

Multilevel Modeling of Periodontal Data

MLwinN 2.32 user manual version 2015.1

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1 Introduction

How clinically collected data are properly statistically analyzed very much depends on its structure. Periodontal and other dental data are usually manifold observations which are made in one oral cavity. For instance, in order to describe the overall periodontal situation in a certain cohort, (i) sites (or gingival units) around (ii) teeth within (iii) patients or subjects are considered by using metric, ordinal, or binary variables. Then, observations may be (iv) repeated in a longitudinal way. This is a typical hierarchical situation with lower (occasions, sites) and upper levels (teeth, subjects). In clinical trials, a further (higher) level is present when patients are assigned to different centers.

A suitable armamentarium for the study of fixed (estimates of covariates) and random effects (variances and covariances) is multilevel modeling which has been applied to dental research data for long (Sterne 1988, Albandar and Goldstein 1992, Gilthorpe et al. 2000). Whereas the methods are well-known and have now been implemented in major statistical software packages such as SAS, STATA, R, even SPSS (and many others; for a comprehensive review of software programs and packages that are designed or can be used for multilevel analyses see de Leeuw and Kreft (2001)), major and somewhat revealing obstacles for applying them has long been at least twofold: a perceived (by clinicians) unwillingness of common biostatisticians to make themselves familiar with the more sophisticated

methods of multilevel modeling, which are otherwise rarely used in medicine; and the simple fact that their application by clinical scientists, if not of most other statistical methods (Tu and Gilthorpe 2012), is vehemently discouraged by some biostatisticians.

The easy-to-apply special software *MLwiN* has been developed more than a decade ago, and the program has been applied in a considerable number of papers in dentistry; see, for instance, Gilthorpe et al. (2000), Ciantar et al. (2005), Müller (2008, 2009a), Müller et al. (2006), Müller and Stadermann (2006), Müller and Barrieshi-Nusair (2010), Tomasi et al. (2007), Fransson et al. (2010). Usually, insights into complex data structure are revealing. Since a respective manual by the *Centre of Multilevel Modelling* in Bristol (Rasbash et al. 2015) explicitly uses examples and data sets from the social sciences, the aim of the present tutorial is to give a rather non-technical description of the basic principles of multilevel modeling using exclusively periodontal datasets which have been collected over the past ten years in order to further promote the correct statistical analysis of frequently hierarchically organized dental data.

1.1 The Problem

As Rasbash et al. (2015) commence in the introduction of the latest *MLwiN* manual, “In the social, medical and biological sciences multilevel or hierarchical structured data are the norm and they are also found in many other areas of application.”

Whereas any statistical model should explicitly recognize a hierarchical structure when it is present, and data structure is expected to be commonly hierarchical in dentistry and, in particular, periodontology, there are essentially two traditional approaches to data analysis.

1.2 Traditional Solutions

1.2.1 Site-specific analysis disregarding the subject

This approach, which can mainly be traced in scientific papers in Periodontology well up into the mid- or end-1980s, has vehemently been condemned by biostatisticians (Imrey 1986). As fact of the matter, clustered or hierarchical observations made in a certain subject are not independent, which is a fundamental assumption required for most statistical hypothesis testing. For instance, measures of periodontal disease within an oral cavity of a given patient are more alike than

observations across oral cavities of other patients or subjects. By ignoring the subject level, standard errors of regression coefficients will inevitably be underestimated with grave consequences for hypothesis testing.

1.2.2 Aggregate analysis

By far the most common approach is, therefore, aggregating observations at the subject level. As an example, consider the cohort of 127 young adults with gingivitis where the association between presence or absence of supragingival dental plaque (a biofilm constantly forming on tooth surfaces, which can and should be removed regularly by toothbrushing) and gingival bleeding on probing (BOP) with a periodontal probe exerted with a more or less defined pressure (a sign for gingival inflammation caused, according to common sense, by dental plaque) had been assessed (Müller et al. 2000a).

In a subject-level, aggregate analysis one could have a look at the correlation between the proportion of tooth surfaces covered by plaque in each subject and the proportion of respective gingival units bleeding on probing. As an example, *Fig. 1.1* displays results of such an analysis.

Ordinary regression was used to assess the relationship between the two variables.

What might be stunning is the considerable scatter of data pairs representing the

subjects. Correspondingly, the correlation between the two sets of proportions was only a moderate with Pearson's r of 0.54.

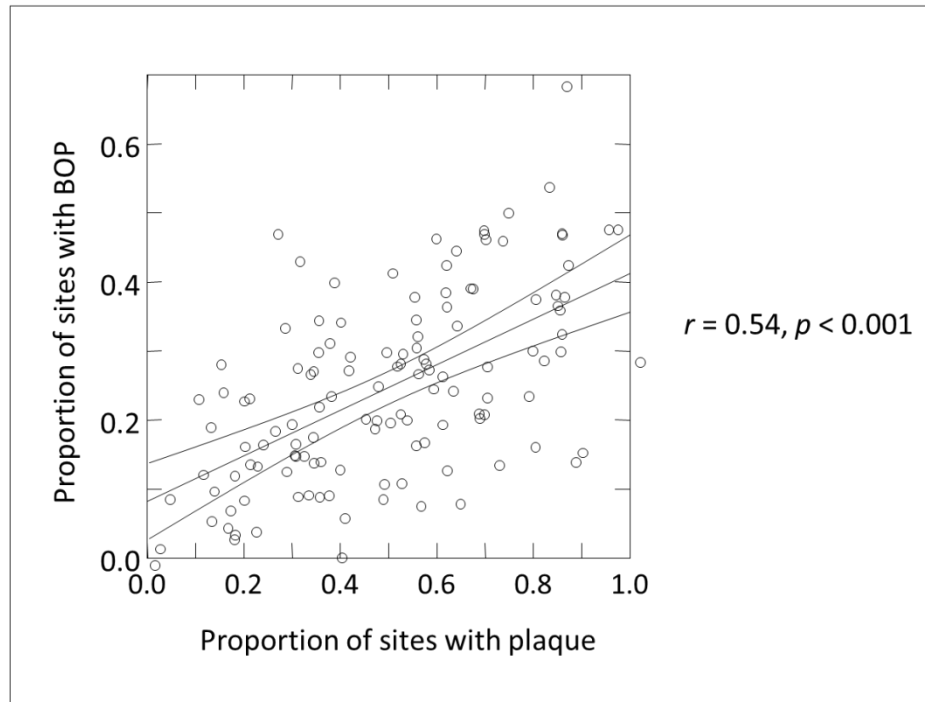


Fig. 1.1 Regression of the proportion of gingival sites bleeding on probing (BOP) on the proportion of sites with supragingival plaque. The regression line and its 95%-confidence interval are given (Müller et al. 2000a).

One has to keep in mind, however, that any causal relationship should be assessed at the lower level, i.e. the gingival unit. Apparently, this information has been discarded. Aggregated analyses are prone to what has been termed the “ecological fallacy”. An early example is Durkheim’s classic study on suicide (Durkheim 1951). Whereas Durkheim concluded that Protestants are more likely to commit suicide than Catholics based on higher prevalence of suicide in 19th century Prussia

(with its majority of Protestants) than in Bavaria (with its mainly Catholic population), when no data are actually missing on the lower subject level, one might also argue that it might mainly be Catholics who had committed suicide in largely Protestant provinces. While ecological analyses become flawed in exactly the same circumstances that individual level analyses do, namely in the presence of confounding, consequences of confounding are more severe in the former (Piantadosi et al. 1988).

1.2.3 Analysis of stratified site-specific associations

In order to preserve the site-specific information, the association between plaque and gingival bleeding on probing was further assessed by Müller et al. (2000) in a stratified analysis, i.e. on a subject-by-subject basis. New and revealing observations were reported. First, the association in this cross-sectional study unexpectedly varied from moderately negative (odds ratio = 0.24) to very strong positive (odds ratio >60). *Fig. 1.2* displays cumulative frequencies of log-transformed odds ratios. A weighted overall estimate, Mantel-Haenszel's odds ratio, was 2.25 ($p < 0.001$).

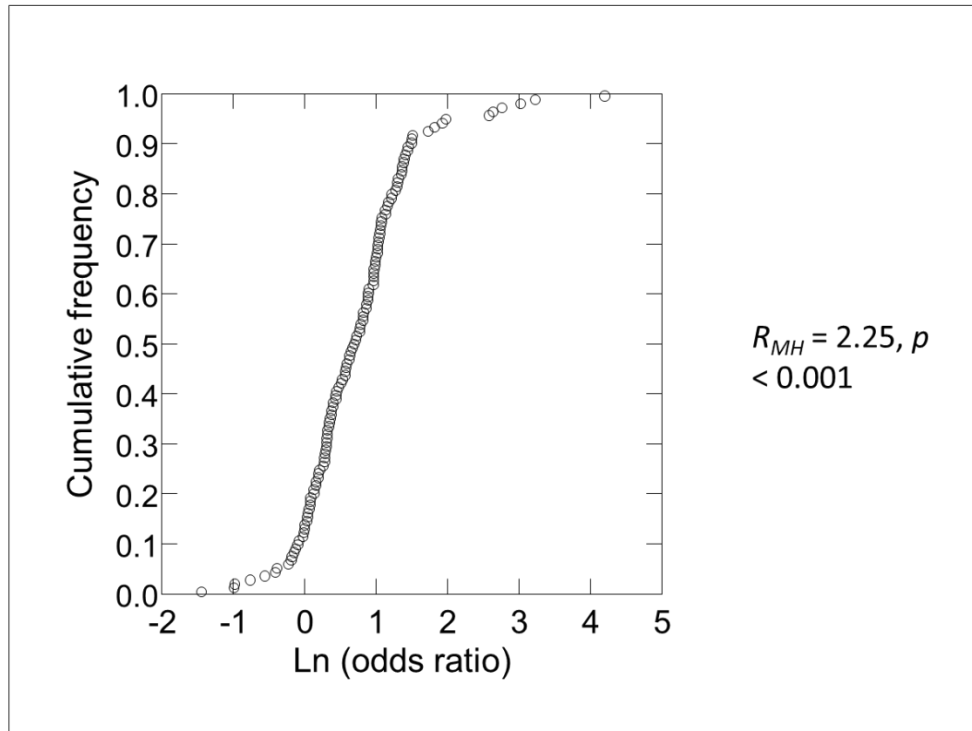


Fig. 1.2 Distribution of ln-transformed individual odds ratios describing the association between supragingival plaque and BOP (Müller et al. 2000a).

Secondly, although the data were cross-sectional, a closer look at subjects with extreme associations (those in the upper and lower 20% of odds ratios) revealed that the two subgroups presented with significantly different mean loss of periodontal attachment, mainly as gingival recession. So, those subjects with a strong positive association between supragingival plaque and BOP had significantly more attachment loss (gingival recession) than those with a weak or negative association. As can be seen in *Fig. 1.3*, there was a weak correlation

between mean recession and log-transformed odds ratios describing the individual association between supragingival plaque and BOP (Müller et al. 2000a).

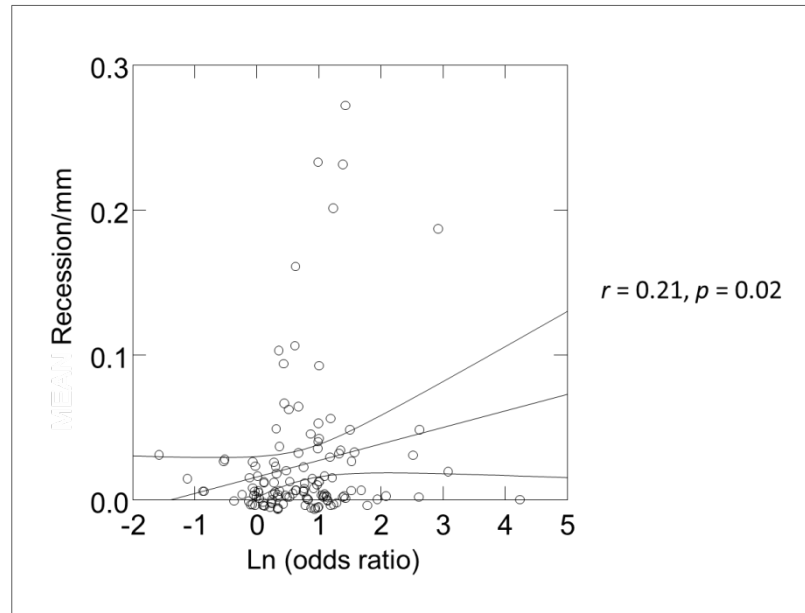


Fig. 1.3 Regression of mean gingival recession on individual ln-transformed odds ratios of supragingival plaque and BOP. The regression line and its 95%-confidence interval are given (Müller et al. 2000a).

It might be important to conclude that careful analysis of the subject-related association between site-specific variables plaque and BOP had revealed certain new observations far beyond the common conclusions derived from aggregated analyses, e.g. that the proportion of plaque-covered surfaces is related to the proportion of gingival units bleeding on probing. The new finding was that a strong association might be related to gingival recession (Müller et al. 2000a).

1.3 Generalized Estimating Equations

Variation between subjects has also been modeled by incorporating separate terms for each subject. So, the level of response (the intercept) was assumed to depend on the individual, see, for instance, Mombelli et al. (1994). However, this procedure does not allow for generalization but may rather yield results just for the cohort under investigation. So, it does not treat subjects as a random sample. It is moreover inefficient since it involves estimating a large number of coefficients. Logistic regression diagnostics have been applied to indicate a number of grave problems with this approach (Müller et al. 1998a).

Generalized Estimating Equation (GEE) methods for correctly considering the clustered structure of data had been introduced as an extension of generalized linear models and the quasi-likelihood method to the analysis of correlated (Liang and Zeger 1986) or longitudinal (Zeger and Liang 1986) data. GEE have been suggested by DeRouen et al. (1991) for correlated periodontal data but application in dentistry has not been widespread (Müller et al. 1997, 1998a, b, 2000a, b, Harrel and Nunn 2001a, b). Specifically, coefficient estimates are defined by the solution of a set of estimating equations, which involve a working correlation matrix, which is assumed to be completely specified by a vector of correlation parameters. The

working correlation matrix can be thought of as a weighting matrix for responses within the same subject. An important property of GEE is that the regression coefficient estimates are consistent, even if the working correlation matrix is not the correct correlation, although there may be a loss in efficiency relative to the correct specification of the correlation structure (DeRouen et al. 1995). A useful specification of a correlation matrix corresponds to the assumption that the pairwise correlation between responses within the same subject are all the same. This correlation structure is called exchangeable correlation (or also “dental common”) and has been shown to be most suitable for periodontal data (DeRouen et al. 1991, 1995).

GEE may be preferred when interest is mainly on the effect of explanatory variables on the response, and correlation structure is generally considered a nuisance. The following chapters will reveal that the main advantage of multilevel modeling with its unbiased dealing with the hierarchical structure of the data is, besides obtaining correct estimates of fixed effects, an analysis of the random part of the model (variances and covariances) which may provide new and deep insights into phenomena and mechanisms operating at the level of interest, the periodontal site.

1.4 Introduction to Multilevel Modeling

The data in a first introductory example for the application of multilevel modeling had been collected in a group of 40 periodontally healthy young adults (21 female) with good oral hygiene and has extensively been published using some of the above methods (Müller et al. 2000b, c). A thorough mucogingival examination consisted of measurements of thickness (as measured with a special ultrasonic device with a resolution of 0.1 mm) and width of gingiva, periodontal probing depth, bleeding on probing, and ratios of crown width to its length of incisors, canines and premolars. The latter were not further considered here.

