_itp ALPHA=0.05;

    run;
ods output close;
```

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Output

Analysis of Mean change in weekly average of Itch/Pruritus (Numeric Rating Scale) from baseline to Each Study Visit - mITT

Visit	Statistic	Trt A 0.5% QD (N=38)	Trt A 0.5% BID (N=32)	Trt A 1% QD (N=28)	Trt A 1% BID (N=39)	Vehicle QD (N=27)	Vehicle BID (N=32)
	E0 [SE]: -2.7 [0.22] ED50 [SE]: 23147.6 [0.00] Emax QD [SE]: 21705.5 [0.00] Emax BID [SE]: 25349.2 [0.00]						
Week 1	n	31	24	20	33	22	26
	Estimate (SE)	-1.1(0.12)	-1.0(0.14)	-1.4(0.11)	-1.4(0.14)	-1.7(0.10)	-1.7(0.13)
	95% CI	-1.4, -0.9	-1.3, -0.8	-1.7, -1.2	-1.7, -1.1	-2.0, -1.5	-2.0, -1.5
	80% CI	-1.3, -1.0	-1.2, -0.9	-1.6, -1.3	-1.6, -1.2	-1.9, -1.6	-1.9, -1.6
Etc..							

SE = Standard Error; CI = Confidence Interval
n = number of subjects with available data at the specified visit.
Analysis was performed by a repeated measures E-max model with integrated two-component prediction (ITP).

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Covariates

- Dose
- Frequency of administration
- Study Day
- Baseline PGA ^
- Dose*Frequency of administration
- Random Effect - Subject

^ will be included in the model only if it is statistically significant.

Summary

- Nonlinear models are common and widely used in Clinical industry for analyzing Pharmacokinetic, Dose-response modelling Etc.,
- They enable us to analyze data that are Normal, Binomial, or Poisson.
- To fit a nonlinear model, we have to rely on iterative methods.
- PROC NLMIXED supports a large number of iterative methods for fitting nonlinear models. The choice is problem-dependent and we need to select the iterative method by trial and error.
- Various Statistical software's such as SAS, R, SPSS, Stata, Minitab etc., help us to analyze Nonlinear models.
- Though the analysis might look complicated, a SAS programmer's challenge in understanding and programming such an analysis can be made simpler by liaising with a study statistician. A statistician's support in educating SAS programmers is the key.

Limitations

Nonlinear regression can be a powerful alternative to linear regression but there are a few drawbacks.

- PROC NLMIXED allows only one RANDOM statement, which makes it difficult to incorporate random effects at different levels.
- Impossible to calculate a valid R-squared.
- The effect each predictor has on the response can be less intuitive to understand.
- P-values are impossible to calculate for the predictors.
- Confidence intervals may or may not be calculable.

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Thank You !!!

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