For a tutorial on how to deal with hierarchical data in periodontal research (Müller 2009b) the question had been asked: Is gingival thickness as measured mid-buccally at each tooth related to gingival width? A very simple expression of the relationship, disregarding sampling in different subjects, may be a linear regression model as described by equation (1.1)

$$\begin{aligned}y_i &= \beta_0 + \beta_1 x_i + e_i \\e_i &\sim N(0, \sigma^2)\end{aligned}\tag{1.1}$$

Teeth, indexed by i , were sampled. The response y is gingival thickness, and x is the predictor, gingival width, as measured with a periodontal probe to the nearest

mm. Both variables were centered on their respective means. The residuals e_i are assumed to have normal distribution with variance σ^2 , of course with the further assumption of being independently distributed. Neither β_0 (estimate -0.002; standard error 0.015) nor β_1 (-0.003; 0.011) were significantly different from 0 (which has of course to be expected for β_0 due to centering). The variance σ^2 was 0.273 (0.011). The relationship between gingival thickness and width (centered on their respective means) is graphically displayed in *Fig. 1.4*.

Since several teeth were sampled in a given subject the assumption of independence is of course not justified. As discussed above, measurements of gingival thickness at two teeth sampled in a certain individual will be more similar than those at teeth sampled in different subjects, even if adjusted for gingival width (x_i).

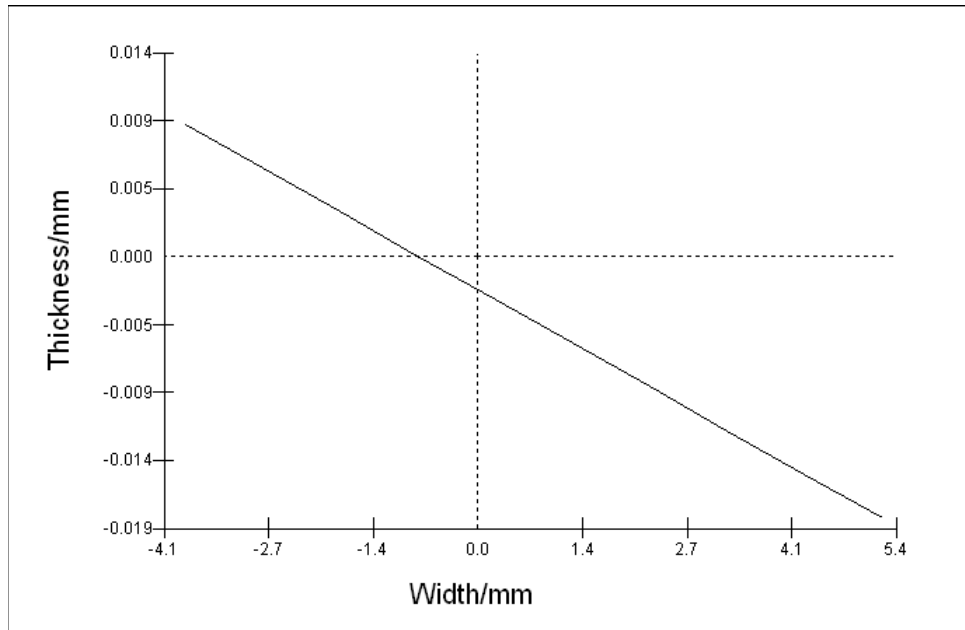


Fig. 1.4 Regression of gingival thickness (y -axis) on gingival width (x -axis, both in mm). Subject effects are disregarded (model 1.1). Neither the intercept nor the regression coefficient differs significantly from 0.

Thus, a more elaborate model may be a natural extension of equation (1.1):

$$\begin{aligned}
 y_{ij} &= \beta_0 + \beta_1 x_{ij} + u_j + e_{ij} \\
 u_j &\sim N(0, \sigma_u^2) \\
 e_{ij} &\sim N(0, \sigma_e^2)
 \end{aligned}
 \tag{1.2}$$

with i indexing teeth and j subjects. Subject effects are described by the residuals u_j . That yields a group of parallel regression lines with different intercepts as is shown in *Fig. 1.5*.

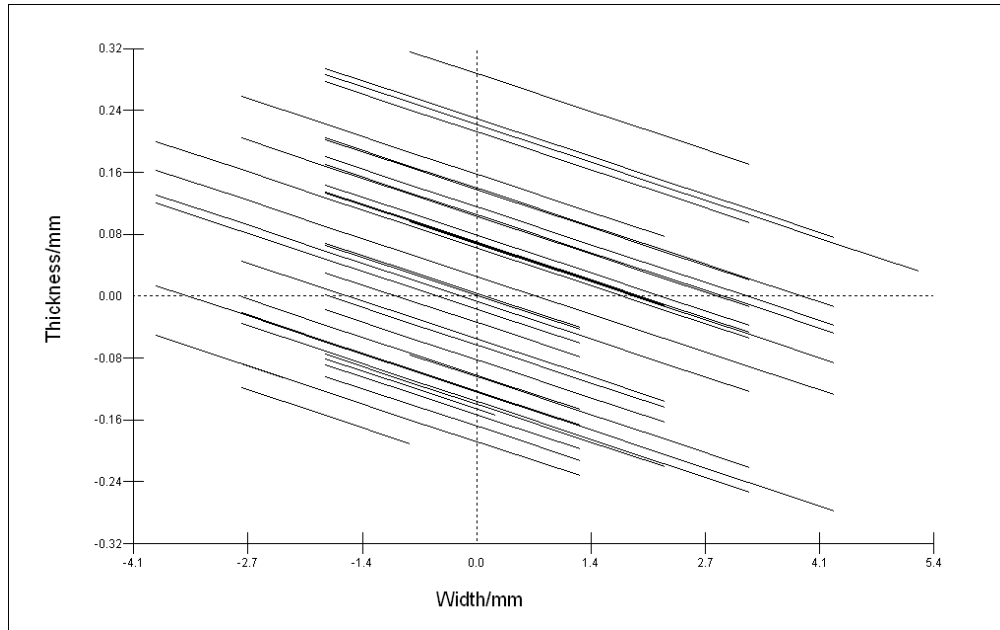


Fig. 1.5 Parallel regression lines for 40 subjects representing regressions of gingival thickness on gingival width according to a random intercept model (model 1.2).

The random intercept model in equation (1.2) is also known as “variance components” model (see Chapter 2) since, given subject and tooth residuals are independent, the total (unexplained) variance is the sum of the between-subject variance σ_u^2 and the between-tooth variance σ_e^2 . In this random effects model, subject effects are modeled as a random variable depending on a single parameter, the variance σ_u^2 . The parallel lines in *Fig. 1.5* have different intercepts and the variation between these intercepts is called *simple* level 2 variation. Subjects are thought of as randomly sampled from a larger population about we wish to make inferences.

When considering the present data, this model points to a significant influence of gingival width; the regression coefficient β_1 was -0.036 with a standard error of 0.011. While the mean intercept β_0 was again close to zero (estimate -0.004; standard error 0.028), subjects' intercepts varied with σ_u^2 of 0.024 (0.007). The tooth level variance σ_e^2 was 0.251 (0.011). The likelihood ratio test statistic (with one additional parameter, thus 1 degree of freedom) for this and the model described in equation (1.1) was 41.52 ($p < 0.001$), pointing to a better fit of the more elaborate model to the data.

But does this model in fact describe the reality in such a way that one can, with justification and some confidence, predict the outcome, gingival thickness?

In the above random intercept model (1.2) the (negative) relationship between gingival thickness and width was assumed to be the same for all subjects. But should we expect this in a biological system, in particular when considering the by far non-significant relationship in the model described in equation (1.1)? It is much more likely that, in reality, the relationship with gingival width varies from subject to subject. A random coefficient model with different slope predictions for subjects' regression lines may be written as

$$\begin{aligned}
 y_{ij} &= \beta_0 + \beta_{1j}x_{ij} + u_{0j} + e_{ij} \\
 \beta_{1j} &= \beta_1 + u_{1j}
 \end{aligned}
 \tag{1.3}$$

where (u_{0j}, u_{1j}) is assumed bivariate normal with $var(u_{0j}) = \sigma_{u0}^2$, $var(u_{1j}) = \sigma_{u1}^2$, $cov(u_{0j}, u_{1j}) = \sigma_{u01}$.

Now, the coefficient of x (gingival width) is assumed to be random across subjects. Its mean is β_1 , its variance σ_{u1}^2 , and its covariance is σ_{u01} . In this model, the mean intercept β_0 was again very close to zero (-0.001; standard error 0.026). Intercepts for different subjects varied significantly ($p = 0.004$) around the mean with a variance σ_{u0}^2 of 0.017 (0.006). The mean coefficient for x (gingival width) was largely attenuated (-0.028) and, due to the larger standard error of 0.019, no longer significant. Coefficients varied around the mean with variance σ_{u1}^2 of 0.009 (0.003). The covariance σ_{u01} was small (-0.002) and, due to its large standard error of 0.003, not significant. The tooth level variance was again further attenuated to 0.236 (0.010). The likelihood ratio test statistic for this and the random intercept model was 40.18 with 2 degrees of freedom. Thus, the random slope model described the situation significantly ($p < 0.001$) better than the previous model. A graphical representation of the data under consideration is shown in *Fig. 1.6*.

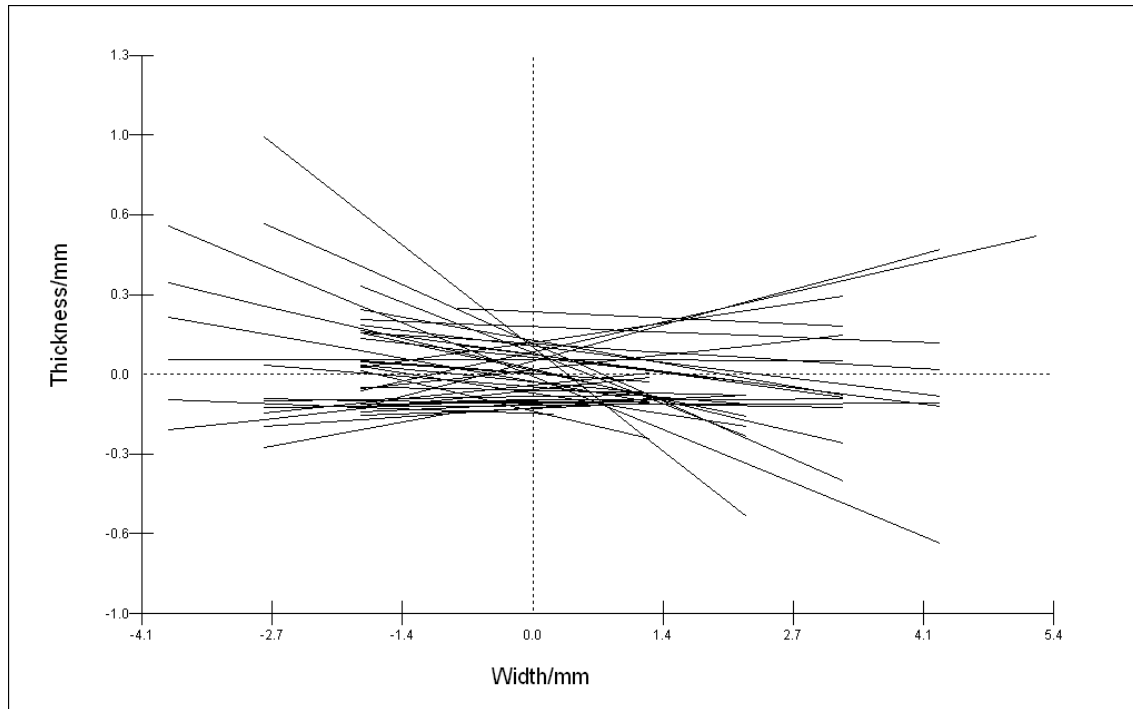


Fig. 1.6 Non-parallel regression lines representing regressions of gingival thickness on gingival width according to the random coefficient model. Each subject provides a regression line with a different slope (model 1.3).

Thus, if we allow the slopes of the lines to vary as in *Fig. 1.6*, then differences between subjects depend on teeth's gingival width. This is an example of *complex* level 2 variation.

So far, only gingival width has been considered as a possible predictor of gingival thickness in two 2-level models, random intercept and random coefficient. It turned out that its influence, if any, is rather low. We can assume, however, that thickness of gingiva may be related to other covariates such as periodontal probing depth at the tooth level, and gender at the subject level, as well. Tooth level covariate

probing depth may again differ from subject to subject. Respective possible extensions of the models described in equations (1.2) and (1.3) and numerous further applications of multilevel modeling will be dealt with in the following chapters.

2 Variance Components

In the previous chapter, the question had been asked whether gingival thickness, as measured mid-buccally at each tooth, was related to width of buccal gingiva.

Several models had been built in a stepwise approach: a model ignoring the subject level, a two-level random intercept model, and a two-level random coefficient model. It could be shown that each model fitted the collected data better than the previous one. Eventually it turned out that the influence of gingival width on gingival thickness, if any, was low in general but depended significantly on the subject.

Gingival dimensions, i.e. its width and thickness, have long been related to the so-called periodontal phenotype, which appears to be a characteristic of a given subject. Gingival dimensions show great intra- and interindividual variation which is associated with tooth type and shape, and which is also mainly genetically determined. Our group has used cluster analysis of gingival appearance at upper anterior teeth and the respective shapes of the teeth of data collected in two independent samples of young adults (Müller and Eger 1997, Müller et al. 2000b) to study the periodontal phenotype in some detail. As cluster analysis is largely explorative, and external validity is questionable, the typical hierarchical structure of data collected in a third sample acquired in dental students was analyzed by

multilevel modeling (Müller and Könönen 2005) with the specific aim to determine subject variation of gingival thickness, a supposed important part of the periodontal phenotype.

A most reasonable way to set up any multilevel model is to start with the basic variance components, or null, model without any covariates. The model should then be built up to increasing complexity by adding possible covariates which are assumed to have an influence on the response variable, and then checking whether they have substantial and/or significant fixed and random coefficients.

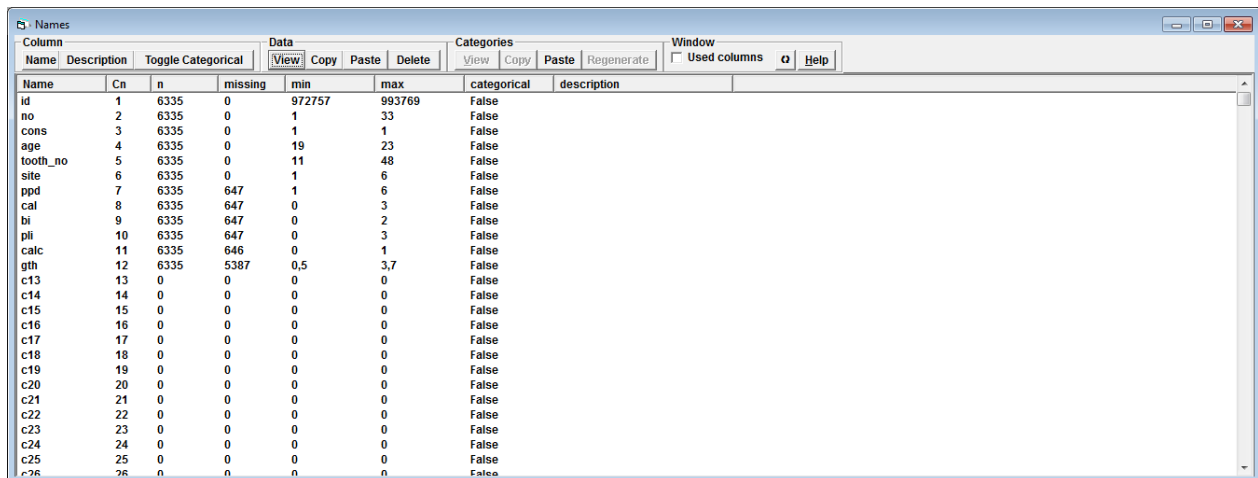
An *MLwiN* worksheet had been prepared already by importing the data from an EXCEL file (*vcgth.wsz*). How to import data from, for instance, an EXCEL file will be explained in Chapter 3. Our *MLwiN* file contains the following variables:

Variable	Description
id	Subject's identifier
no	Subject number (1-33)
cons	A column of ones. If included as an explanatory variable in a regression model, its coefficient is the intercept
age	Subject's age in years
tooth_no	FDI notation of teeth (11-48)
site	Site code (mb: 1, b: 2, db: 3, dl: 4, l: 5, ml: 6)
ppd	Periodontal probing depth (mm)
cal	Clinical attachment level (mm)
bi	Bleeding index (0-2)
pli	Plaque index (0-3)
calc	Calculus (0, 1)
ght	Gingival thickness (mm)

Since all subjects were female, gender was not a variable. Note that the data have to be sorted in *MLwiN* by level 1 (here tooth) nested within level 2 (subject), and nested in higher levels if that was the case.

2.1 Setting up a Variance Components Model

After we have installed *MLwiN*, we may open the file *vcgth.wsz*. The worksheet will probably automatically open. *MLwiN* worksheets contain data and other information in a series of columns, as on a spreadsheet. For a general description of the program, the user is referred to Rasbash et al. (2015).



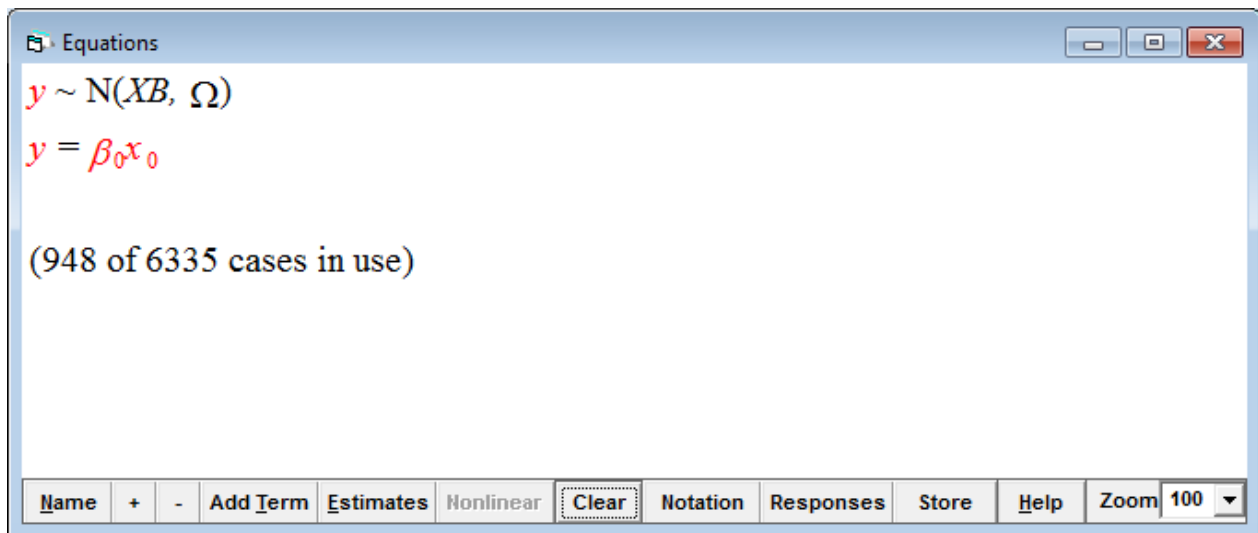
Name	Description	Toggle Categorical	Data				Categories				Window		
Name	Cn	n	missing	min	max	categorical	description	View	Copy	Paste	Regenerate	Used columns	Help
id	1	6335	0	972757	993769	False							
no	2	6335	0	1	33	False							
cons	3	6335	0	1	1	False							
age	4	6335	0	19	23	False							
tooth_no	5	6335	0	11	48	False							
site	6	6335	0	1	6	False							
ppd	7	6335	647	1	6	False							
cal	8	6335	647	0	3	False							
bi	9	6335	647	0	2	False							
pli	10	6335	647	0	3	False							
calc	11	6335	646	0	1	False							
gth	12	6335	5387	0,5	3,7	False							
c13	13	0	0	0	0	False							
c14	14	0	0	0	0	False							
c15	15	0	0	0	0	False							
c16	16	0	0	0	0	False							
c17	17	0	0	0	0	False							
c18	18	0	0	0	0	False							
c19	19	0	0	0	0	False							
c20	20	0	0	0	0	False							
c21	21	0	0	0	0	False							
c22	22	0	0	0	0	False							
c23	23	0	0	0	0	False							
c24	24	0	0	0	0	False							
c25	25	0	0	0	0	False							
c26	26	0	0	0	0	False							

In order to start tackling the question about subject variation of gingival thickness as compared to tooth variation we need to set up a random effects or multilevel model with no further explanatory variables (cf. model (1.2) in chapter 1), which can be written as:

$$\begin{aligned}
y_{ij} &= \beta_{0j} + e_{ij} \\
\beta_{0j} &= \beta_0 + u_{0j} \\
u_{0j} &\sim N(0, \sigma_{u_0}^2) \\
e_{ij} &\sim N(0, \sigma_e^2)
\end{aligned}
\tag{2.1}$$

In this model, u_{0j} , the subject effects, are assumed to be random variables coming from a Normal distribution with variance $\sigma_{u_0}^2$. β_0 is regarded the overall population mean with the u_{0j} 's representing each subject's difference from this mean. Thus, the mean of the random variable u_{0j} is zero.

We start by selecting from the **Model** menu **Equations**. The following window will appear:



In order to specify the response variable, i.e., gingival thickness, just click on so far red **y** (indicating that it has not yet been identified) in the equation window. In the appearing window, we select **gth** from the drop-down list labeled **y**, and from the

drop-down list labeled **N levels** we select **2-ij**. Then we select **id** from the appearing drop-down list labeled **level 2(j)** and **tooth_no** from the drop-down list labeled **level 1(i)**. We click **done** and the equation window looks as follows:



Still, fixed parameter x_0 appears red, meaning that it has not yet been specified. Since we are interested in variances only (at the subject and tooth levels), we select **cons**, a column of ones. In the appearing window we check both boxes labeled **j(id)** and **i(tooth_no)** and click **done**. Note that the equation window has changed its appearance. When now clicking the **Start** button on the main window's tool bar, the model is run.

Equations

$$gth_{ij} \sim N(XB, \Omega)$$

$$gth_{ij} = \beta_{0ij} \text{cons}$$

$$\beta_{0ij} = 0.931(0.021) + u_{0j} + e_{0ij}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.008(0.003) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 0.183(0.009) \end{bmatrix}$$

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

The model has instantly converged, and all estimates have turned from blue to green.

In *Table 2.1* we see the results of a two-level variance components model without further covariates, i.e., the null model, displayed. Mean gingival thickness (the intercept β_0) is 0.931 mm with a standard error (SE) of 0.021 mm. Variation at both the subject and the tooth level (see the respective variances of residuals u_{0j} and e_{0ij}) is substantial. However, subject variance amounts to only 0.008 (SE 0.003), which means that it is just 4.2% of the total variance which amounts to 0.191 (0.008 + 0.183). The *variance partition coefficient* (VPC) $\sigma_{u0}^2 / (\sigma_{u0}^2 + \sigma_e^2)$ which is interpreted as the proportion of the total residual variation that is due to differences between subjects is frequently called intra-class correlation coefficient which measures the similarity between subunits (here, teeth) in the same “class” (subject).

<i>Table 2.1</i> Two-level variance components model (null model) of facial thickness.		
	Estimates	95% confidence interval
Fixed effects		
Intercept	0.931	0.891; 0.971
Random effects (variances)		
Subject (σ_{u0}^2)	0.008	0.001; 0.015
Tooth (σ_{e0}^2)	0.183	0.166; 0.200

-2*log likelihood = 1108.529

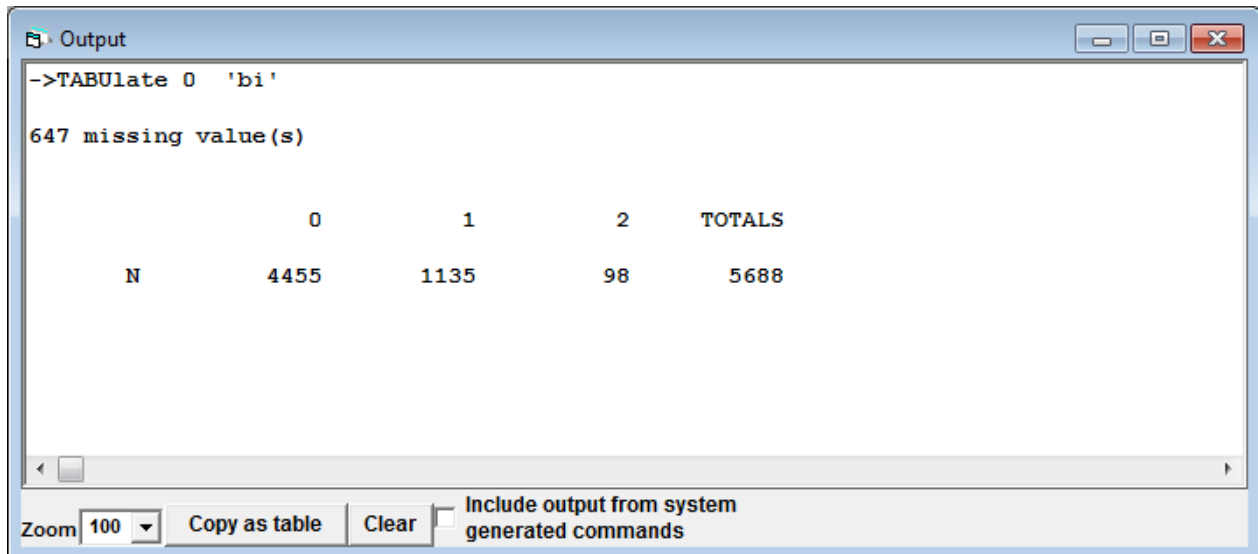
We may save the model under a new name, say, *VCgth01.wsz*.

2.2 Extension of the Variance Components Model

We now may want to know whether gingival thickness is associated with other clinical variables which have routinely been recorded when subjects had been examined. For instance, at the tooth level, periodontal probing depth (ppd), bleeding on probing (bop) and visible plaque index (vpi) may be of interest.

Now, bleeding after probing had been assessed according to a rather subjective bleeding index which differentiates slight from profuse bleeding. We want to know, how often “profuse bleeding” had actually occurred. In the **Basic Statistics** menu we select **Tabulate** and from the drop-down list in **Columns** we select **bi**.

By clicking on **Tabulate**, we see in an output that the vast majority of sites (4455) did not bleed after probing (bi=0) while slight bleeding occurred at 1135 sites (bi=1). Ninety-eight sites profusely bled (bi=2).



```
->TABULATE 0 'bi'  
647 missing value(s)
```

	0	1	2	TOTALS
N	4455	1135	98	5688

We want to join slight and profuse bleeding to a new variable, bleeding on probing, bop. Thus, we need to recode the variable bi. We click in the **Data Manipulation** menu **recode** and select **by Value**. From the drop-down list we select **bi**. **Old values** for **bi** are 0, 1 or 2. In the **New Values** column we want to change 2 to 1. We want to save the new variable bop in **Destination Column c13**. We then click on **execute**. We click on **c13** in the worksheet and rename the variable as **bop**. We then change the variable to categorical by clicking **Toggle Categorical** in the **Names** window.

In a similar way, we want to recode pli. Scores 0 and 1 should be 0, and scores 2 and 3 should be 1 in the new variable, visible plaque index, vpi. In the **Data Manipulation** menu we select **recode**, and this time **by Range**. First we select **pli** from **Input columns** and **c14** from the **Output columns**. **Values in range** 0 to 1 are recoded **to new value** of 0. We click **Add to action list** and the recoding appears on the right side of the window. Then we recode **Values in range** of 2 to 3 **to new value** 1, click on **Add to action list**, and the recoding appears on the action list. We then click **Execute**. In the worksheet, we click on **c14** and rename the variable as **vpi**.

And finally, gingival thickness might depend, for instance, on (subject level) average ppd, bi, or pli. In the **Data Manipulation** menu, we select **MultiLevel data manipulations**, and from the **Operation** drop-down list **Average** and **On blocks defined by** we select **id**.

From the drop-down list of **Input columns**, we select **ppd**, and **c15** from **Output columns**. We **Add to action list** by clicking on the respective button, where the operation appears. Then we select **bi** from **Input columns** and **c16** from **Output columns** and add this to the action list. And finally, the average **pli** of each subject should be listed in **c17**. After clicking on **Execute**, we need to change the names in the worksheet accordingly:

Name	Cn	n	missing	min	max	categorical	description
id	1	6335	0	972757	993769	False	
no	2	6335	0	1	33	False	
cons	3	6335	0	1	1	False	
age	4	6335	0	19	23	False	
tooth_no	5	6335	0	11	48	False	
site	6	6335	0	1	6	False	
ppd	7	6335	647	1	6	False	
cal	8	6335	647	0	3	False	
bi	9	6335	647	0	2	False	
pli	10	6335	647	0	3	False	
calc	11	6335	646	0	1	False	
gth	12	6335	5387	0,5	3,7	False	
bop	13	6335	647	0	1	True	
vpi	14	6335	647	0	1	True	
aveppd	15	6335	0	1,297619	2,373563	False	
avebi	16	6335	0	3,571429E-02	0,5517241	False	
avepli	17	6335	0	0,4133333	1,827957	False	
c18	18	0	0	0	0	False	
c19	19	0	0	0	0	False	
c20	20	0	0	0	0	False	
c21	21	0	0	0	0	False	
c22	22	0	0	0	0	False	
c23	23	0	0	0	0	False	
c24	24	0	0	0	0	False	
c25	25	0	0	0	0	False	
c26	26	0	0	0	0	False	

After we have executed these recoding and manipulation of the data we turn again to our variance components model. We click the **Add Term** button in the model equation window and select from the **variable** drop-down list **ppd**. The default is **uncentred**, and we just click on **Done**. The variable appears (in blue) in the equation window. In a similar way, we then add bop and vpi and finally aveppd, avebi and avepli. When now clicking on the **More** button in the main window's tool bar, the model is run and instantly converges.


```

Equations
gthy ~ N(XB, Ω)
gthy = β0ycons + 0.333(0.027)ppdy + 0.070(0.045)bop_1y + 0.106(0.032)vpi_1y + -0.155(0.081)aveppd + -0.341(0.170)avebi + 0.059(0.054)avepli
β0y = 0.724(0.132) + u0y + e0y

[u0y] ~ N(0, Ωu) : Ωu = [0.006(0.003)]
[e0y] ~ N(0, Ωe) : Ωe = [0.149(0.007)]

-2*loglikelihood(IGLS Deviance) = 912.656(948 of 6335 cases in use)

```

Gingival thickness was positively associated with the respective, tooth-level, periodontal probing depth . The estimate was 0.333 with a standard error (SE) of 0.027. A 95% confidence interval (CI) may be calculated by multiplying the SE by 1.96, i.e. 0.053, and add and subtract this to and from the point estimate, so 0.280 to 0.386. *MLwiN* offers a useful tool for calculating the 95% CI. We click in the **Model** menu on **Intervals and tests**. We want to know the 95% CI for the fixed parameter *ppd*, so we check **fixed** at the bottom of the window. We then enter 1 for **fixed: *ppd*** and click **Calc**. The value of 0.053 for **+/- 95% sep.** appears at the bottom.

There was a tendency of increased gingival thickness at sites bleeding after probing and a positive association with visible plaque. At the subject level, in particular average bleeding index and periodontal probing depth were negatively associated with gingival thickness (*Table 2.2*).

The random part of the model indicates that, as expected, (unexplained) variation at both subject and tooth level was reduced as compared with the null model in the previous chapter.

<i>Table 2.2</i> Two-level random intercept model of facial gingival thickness		
	Estimate	95% confidence interval
Fixed effects		
Intercept	0.724	0.465; 0.983
<i>Tooth level</i>		
ppd	0.333	0.280; 0.386
bop	0.070	-0.018; 0.158
vpi	0.106	0.044; 0.168
<i>Subject level</i>		
Average ppd	-0.155	-0.313; 0.003
Average bi	-0.341	-0.675; -0.007
Average pli	0.059	-0.046; 0.164
Random effects		
Subject (σ_{u0}^2)	0.006	0.001; 0.011
Tooth (σ_{e0}^2)	0.149	0.135; 0.163

-2*log likelihood = 912.656

The likelihood (L) ratio statistic is computed as $-2*\log L_1 - (-2*\log L_2)$ which, under the null hypothesis H_0 , follows a chi-squared distribution on q degrees of freedom, where q is the difference in the number of parameters between the models. So, for the two models under consideration here it was $1108.529 - 912.656 = 195.873$ with 6 degrees of freedom. A p -value for the test can be obtained by selecting **Tail Areas** from the **Basic Statistics** menu. Under **Operation**, we select **Chi-Squared**.

We type the **Value** of 195.873 and then 6 for **Degrees of freedom**. After clicking **Calculate** we obtain an extremely small value for p . Thus, the model was significantly improved by adding tooth- and subject-related covariates.

As a further extension of the model we want to assess the influence of different tooth types on gingival thickness. The FDI tooth notation has first to be recoded.

We click in the **Data Manipulation** menu **recode** and select **by Value**. From **Source Column** we select **tooth_no** and for **Destination Column** **c20**. **Old values** 11 and 21 (central incisors in the maxilla) should be changed to 1, old values 12 and 22 (lateral incisors in the maxilla) to 2 and so forth. Old values 31 and 41 should be changed to 9, old values 32 and 42 to 10, so that there will be 16 types of teeth (since the dentition is symmetric). After we have clicked **Execute**, we change the name of c20 to **tooth_type** and click **Toggle Categorical**.

We now want to add the new variable for tooth type to our model. We click on the **Add Term** button in the model equation window and select **tooth_type** from the drop-down list. Since the variable is now categorical, we are immediately informed that tooth type 1 (central incisor in the maxilla) will be the reference category by default (from the respective drop-down list of **ref. cat.** we might select a different reference category).

In the model equation window, all tooth types are now included in the model. We click on the **More** button in the main window's tool bar, the model is run and instantly converges. Estimates have changed color to green.

```

Equations
gthy ~ N(XB, Ω)
gthy = β0ycons + 0.067(0.025)ppdy + 0.047(0.036)bop_1y + -0.011(0.028)vpi_1y + 0.120(0.071)aveppd + -0.395(0.149)avebi + 0.125(0.047)avepli +
-0.005(0.053)tooth_2 + -0.205(0.053)tooth_3 + -0.222(0.055)tooth_4 + -0.178(0.053)tooth_5 + -0.149(0.054)tooth_6 + -0.055(0.056)tooth_7 +
0.158(0.070)tooth_8 + -0.259(0.053)tooth_9 + -0.242(0.053)tooth_10 + -0.258(0.053)tooth_11 + -0.284(0.055)tooth_12 + -0.226(0.053)tooth_13 +
0.084(0.053)tooth_14 + 0.635(0.056)tooth_15 + 0.923(0.077)tooth_16
β0y = 0.636(0.122) + u0y + e0y
[u0y] ~ N(0, Ωu) : Ωu = [0.005(0.002)]
[e0y] ~ N(0, Ωe) : Ωe = [0.091(0.004)]
-2*loglikelihood(IGLS Deviance) = 453.904(948 of 6335 cases in use)

```

After tooth type had been included in the model, significant changes have occurred to the previously entered periodontal probing depth, bleeding on probing and visible plaque index. All respective parameter estimates are largely attenuated. As can be expected, the still unexplained variation at the tooth level was also largely reduced as compared to the previous model. The likelihood ratio test indicates that the model was further improved with a test statistic of 458.752 and 15 degrees of freedom.

Table 2.3 Two-level random intercept model of facial gingival thickness adjusted for tooth type

	Estimate	95% confidence interval
Fixed effects		
Intercept	0.636	0.397; 0.875
<i>Tooth level</i>		
ppd	0.067	0.018; 0.116
bop	0.047	-0.023; 0.117
vpi	-0.011	-0.066; 0.044
<i>Tooth types</i>		
Upper lateral incisor	-0.005	-0.108; 0.098
Upper canine	-0.205	-0.309; -0.101
Upper 1 st premolar	-0.222	-0.331; -0.113
Upper 2 nd premolar	-0.178	-0.283; -0.073
Upper 1 st molar	-0.149	-0.254; -0.044
Upper 2 nd molar	-0.055	-0.165; 0.055
Upper 3 rd molar	0.158	0.021; 0.295
Lower central incisor	-0.259	-0.363; -0.155
Lower lateral incisor	-0.242	-0.346; -0.138
Lower canine	-0.258	-0.362; -0.258
Lower 1 st premolar	-0.284	-0.357; -0.175
Lower 2 nd premolar	-0.226	-0.331; -0.121
Lower 1 st molar	0.084	-0.020; 0.188
Lower 2 nd molar	0.635	0.526; 0.744
Lower 3 rd molar	0.923	0.773; 1.073
<i>Subject level</i>		
Average PPD	0.120	-0.019; 0.259
Average BI	-0.395	-0.686; -0.104
Average PII	0.125	0.033; 0.217
Random effects		
Subject (σ_{u0}^2)	0.005	0.001; 0.009
Tooth (σ_{e0}^2)	0.091	0.083; 0.099

-2*log likelihood = 453.904

A major conclusion may be that gingival thickness is mainly associated with tooth-related variables. But there are also subject-related factors. For instance, gingiva

was thin if average bleeding tendency was higher. Altogether, subject variability of gingival thickness, which may be related to the periodontal phenotype, was low. It may add to total variance, but to a very low extent of about 4-5%.

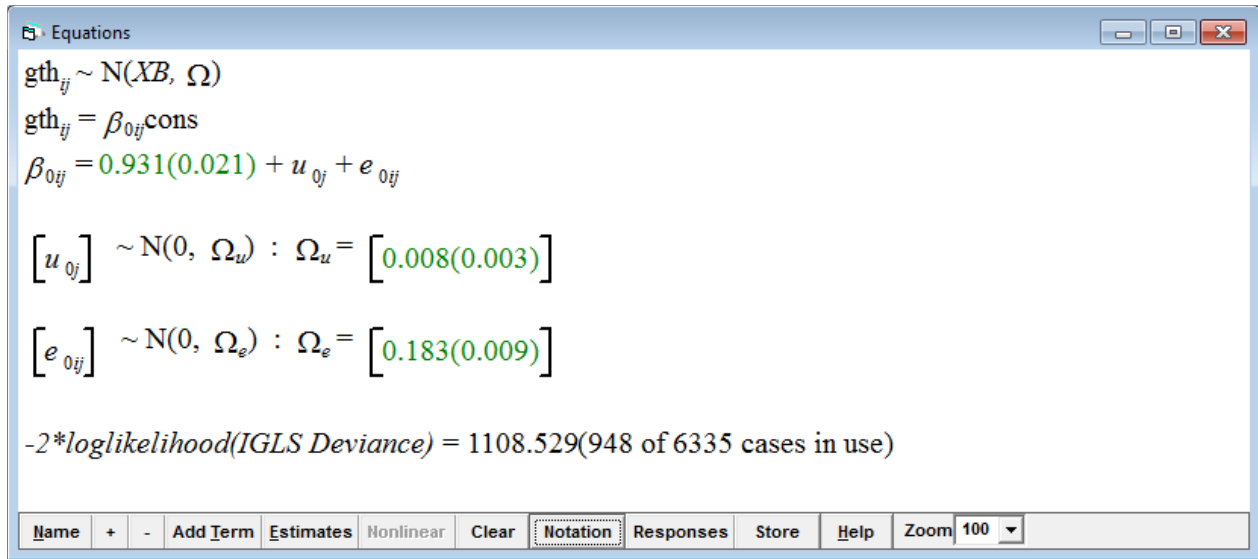
2.3 Multilevel Residuals

When setting up the previous model, we had started with a variance components, or null, model given in equation (2.1)

$$\begin{aligned}y_{ij} &= \beta_{0j} + e_{ij} \\ \beta_{0j} &= \beta_0 + u_{0j} \\ u_{0j} &\sim N(0, \sigma_{u_0}^2) \\ e_{ij} &\sim N(0, \sigma_e^2)\end{aligned}\tag{2.1}$$

As we have mentioned above, the u_{0j} terms are the subject random effects, or subject residuals. In a random effects model, the subject effects are random variables whose distribution is summarized by its mean (zero) and variance $\sigma_{u_0}^2$.

After having run the model, we got the results below.



Equations

$$gth_{ij} \sim N(XB, \Omega)$$

$$gth_{ij} = \beta_{0ij} \text{cons}$$

$$\beta_{0ij} = 0.931(0.021) + u_{0j} + e_{0ij}$$

$$[u_{0j}] \sim N(0, \Omega_u) : \Omega_u = [0.008(0.003)]$$

$$[e_{0ij}] \sim N(0, \Omega_e) : \Omega_e = [0.183(0.009)]$$

-2*loglikelihood(IGLS Deviance) = 1108.529(948 of 6335 cases in use)

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

The model is a two-level variance components model, with the overall mean of the outcome gingival thickness defined by the fixed coefficient β_0 . The second level was introduced by allowing the mean of the j th subject to deviate from the overall mean by u_{0j} , the level 2 residuals. Their mean is zero and in this case their estimated variance is 0.008.

In order to estimate multilevel residuals, suppose that y_{ij} is the observed value of gingival thickness for the i th tooth in the j th subject and that \hat{y}_{ij} is the predicted value from the regression, in the current null model the overall mean of gingival thickness. The *raw residual for this tooth* is $r_{ij} = y_{ij} - \hat{y}_{ij}$. The *raw residual for the j th individual* is then the mean of the r_{ij} for the teeth in the individual, r_{+j} . The estimated level 2 residual for this particular subject is obtained by multiplying r_{+j} by what is known as shrinkage factor:

$$\hat{u}_{0j} = \frac{\sigma_{u0}^2}{\sigma_{u0}^2 + \sigma_e^2/n_j} r_{+j}$$

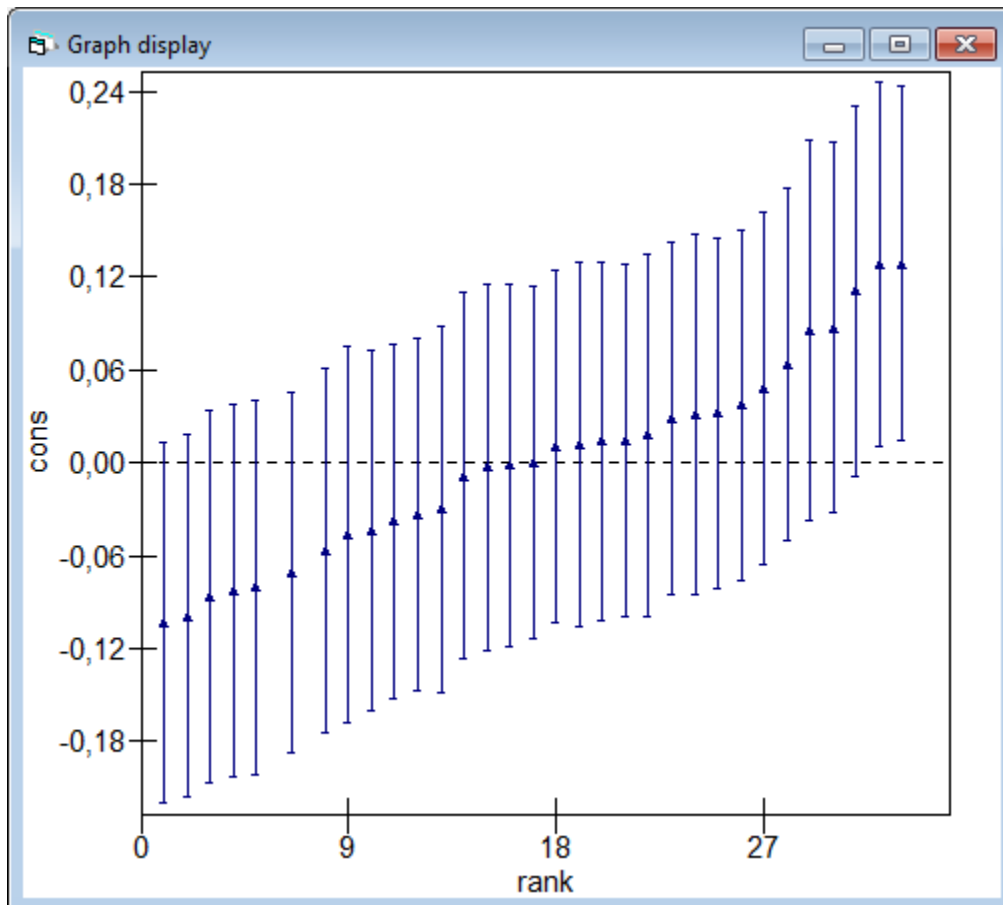
Where n_j is the number of teeth in subject j . Since the multiplier is always less or equal to 1, the estimated residual is usually less in magnitude than the raw residual, it has been *shrunk*. The shrinkage factor will be noticeably less than 1 when σ_e^2 is large compared to σ_{u0}^2 and/or when n_j is small. In either case, there is not so much information about the subject since variation of the outcome variable is large and/or only few teeth were sampled. See for further information on shrinkage factor and shrunken residuals also Healy (2001).

Having estimated the level 2 residuals the level 1 residuals can simply be estimated by the formula $\hat{e}_{ij} = r_{ij} - \hat{u}_{0j}$.

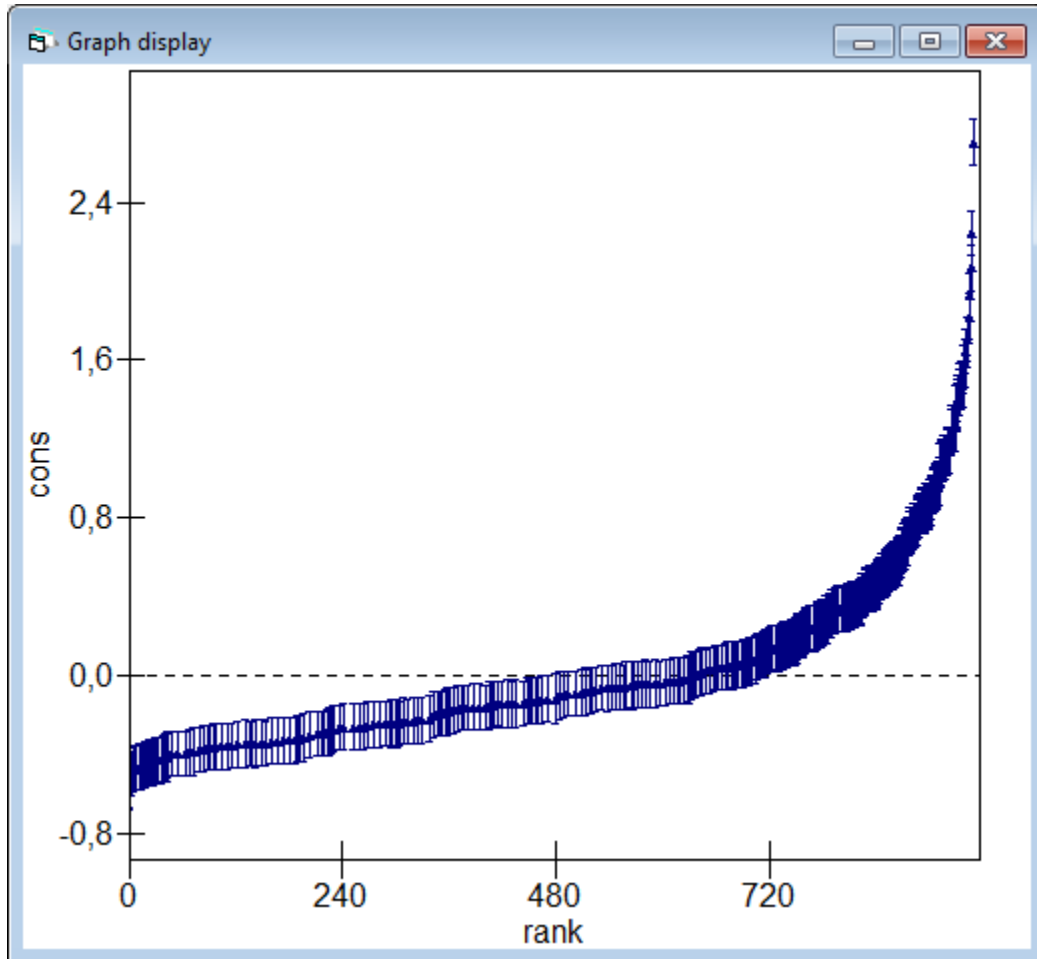
In order look at level 2 residuals we open again the file *VCgth01.wsz*. We select **Model** in the main menu and then **Residuals**. We select the **Settings** tab of the **Residuals** window. The comparative standard deviation (SD) of the residual defined as the SD of $\hat{u}_{0j} - u_{0j}$ is used for making inferences about the unknown underlying value of u_{0j} , given the estimate \hat{u}_{0j} . The standardized residual is defined as $\hat{u}_{0j}/SD(\hat{u}_{0j})$ and may be used for diagnostic plotting to ascertain

Normality etc. From the **level** drop-down list at the bottom we select **2:no**. We

may change the multiplier applied to the **start output at** box to, say, 1.96 to get 95% confidence intervals. We click the **Set column** button to specify the columns into which the computed values of the function will be placed. Nine boxes will appear (from C300 to C308). We then click on **Calc**. Now we click on the **Plots** tab and select the third option in the single frame (residual ± 1.96 SD \times rank). After clicking **Apply**, the following caterpillar plot appears showing residuals of 33 subjects with its respective 95% confidence intervals.



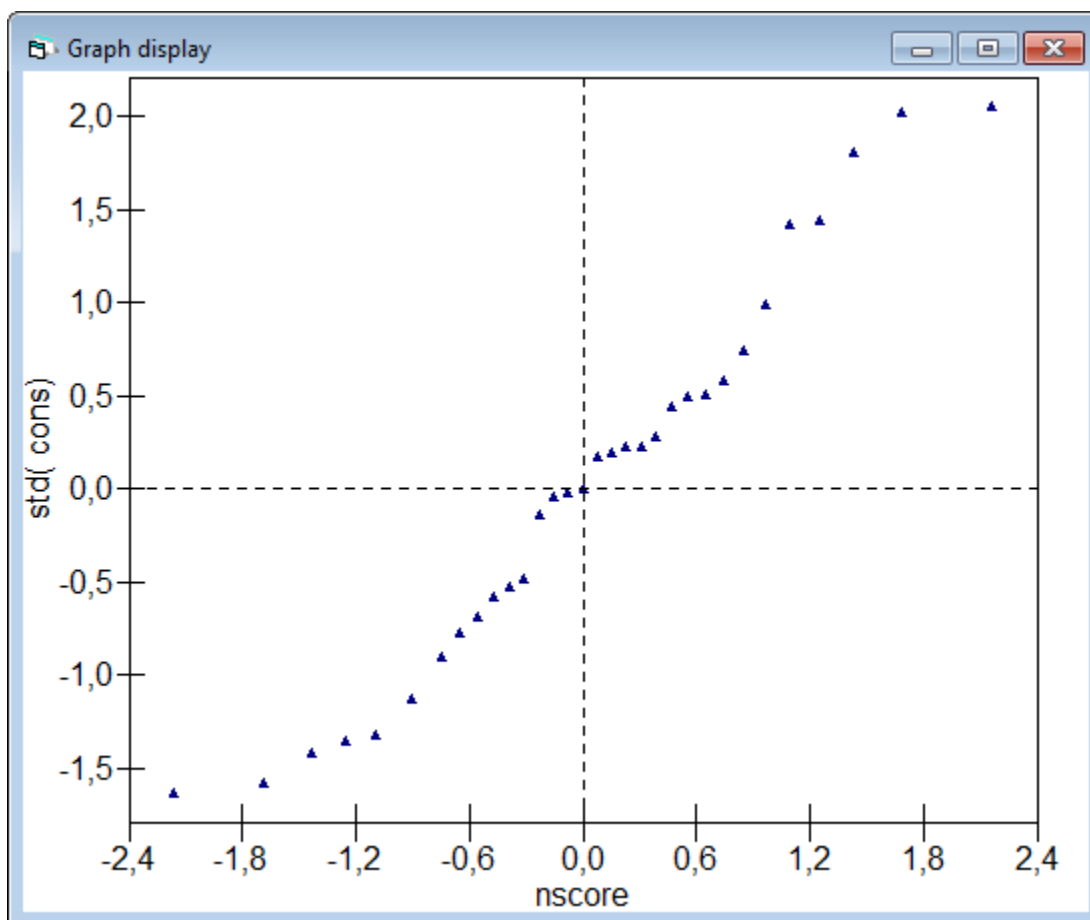
By clicking the **Settings** bar and selecting **1:tooth_no** in the **level** drop-down list at the bottom, one gets a caterpillar plot of the level-1 residuals.



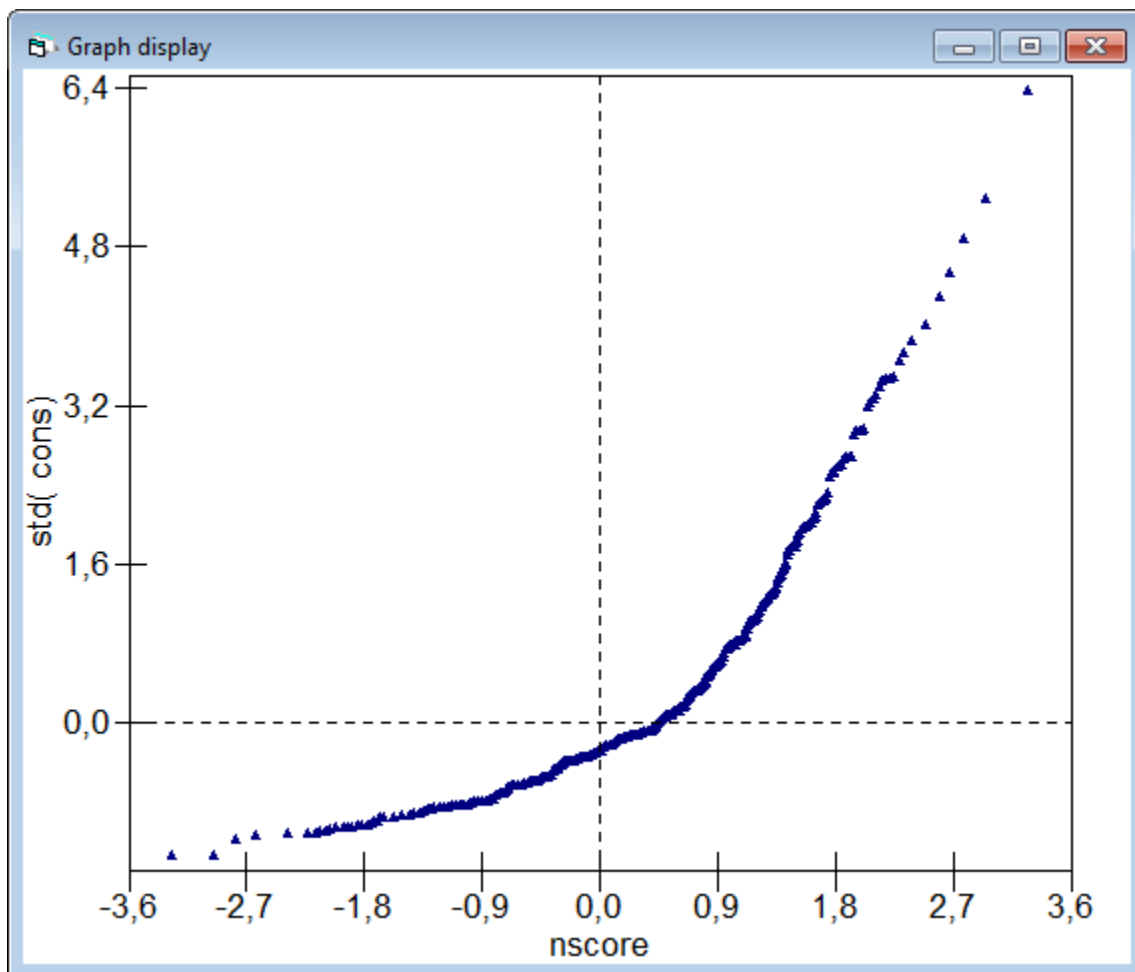
The estimated residuals can (and should) be used to check model assumption. One assumption is that they follow Normal distribution at each level. This can be checked using the Normal probability plot, in which the ranked residuals are plotted against corresponding points on a Normal distribution curve. The points on a Normal plot should lie in approximately on a straight line if the Normality assumption is valid.

We select from the **Model** menu **Residuals** and click on the **Settings** tab of the **Residuals** window. We select **2:no** from the **level** drop-down list. We click on the **Set columns** button and click on **Calc**, after that we click on the **Plots** tab. We click on the first option, **standardized residual x normal scores** and then click **Apply**.

The points lie in fact more or less on a straight line indicating that the Normal assumption was valid.



In order to produce a Normal plot of the level 1 residuals, we just repeat the steps described above but select from the **level** drop-down list **1:tooth_no** and obtain the plot below. We should save the worksheet at this point by clicking on the **File** menu and select **Save worksheet as ...**. We type **VCgth01_residuals** in the box next to **Filename** and click **Save**.



3 Time Series Models

In the two previous chapters, observations have been modeled which had been made at teeth which were nested in subjects. Now, consider that observations had been repeated in a longitudinal way, for example after therapy. For that purpose, we want to define a lower level (one) as repeated measures, or occasion, while teeth and subjects would define levels two and three, respectively.

Consider, for instance changes of the entire gingival unit after the implantation of a bio-resorbable membrane for surgical root coverage employing the principle of guided tissue regeneration. Apart from achievable root coverage, the implantation of the membrane and concomitant coronal advancement of the mucoperiosteal flap leads to an immediate increase in thickness of gingiva and later in width of keratinized tissue. Of course, the mucogingival border is displaced but may re-establish itself later in its original position. Note that these alterations at teeth are non-linear and, since wound healing proceeds and regenerated tissue matures over time, non-monotonic (see example (C) in Fig. 13.1 in Rasbash et al. 2015). And they certainly depend on the subject. So, we have a three-level structure with a sample of subjects in which we study gingival dimensions at teeth, which have been surgically treated, over time. The data had been analyzed by multilevel modeling in some detail by Müller (2008).

In this chapter we want to introduce the data set which had been created in a longitudinal study (Müller et al. 2000d) and set up several multilevel models further elaborating the basic time series model.

3.1 Repeated Measures Data on Gingival Dimensions after Surgical Root Coverage

The data set consists of observations which have been made in 14 patients who had presented with a large variety of recession types at altogether 31 teeth. They had been treated according to the principles of guided tissue regeneration employing a bio-resorbable membrane. Surgical root coverage consisted, after periosteal dissection, of a coronally advanced flap which was secured with sling sutures. Several preoperative clinical parameters and intrasurgical observations were assessed. Patients were followed up for 1 year, and re-examinations of the clinical situation were carried out after 3, 6, 9 and 12 months.

An EXCEL file (*dimension.xlsx*) contains the following primary variables:

<i>Variable</i>	<i>Description</i>
ID	Subject's identifier (1-14)
TOOTH	FDI notation of teeth (11-48)
GI	Gingival index (0-3)
PLI	Plaque index (0-3)
RD	Recession depth (mm)
RW	Recession width (mm)
GW	Gingival width (mm)
MILLER	Miller's classification of recession (1-4)
GTH1	Gingival thickness (mm) at the gingival margin
GTH2	Gingival thickness (mm) at the mucogingival border
GTH3	Thickness of the lining mucosa (mm)
PD	Probing depth (mm)
DEHIS	Bony dehiscence (mm) from the cement-enamel junction as measured intrasurgically

Certain secondary variables, which were composed of primary variables, such as clinical attachment level (CAL), the width of attached gingiva (AG), the location of the mucogingival border (MGB) and the true bony dehiscence (DEHISTRUE), are not further discussed here.

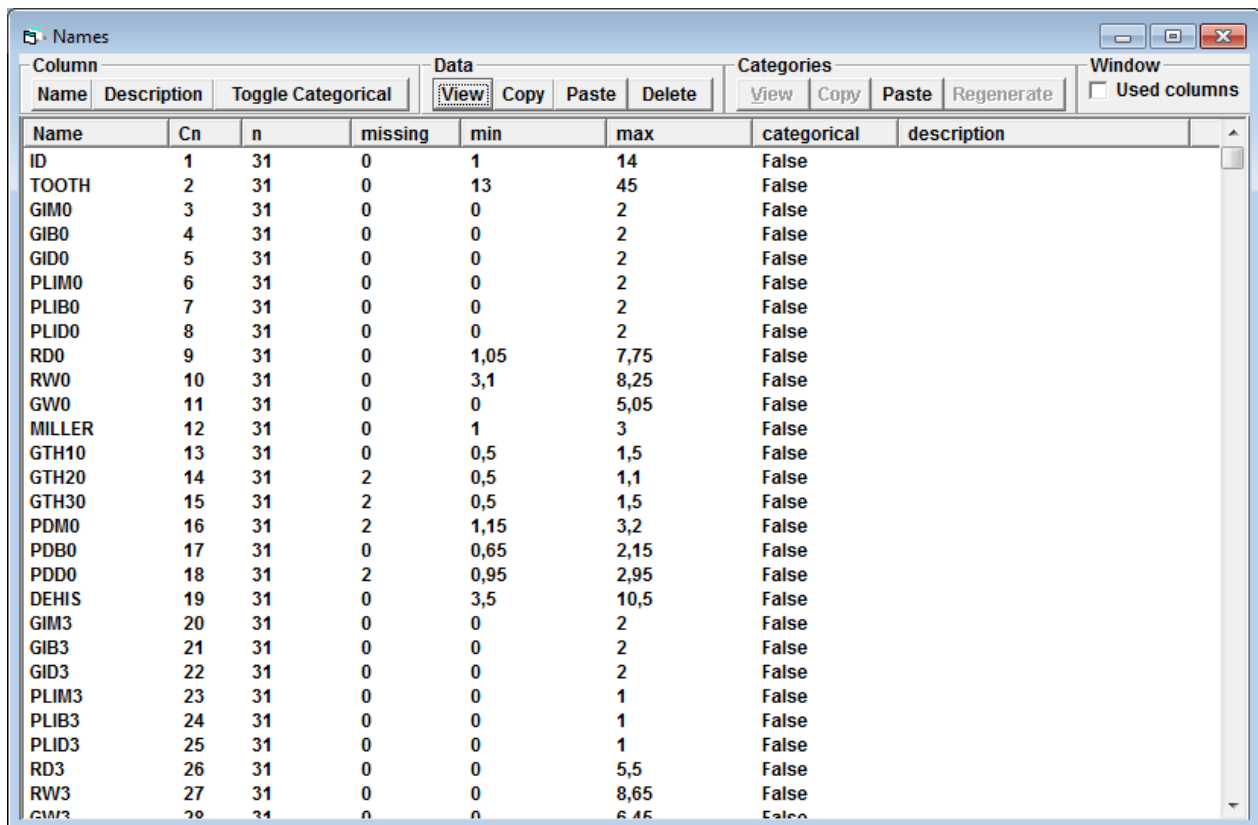
Except for DEHIS which was measured only intrasurgically, all variables were assessed at baseline (0) and after 3, 6, 9 and 12 months. GI, PLI, PD were measured at mesio-buccal (M), mid-buccal (B) and disto-buccal aspects (D) of every treated tooth. RD and GW were measured mid-buccally. RW was the

distance between the intersections of the cemento-enamel junction and the gingival margin.

Now, in order to import the data to *MLwin*, we have to copy them to the clipboard.

From the **File** menu we select **New worksheet**, and from the **Edit** menu **Paste**.

The **Paste View Window** appears and the **Use first row as names** at the bottom is already tagged. We click **Paste**, and the created *MLwin* worksheet appears which we want to save, *dimension_01.wsz*.



The screenshot shows the 'Names' window in MLwin software. The window has a menu bar with 'Column', 'Data', 'Categories', and 'Window'. The 'Data' menu is open, showing options: 'View', 'Copy', 'Paste', and 'Delete'. The 'Categories' menu is also open, showing options: 'View', 'Copy', 'Paste', and 'Regenerate'. The 'Window' menu has a checkbox for 'Used columns'. The main area displays a table with the following data:

Name	Cn	n	missing	min	max	categorical	description
ID	1	31	0	1	14	False	
TOOTH	2	31	0	13	45	False	
GIM0	3	31	0	0	2	False	
GIB0	4	31	0	0	2	False	
GID0	5	31	0	0	2	False	
PLIM0	6	31	0	0	2	False	
PLIB0	7	31	0	0	2	False	
PLID0	8	31	0	0	2	False	
RDO	9	31	0	1,05	7,75	False	
RW0	10	31	0	3,1	8,25	False	
GW0	11	31	0	0	5,05	False	
MILLER	12	31	0	1	3	False	
GTH10	13	31	0	0,5	1,5	False	
GTH20	14	31	2	0,5	1,1	False	
GTH30	15	31	2	0,5	1,5	False	
PDM0	16	31	2	1,15	3,2	False	
PDB0	17	31	0	0,65	2,15	False	
PDD0	18	31	2	0,95	2,95	False	
DEHIS	19	31	0	3,5	10,5	False	
GIM3	20	31	0	0	2	False	
GIB3	21	31	0	0	2	False	
GID3	22	31	0	0	2	False	
PLIM3	23	31	0	0	1	False	
PLIB3	24	31	0	0	1	False	
PLID3	25	31	0	0	1	False	
RD3	26	31	0	0	5,5	False	
RW3	27	31	0	0	8,65	False	
GW3	28	31	0	0	6,45	False	

Note that several data points are missing. While in any longitudinal study participants may leave the study or miss one or more examination occasions, one may assume that the probability of being missing is independent of any random variables in the model, i.e. *completely random dropout*. If the missing mechanism depends on observed measurement one might assume random dropout. As long as a full information estimation procedure is used (as is the case with maximum likelihood for Normal data in *MLwiN*), the actual mechanism of missing can be ignored (see Rasbash et al. 2015, p. 196). Moreover, in multilevel structures we do not require balanced data to obtain efficient estimates. So, it is not necessary to have the same number of lower-level units within higher-level units. To check, we may tabulate the numbers of treated teeth by subjects. We may click on the **Basic Statistics** menu and on **Tabulate** in the drop-down list. While the default for **Columns** is already **ID**, we check the box labeled **Rows**, select **TOOTH** and click **Tabulate**. So, between 1 and 8 teeth per subject had been treated by root coverage with a median of just 1.5.

3.2 Some Basic Models

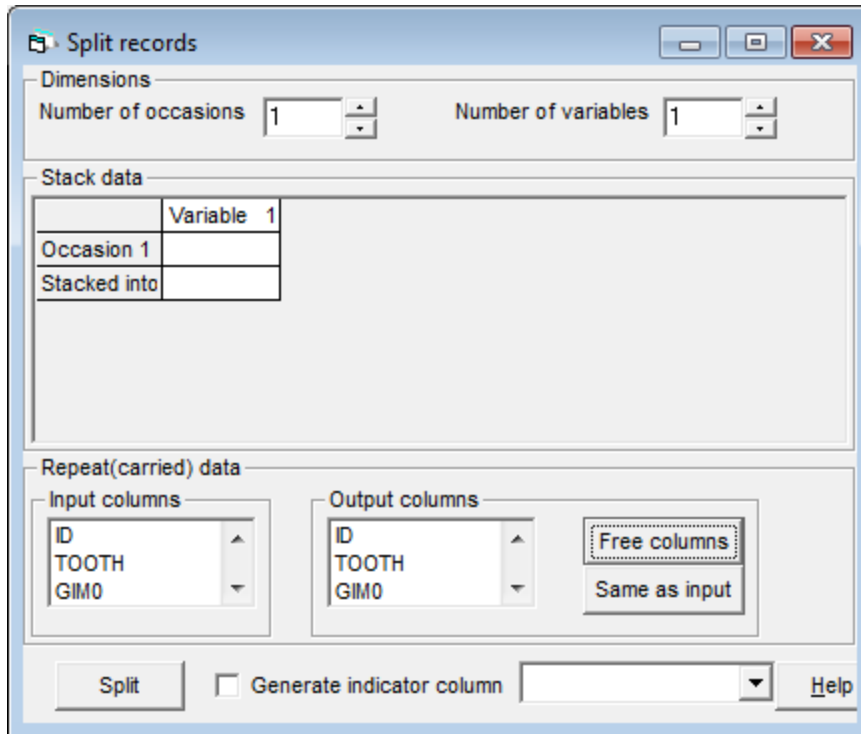
To have a closer look at the above worksheet, we may click on **View** in the **Data** menu and on **view** where we mark all of the appearing variables in the drop-down list.

	ID(31)	TOOTH(31)	GIM0(31)	GIB0(31)	GID0(31)	PLIM0(31)	PLIB0(31)	PLID0(31)	RD0(31)	RW0(31)	GW0(31)	MILLER(31)	GTH10
1	1.000	33.000	0.000	0.000	0.000	0.000	0.000	0.000	3.000	3.850	0.500	2.000	0.500
2	2.000	13.000	0.000	0.000	0.000	1.000	1.000	1.000	2.900	4.400	0.200	2.000	0.600
3	2.000	43.000	0.000	0.000	0.000	0.000	0.000	0.000	2.250	3.750	0.350	1.000	1.050
4	2.000	44.000	0.000	0.000	0.000	0.000	0.000	0.000	2.200	3.750	0.700	1.000	0.900
5	2.000	45.000	0.000	0.000	1.000	0.000	0.000	0.000	2.500	3.950	0.350	1.000	0.700
6	2.000	23.000	1.000	0.000	0.000	0.000	0.000	0.000	1.700	4.650	2.650	1.000	0.800
7	2.000	24.000	0.000	0.000	2.000	0.000	0.000	0.000	2.950	3.950	3.950	1.000	1.400
8	2.000	26.000	0.000	0.000	1.000	0.000	0.000	0.000	4.350	8.250	0.850	2.000	0.950
9	2.000	33.000	1.000	0.000	1.000	2.000	0.000	1.000	2.200	4.800	0.000	3.000	0.550
10	3.000	24.000	2.000	2.000	2.000	2.000	2.000	2.000	3.150	3.450	1.300	1.000	0.550
11	4.000	33.000	1.000	0.000	0.000	0.000	0.000	0.000	2.200	4.950	3.250	3.000	0.900
12	4.000	34.000	0.000	0.000	1.000	0.000	0.000	0.000	2.300	3.850	2.000	1.000	0.750
13	5.000	35.000	2.000	1.000	2.000	0.000	1.000	1.000	3.600	4.600	2.700	1.000	1.500
14	6.000	16.000	0.000	0.000	0.000	0.000	0.000	0.000	2.950	7.500	2.800	1.000	1.000
15	7.000	13.000	0.000	1.000	0.000	0.000	0.000	0.000	4.100	5.150	1.300	1.000	0.750
16	7.000	14.000	0.000	1.000	0.000	0.000	0.000	0.000	3.400	4.650	1.350	1.000	0.700
17	7.000	23.000	0.000	0.000	0.000	0.000	0.000	0.000	4.550	5.500	1.100	3.000	0.600
18	7.000	24.000	0.000	0.000	1.000	0.000	0.000	0.000	3.450	4.950	2.400	3.000	1.000
19	8.000	23.000	0.000	0.000	0.000	0.000	0.000	0.000	3.100	3.450	0.000	2.000	0.600
20	9.000	13.000	0.000	0.000	0.000	0.000	0.000	0.000	1.950	3.100	4.000	1.000	0.900
21	9.000	14.000	0.000	0.000	0.000	0.000	0.000	0.000	2.550	4.050	3.500	1.000	0.800
22	10.000	13.000	0.000	0.000	0.000	0.000	0.000	0.000	7.750	5.650	1.800	2.000	0.650
23	11.000	33.000	0.000	1.000	0.000	0.000	0.000	0.000	2.900	4.300	1.700	3.000	1.000

We notice that most variables have been assessed five times, at baseline (0), and 3, 6, 9 and 12 months after surgery. However, as the data are arranged in the worksheet (each row of the rectangular array corresponds to a certain tooth which has been treated by surgery and contains all data of that particular tooth) the hierarchical structure of the data is not reflected.

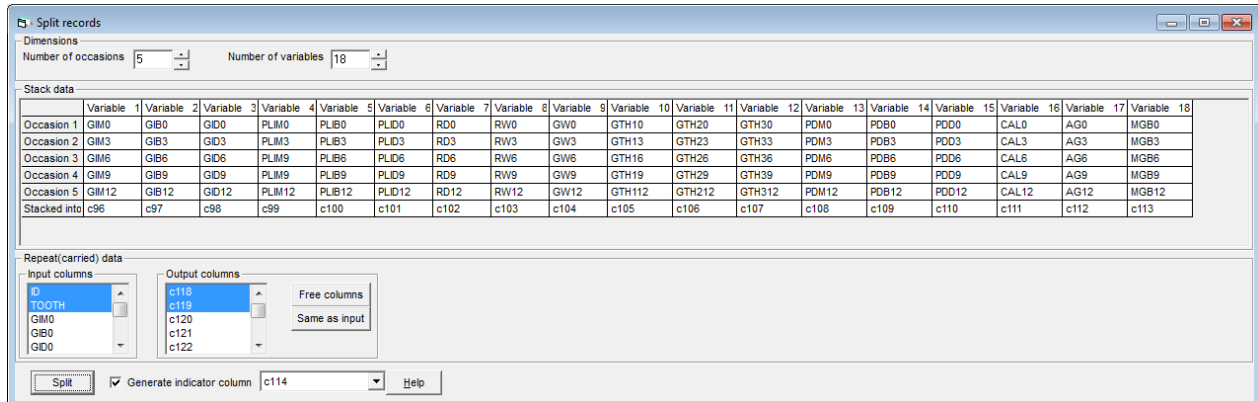
3.2.1 Setting up the data structure

In order to transform a tooth's data record into separate records (or rows) for each occasion, we want to split the records. Thus, in the main menu we click on **Data manipulation** and select **Split records**. The following window appears.



Since data were recorded five times, we set 5 in **Number of occasions**. The **Number of variables** to be split is set 18. In the **Stack data** grid we click on **Variable 1** and select in the drop-down the five variables **GIM0, GIM3, GIM6, GIM9, and GIM12**. Then we click **Done**. We repeat the two above steps for **Variable 2 (GIMB0 ...GIMB12)**, and all the other variables to be stacked. Eventually we want to stack the data into free columns **c96 to c113**. For that purpose we click in the **Stacked into** row of the **Stack data** grid and select in the appearing drop-down lists the respective columns **c96 ... c113**. We tick the **Generate indicator** column check box and select, in the neighboring drop-down list, **c114** for the five occasions.

Four variables have to be repeated (carried data). In the **Repeat (carried data)** frame, we select **ID, TOOTH, MILLER, DEHIS**, and **DEHISTRUE** as input columns and assign to them **c115 ...c119** as the respective outputs.



We then click the **Split** button to execute the changes. Before saving the worksheet, we want to first assign names to columns **c96 ... c119** and thus select **No** when being asked whether we want to save the worksheet. After having renamed the respective columns, the worksheet, which should now be saved under a different name, for instance *dimension_02.wsz*, looks as follows.

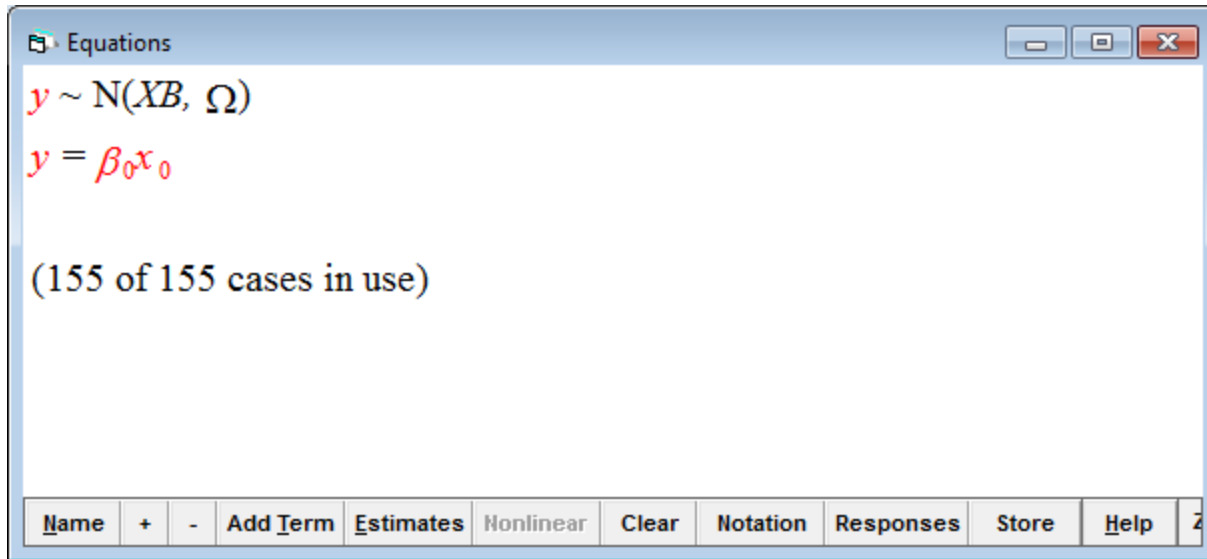
Name	Cn	n	missing	min	max	categorical	description
AG12	89	31	0	-2,65	1,9	False	
MGB0	90	31	0	1,15	9,55	False	
MGB3	91	31	0	0,3	7,05	False	
MGB6	92	31	0	0,55	9,1	False	
MGB9	93	31	0	0,65	6,15	False	
MGB12	94	31	0	0,7	12,55	False	
DEHISTRUE	95	31	0	1,6	7,7	False	
GIM	96	155	0	0	2	False	
GIB	97	155	0	0	2	False	
GID	98	155	0	0	2	False	
PLIM	99	155	0	0	2	False	
PLIB	100	155	0	0	2	False	
PLID	101	155	0	0	2	False	
RD	102	155	0	0	7,75	False	
RW	103	155	0	0	15	False	
GW	104	155	0	0	6,45	False	
GTH1	105	155	0	0,5	2,7	False	
GTH2	106	155	5	0,5	4,3	False	
GTH3	107	155	5	0,5	4,15	False	
PDM	108	155	5	0,85	4,45	False	
PDB	109	155	0	0,4	9,05	False	
PDD	110	155	5	0,55	3,55	False	
CAL	111	155	0	0,9	10,15	False	
AG	112	155	0	-6,5	4,15	False	
MGB	113	155	0	0,3	12,55	False	
OCC	114	155	0	1	5	True	
ID2	115	155	0	1	14	False	
TOOTH2	116	155	0	13	45	False	
MILLER2	117	155	0	1	3	False	
DEHIS2	118	155	0	3,5	10,5	False	
DEHISTRUE2	119	155	0	1,6	7,7	False	
c120	120	0	0	0	0	False	
c121	121	0	0	0	0	False	
c122	122	0	0	0	0	False	
c123	123	0	0	0	0	False	

Next, we want to recode the categorical occasion variable OCC (1-5) into the continuous **TIME** variable (0, 3, 6, 9 and 12 months) first. For that purpose, in the **Data manipulation** menu we click **recode**, and, from the drop-down list, by **value**. We select **OCC** from the **Source column** and enter **New values** 0, 3, 6, 9, and 12, respectively. We select **c120** as **Destination Column** and click **execute**. We then click on **Names** and rename the column **TIME**.

We can now almost set up a simple variance components model but still have to create a constant column (**CONS**). We access the **Generate Vector** window via the **Data Manipulation** menu. We select **c121** as **Output column**, type 155 next to **Number of copies** and assign the **Value** of 1 to them. We click on **Generate** and rename the column as before, **CONS**. Now we want to save the worksheet, for instance as *dimension_03.wsz*.

3.2.2 Variance components models

We start by exploring how the total variance of, say, gingival thickness at the gingival margin (GTH1) is partitioned into three components: between subjects, between teeth treated for gingival recession within subjects and between occasions within teeth within subjects. This variance components model provides a baseline for more complex models (see chapter 2). We may define this model and display it after clicking on **Model** in the main menu and then **Equations**.



We click on y and select from the drop-down list in the appearing window **GTH1**. From **N-levels** we select **3-ijk** and select **level 3(k) ID2, TOOTH2** for **level 2(j)**, and **TIME** for **level 1(i)**. We then click **Done**. In the **Equations** window, we click on x_0 and select **CONS** from the drop-down list. We tick all three check boxes for **k(ID2)**, **j(TOOTH2)** and **i(TIME)** and click **Done**. At the bottom of the **Equations** window we click twice on **+** and then on **Estimates**.

Equations

$$GTH1_{ijk} \sim N(XB, \Omega)$$

$$GTH1_{ijk} = \beta_{0ijk} CONS$$

$$\beta_{0ijk} = \beta_0 + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\begin{bmatrix} v_{0k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} \sigma_{v0}^2 \end{bmatrix}$$

$$\begin{bmatrix} u_{0jk} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma_{u0}^2 \end{bmatrix}$$

$$\begin{bmatrix} e_{0ijk} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} \sigma_{e0}^2 \end{bmatrix}$$

(155 of 155 cases in use)

Name	+	-	Add Term	Estimates	Nonlinear	Clear	Notation	Responses	Store	Help	Zc
------	---	---	----------	------------------	-----------	-------	----------	-----------	-------	------	----

We now click on **Start** in the main menu and the model instantly converges.

Clicking again on **Estimates** gives the following results.

Equations

$$GTH1_{ijk} \sim N(XB, \Omega)$$

$$GTH1_{ijk} = \beta_{0ijk} \text{CONS}$$

$$\beta_{0ijk} = 1.112(0.057) + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\begin{bmatrix} v_{0k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.003(0.016) \end{bmatrix}$$

$$\begin{bmatrix} u_{0jk} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.058(0.028) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ijk} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 0.161(0.020) \end{bmatrix}$$

$-2 * \text{loglikelihood(IGLS Deviance)} = 189.953(155 \text{ of } 155 \text{ cases in use})$

Name + - Add Term **Estimates** Nonlinear Clear Notation Responses Store Help Zc

As the intercept β_{0ij} reveals, the mean value for gingival thickness at the gingival margin is 1.112 mm (SE 0.057). The variation between occasions within teeth within subjects is large, 0.161 with a SE of 0.020, as compared to the variation at the tooth level, 0.058 (0.028) while variation at the subject level is very low, 0.003 (0.016). The likelihood statistic (-2 loglikelihood), found at the bottom of the Equation window (189.953), can be used as basis when assessing the more elaborate models to come.

3.3 Modeling Repeated Measures Nonlinear, Non-monotonic Responses

Mucosal thickness after implantation of a bio-resorbable membrane is expected not to be linear over time. One simple way of introducing nonlinearity is to define quadratic and cubic terms for TIME. From the **Data manipulation menu**, we select the **Command interface** and type `calc c122 = 'TIME'^2` and thereafter `calc c123 = 'TIME'^3` in the bottom box. We rename the columns to **TIMESQ** and **TIMECB**, respectively, and save the model.

We then add **TIME**, **TIMESQ** and **TIMECB** to the model, and click on **More**, which yields the following results.

```
Equations
GTH1ijk ~ N(XB, Ω)
GTH1ijk = β0ijkCONS + 0.371(0.049)TIMEijk + -0.069(0.010)TIMESQijk + 0.003(0.001)TIMECBijk
β0ijk = 0.838(0.077) + v0kc + u0jk + e0ijk

[v0kc] ~ N(0, Ωv) : Ωv = [0.003(0.016)]
[u0jk] ~ N(0, Ωu) : Ωu = [0.070(0.027)]
[e0ijk] ~ N(0, Ωe) : Ωe = [0.104(0.013)]

-2*loglikelihood(IGLS Deviance) = 136.157(155 of 155 cases in use)
```

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

Apparently, gingival thickness at the gingival margin (GTH1) increased by an estimated 0.371 mm per month ($TIME_{ijk}$). However, deceleration was considerable with -0.069 mm per month squared, and the cubic term was 0.003. The standard

errors of 0.049, 0.010 and 0.001, respectively, may be used to determine 95% confidence intervals. For that purpose, we click in the main menu on **Model** and select **Intervals and tests**. At the bottom, we check **fixed**, enter 3 in **# of functions** and 1 in column **#1, fixed:TIME**, 1 in column **#2, fixed:TIMESQ**, and 1 in column **#3, fixed:TIMESCB**. When we then click on **Calc**, the following window will appear.

	#1	#2	#3
fixed : CONS	0.000	0.000	0.000
fixed : TIME	1.000	0.000	0.000
fixed : TIMESQ	0.000	1.000	0.000
fixed : TIMECB	0.000	0.000	1.000
constant(k)	0.000	0.000	0.000
function result(f)	0.371	-0.069	0.003
f-k	0.371	-0.069	0.003
chi sq, (f-k)=0. (1df)	57.652	44.215	33.141
+/- 95% sep.	0.096	0.020	0.001
+/- 95% joint	0.137	0.029	0.002

joint chi sq test(3df) = 67.353

random
 fixed # of functions

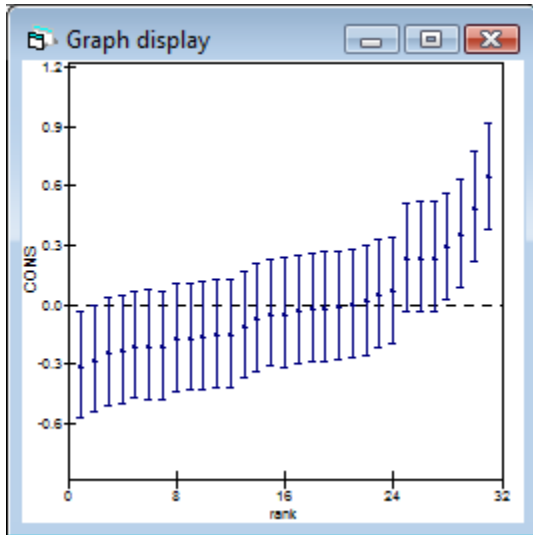
For each column the function is formed by multiplying the value in each row by the coefficient estimate and summing these to give the **function result(f)**. A large sample chi squared test statistic is computed testing $f-k=0$ where k may also be

specified - the default being zero. The row **+/- 95% sep.** is a Normal approximation 95% confidence interval for $f-k$. The row **+/- 95% joint** is a joint 95% interval for the set of functions specified. The **joint chi sq test (2df)** row is a large sample joint test for the triplet of functions $f-k=0$.

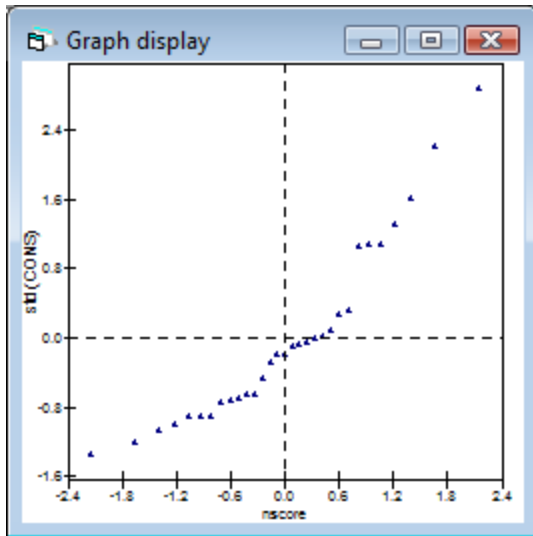
Based on the information given (**+/- 95% sep.** equal 0.096, 0.020, and 0.001, respectively) we may calculate 95% confidence intervals for the set of functions specified, i.e. for TIME_{ijk} (0.275; 0.467 mm), TIMESQ_{ijk} (-0.089; -0.049 mm), and TIMECB_{ijk} (0.002; 0.004 mm). (Note that adjustment for multiple testing may be done by using joint estimates for 95% confidence intervals.) A glance at the random part of the model reveals that 59% of the unexplained variance of gingival thickness at the gingival margin is still found at the occasion level, i.e. $0.104/(0.003+0.070+0.104)$; and 40% at the tooth level.

Now we want to have a look at, say, level 2 residuals. For that purpose, we select **Model** in the main menu and then **Residuals**. We select the **Settings** tab of the **Residuals** window. From the **level** drop-down list at the bottom we select **2:TOOTH2**. We change the multiplier applied to the **start output at** box to 1.96 to get 95% confidence intervals. We click the **Set column** button to specify the columns into which the computed values of the function will be placed (the nine boxes from **C300** to **C308**). We then click on **Calc**. Now we click on the **Plots** tab and select the third option in the single frame (**residual +/- 1.96 SD x rank**). The

following caterpillar plot appears showing residuals of 31 teeth with its respective 95% confidence intervals.

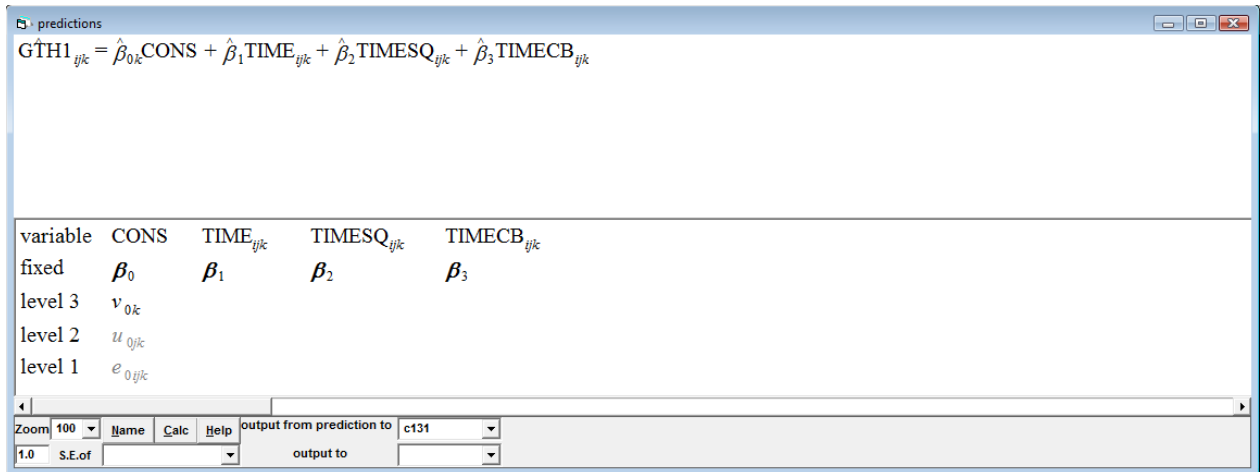


We may now check the assumption that estimated residuals follow Normal distribution at each level. For that purpose we have a look at the **Normal probability plots**, in which the ranked residuals are plotted against corresponding points on a Normal distribution curve. The points on a Normal plot should lie approximately on a straight line if the Normality assumption is valid. Since we have already calculated level 2 residuals (TOOTH2), we may check them first. We click on the first option, **standardized residual x normal scores**, and then click **Apply**.

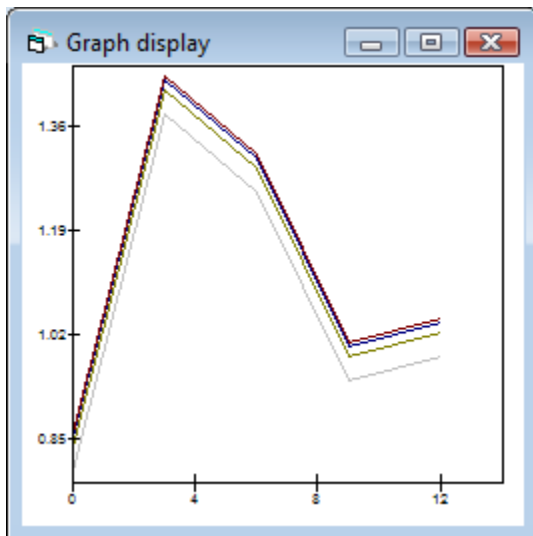


Since the points lie more or less on a straight line this indicates that the Normal assumption was valid.

Our principle interest lies in how gingival thickness of individual patients varies over time after surgical implantation of a bio-resorbable membrane. We can easily display estimated patterns (predictions) for selected patients. For example, to plot the lines for seven patients with ID 7, 8, 9, 10, 11, 12 and 13, we may set up a *filter* column, say **c130**, which is 1 if the record belongs to one of these individuals and zero otherwise. We click on Data Manipulation in the main menu, click on **Calculate** and select **c130** from the drop-down list of columns. We type 'c131' = "ID2" >=7 & "ID2" <14 and click on **Calculate**. In the **Model** menu we open the **Predictions** window and compute predicted values using the fixed part coefficients plus level 3 random coefficients. We want to place the results in column 131.

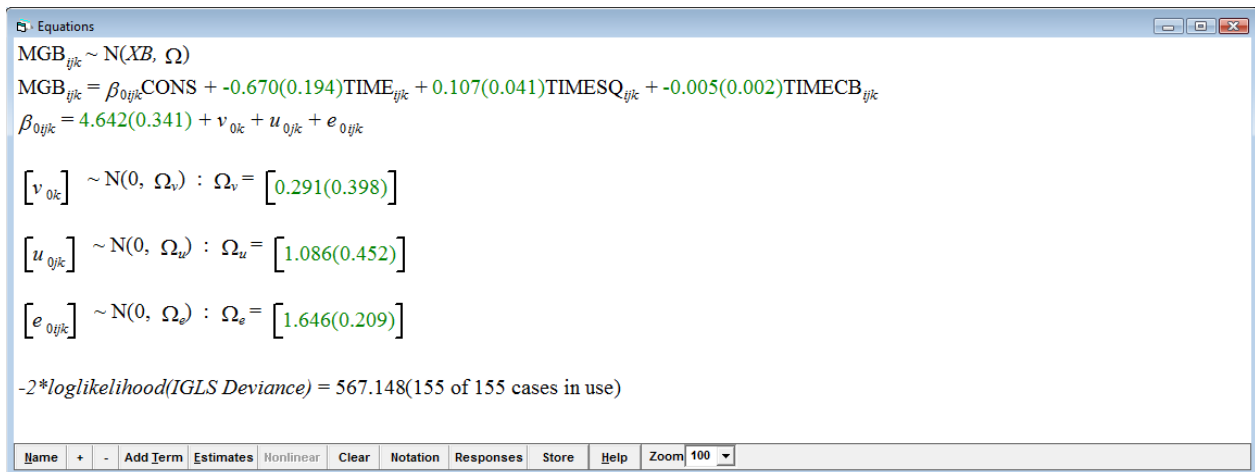


Now we open the **Customized graph** window and make the following selections on **plot what?: c131** for **y**, **TIME** for **x**, **c130** as the **filter**, **ID2** as the **group** variable and **line** as the **plot type**. In the **colour** selector on the **plot style** tab, we select **16 rotate** and click on **Apply**. The following graph appears.



Since during the surgical operation the entire mucoperiosteal flap was coronally advanced, we would not expect any postoperative changes of gingival width. In order to check this, we may click on the response **GTH1** in the model, select in the appearing drop-down menu instead **GW** (gingival width) and click **done**. We then click on **More**, and the model converges instantly. Standard errors of TIME, TIMESQ and TIMECB are larger or much larger than very small estimates, so it may be concluded that there was hardly any influence of time on gingival width.

The position of the mucogingival border relative to the cemento-enamel junction is a different story, though. A specific model might answer the questions as to how much the mucoperiosteal flap was raised and to what extent would a postoperative relapse occur. The respective model is shown below.



There was a great postoperative shift of the mucogingival border toward the cemento-enamel junction of 0.670 mm per month (95% confidence interval -1.050;

-0.290). However, deceleration (TIMESQ) was considerable, 0.107 mm (0.027; 0.187), as was the cubic term for TIME. Again, most of the unexplained variation (54%) was at the occasion level, while 36% was observed at the tooth level.

The results of the three models so far are displayed in Table 3.1.

Table 3.1 Three-level (occasion, tooth, subject) time series models of gingival thickness at the gingival margin (GTH1), gingival width (GW), and location of the mucogingival border in relation to the cement-enamel junction (MGB).

	Estimate (SE)		
	GTH1	GW	MGB
Fixed effects			
Intercept β_{0ijk}	0.838 (0.077)	1.853 (0.234)	4.641 (0.341)
t (months)	0.371 (0.049)	-0.034 (0.147)	-0.670 (0.194)
t^2	-0.069 (0.010)	0.018 (0.031)	0.107 (0.041)
t^3	0.003 (0.001)	-0.001 (0.002)	-0.005 (0.002)
Random effects			
Subject (σ_{v0}^2)	0.003 (0.016)	0.229 (0.167)	0.291 (0.398)
Tooth (σ_{u0}^2)	0.070 (0.027)	0.149 (0.116)	1.086 (0.452)
Occasion (σ_{e0}^2)	0.104 (0.013)	0.948 (0.120)	1.646 (0.209)
-2*log L	136.157	461.053	567.148

It may be checked whether the TIME coefficients vary across subjects in the respective models, i.e. whether a random coefficient model fits better. This random coefficient model may be written as follows.

$$y_{ijk} = \sum_{h=0}^3 \beta_{hk} t_{ijk}^h$$

$$\beta_{0k} = \beta_0 + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\beta_{1k} = \beta_1 + v_{1k}; \beta_{2k} = \beta_2; \beta_{3k} = \beta_3$$

$$\begin{pmatrix} v_0 \\ v_1 \end{pmatrix} \sim N(0, \Omega_v); \Omega_v = \begin{pmatrix} \sigma_{v0}^2 & \\ & \sigma_{v1}^2 \end{pmatrix}$$

$$u_0 \sim N(0, \sigma_{u0}^2); e \sim N(0, \sigma_e^2) \quad (3.2)$$

To set up this model, we click on **TIME**, check the box **k(ID2)** and click on **done**.

While the subject variance in the above random intercept model for GTH1 is very small, a random coefficient model won't make sense. In case of GW, however, the likelihood (L) ratio statistic, which is computed as $-2*\log L_1 - (-2*\log L_2)$, is at least 6.261. In **Basic statistics** in the main menu we click **Tail Areas**. The default chi squared is already tagged and we enter the **Value** of 6.261 and, in **Degrees of Freedom** we enter 2, since there are 2 additional parameters, a variance estimate for TIME and a covariance estimate for CONS and TIME. By clicking on **Calculate** we get a probability of about 0.044. So, this model does marginally better fit than the previous one.

Equations

$$GW_{ijk} \sim N(XB, \Omega)$$

$$GW_{ijk} = \beta_{0ijk}CONS + \beta_{1k}TIME_{ijk} + 0.018(0.030)TIMESQ_{ijk} + -0.001(0.002)TIMECB_{ijk}$$

$$\beta_{0ijk} = 1.936(0.296) + v_{0k} + u_{0jk} + e_{0ijk}$$

$$\beta_{1k} = -0.048(0.141) + v_{1k}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.656(0.404) & \\ -0.049(0.034) & 0.004(0.003) \end{bmatrix}$$

$$[u_{0jk}] \sim N(0, \Omega_u) : \Omega_u = [0.173(0.115)]$$

$$[e_{0ijk}] \sim N(0, \Omega_e) : \Omega_e = [0.857(0.114)]$$

-2*loglikelihood(IGLS Deviance) = 454.792(155 of 155 cases in use)

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

There is little evidence that the **TIME** coefficient varies across subjects in case of MGB, the likelihood ratio statistic is just 3.915 with 2 degrees of freedom ($p = 0.141$).

Apart from gingival parameters we may be interested in recession depth and how postoperative root coverage and relapse can be modeled in a time series model. We just click again on the response variable in the model and select **RD** (recession depth) from the drop-down list and click on **done**. We run the model by clicking on **More** and get the results below.

```

Equations
RD_{ijk} ~ N(XB, Omega)
RD_{ijk} = beta_{0ijk}CONS + -0.674(0.089)TIME_{ijk} + 0.102(0.019)TIMESQ_{ijk} + -0.004(0.001)TIMECB_{ijk}
beta_{0ijk} = 2.898(0.289) + v_{0ik} + u_{0jk} + e_{0ijk}

[v_{0ik}] ~ N(0, Omega_v) : Omega_v = [0.615(0.406)]
[u_{0jk}] ~ N(0, Omega_u) : Omega_u = [0.634(0.236)]
[e_{0ijk}] ~ N(0, Omega_e) : Omega_e = [0.347(0.044)]

-2*loglikelihood(IGLS Deviance) = 361.233(155 of 155 cases in use)

```

We may let the **TIME** coefficient vary across subjects and introduce complex level 1 variation, i.e. we would expect that both level 3 and level 1 variances to be non-constant. We click on **TIME** and check the boxes **k(ID2)** and **i(OCC)** in the window.

Equations

$$RD_{ijk} \sim N(XB, \Omega)$$

$$RD_{ijk} = \beta_{0ijk} \text{CONS} + \beta_{1ijk} \text{TIME}_{ijk} + 0.092(0.019) \text{TIMESQ}_{ijk} + -0.004(0.001) \text{TIMECB}_{ijk}$$

$$\beta_{0ijk} = 2.862(0.272) + v_{0jk} + u_{0jk} + e_{0ijk}$$

$$\beta_{1ijk} = -0.626(0.099) + v_{1jk} + e_{1ijk}$$

$$\begin{bmatrix} v_{0jk} \\ v_{1jk} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.345(0.335) & \\ & 0.006(0.011) \ 0.001(0.001) \end{bmatrix}$$

$$\begin{bmatrix} u_{0jk} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.735(0.257) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ijk} \\ e_{1ijk} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 0.604(0.151) & \\ -0.024(0.022) \ 0.000(0.003) \end{bmatrix}$$

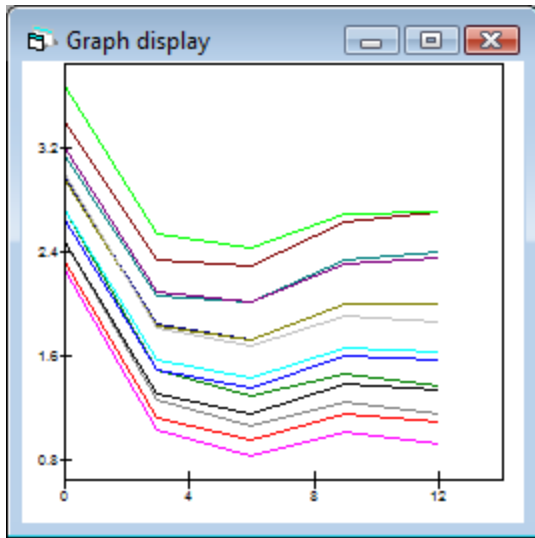
-2*loglikelihood(IGLS Deviance) = 344.401(155 of 155 cases in use)

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There are 4 further terms in the model (4 df) and the likelihood statistic for the two models is $361.233 - 344.401 = 16.832$. We can check for a p -value by entering the statistic and degrees of freedom in the **Tail Areas** window in **Basic Statistics**.

Thus, the model fits significantly ($p=0.002$) better than the previous one.

The graph below displays predictions for RD of all 14 individuals over time based on the final model.



So far, we have set up basic and more complex repeated measures time series models which allowed the assessment of the effect of time on, for instance, gingival parameters and recession depth. In the next chapter, we want to extend these models by including various other covariates and, in particular, considering multivariate responses.

4 Multivariate Response Models

In the previous chapter, increasingly complex time series models have been set up in order to model gingival thickness, its width, the position of the mucogingival border relative to the cemento-enamel junction, and gingival recession after surgical implantation of a bio-resorbable membrane for guided tissue regeneration for the treatment of gingival recession. While some of these variables, such as thickness and width of gingiva might be positively related, others are not, for example gingival thickness and recession. Mucosal thickness had been measured at three locations: at the gingival margin, as well as at and below the mucogingival border (Müller et al. 2000d). In order to create general predictions of alterations of gingival dimensions after surgery, one single model would be preferred which might include mucosal thickness as measured at different locations as three different responses.

Multivariate response data are most conveniently incorporated into a multilevel model by creating a lower level below the original level 1 units. This will define the multivariate structure. Here we want to set up a 4-level model with multivariate responses (level 1) measured at different occasions (level 2) nested in higher-level units, i.e. teeth (level 3) and patients (level 4).

Measurements or assessments of a couple of primary variables (see below) have been done five times during 12 months: before surgery and every three months after surgery.

<i>Variable</i>	<i>Description</i>
ID	Subject's identifier (1-14)
TOOTH	FDI notation of teeth (11-48)
GI	Gingival index (0-3)
PLI	Plaque index (0-3)
RD	Recession depth (mm)
RW	Recession width (mm)
GW	Gingival width (mm)
MILLER	Miller's classification of recession (1-4)
GTH1	Gingival thickness (mm) at the gingival margin
GTH2	Gingival thickness (mm) at the mucogingival border
GTH3	Thickness of the lining mucosa (mm)
PD	Probing depth (mm)
DEHIS	Bony dehiscence (mm) from the cement-enamel junction as measured intrasurgically

Secondary variables were composed of primary variables and the reader is referred to Chapter 3 for further information.

All data are stored in *dimension_04.wsz*. Note that the data structure has already been set up for repeated measures, i.e. a tooth's data record has been transformed into separate records (or rows) for each occasion.

Name	Cn	n	missing	min	max	categorical	description
GIB	97	155	0	0	2	False	
GID	98	155	0	0	2	False	
PLIM	99	155	0	0	2	False	
PLIB	100	155	0	0	2	False	
PLID	101	155	0	0	2	False	
RD	102	155	0	0	7.75	False	
RW	103	155	0	0	15	False	
GW	104	155	0	0	6.45	False	
GTH1	105	155	0	0.5	2.7	False	
GTH2	106	155	5	0.5	4.3	False	
GTH3	107	155	5	0.5	4.15	False	
PDM	108	155	5	0.85	4.45	False	
PDB	109	155	0	0.4	9.05	False	
PDD	110	155	5	0.55	3.55	False	
CAL	111	155	0	0.9	10.15	False	
AG	112	155	0	-6.5	4.15	False	
MGB	113	155	0	0.3	12.55	False	
OCC	114	155	0	1	5	True	
ID2	115	155	0	1	14	False	
TOOTH2	116	155	0	13	45	False	
MILLER2	117	155	0	1	3	False	
DEHIS2	118	155	0	3.5	10.5	False	

We want to model $m=3$ responses (GTH1, GTH2 and GTH3) simultaneously in a multivariate model. Each level 1 measurement “record” has a response which is either gingival thickness at the gingival margin (GTH1) or at the mucogingival border (GTH2), or thickness of the lining mucosa below the mucogingival border (GTH3). Hence, the basic explanatory variables are a set of two dummy variables Z_{mjkl} that indicate which response variable is present. Repeated measures are treated as level 2 units, surgically treated teeth as level 3 and patients as level 4 units.

The multivariate, three level (occasion, tooth, subject), time series random intercept model including a squared and cubic term for time (t) in months may be written as (4.1)

$$\begin{aligned}
y_{jkl} &\sim N(XB, \Omega) \\
y_{jkl} &= \sum_{h=0}^3 \sum_{n=1}^3 \beta_{mjkl} t_{jkl}^h z_{njkl} \\
z_{1jkl} &= \begin{cases} 1 & \text{if } m = 0 \\ 0 & \text{if } m = 1 \\ 0 & \text{if } m = 2 \end{cases}; z_{2jkl} = \begin{cases} 0 & \text{if } m = 0 \\ 1 & \text{if } m = 1 \\ 0 & \text{if } m = 2 \end{cases}; z_{3jkl} = \begin{cases} 0 & \text{if } m = 0 \\ 0 & \text{if } m = 1 \\ 1 & \text{if } m = 2 \end{cases} \\
\beta_{0jkl} &= \beta_0 + f_{0l} + v_{0kl} + u_{0jkl} \\
\beta_{1jkl} &= \beta_1 + f_{1l} + v_{1kl} + u_{1jkl} \\
\beta_{2jkl} &= \beta_2 + f_{2l} + v_{2kl} + u_{2jkl} \\
\begin{bmatrix} f_{0l} \\ f_{1l} \\ f_{2l} \end{bmatrix} &\sim (N, \Omega_f); \Omega_f = \begin{pmatrix} \sigma_{f0}^2 & & \\ \sigma_{f01} & \sigma_{f1}^2 & \\ \sigma_{f02} & \sigma_{f12} & \sigma_{f2}^2 \end{pmatrix} \\
\begin{bmatrix} v_{0kl} \\ v_{1kl} \\ v_{2kl} \end{bmatrix} &\sim (N, \Omega_v); \Omega_v = \begin{pmatrix} \sigma_{v0}^2 & & \\ \sigma_{v01} & \sigma_{v1}^2 & \\ \sigma_{v02} & \sigma_{v12} & \sigma_{v2}^2 \end{pmatrix} \\
\begin{bmatrix} u_{0jkl} \\ u_{1jkl} \\ u_{2jkl} \end{bmatrix} &\sim (N, \Omega_u); \Omega_u = \begin{pmatrix} \sigma_{u0}^2 & & \\ \sigma_{u01} & \sigma_{u1}^2 & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 \end{pmatrix} \tag{4.1}
\end{aligned}$$

There are several interesting features of this model. First, there is no level 1 variation specified because level 1 solely defines the multivariate structure. The higher level variances and covariances are the residual between-occasion, between-teeth and between-subject variances, respectively. The formulation of this 3-level model allows for the efficient estimation of a covariance matrix with missing responses as long as “missing” responses are considered as random. In the case

where measurements have a multivariate Normal distribution, IGLS/RGLS provides maximum likelihood estimates. Thus, studies can be designed where not every individual has every measurement, with measurements randomly allocated to individuals. Such “rotation” or “matrix” designs are common in many areas and may be modeled in this way.

4.1 Setting up a Basic Multivariate Model

When clicking on **Equation** in the **Model** menu, the random intercept time series model of GTH1 from the previous Chapter 3 appears. Before setting up the model described in formula 4.1 in *MLwiN*, we start with a variance components (or null) model without covariates. We therefore click on **Clear** at the bottom of the **Equation** window.

After clicking on **Responses** we select **GTH1**, **GTH2** and **GTH3**. We **Add Term CONS** from the drop down menu and click on **add Separate coefficients**. (Note that **uncentred** is the default.) In order to set up the multilevel structure we click on **resp₁** and select for **N-levels 4-ijkl**. We select **ID2** for **level 4(l)**, **TOOTH2** for **level 3(k)**, and **OCC** for **level 2(j)** and click on **done**. We then click on the beta coefficients and check the boxes for **l(ID2_long)**, **k(TOOTH2_long)** and **j(OCC_long)**, respectively. We click on **done** and then twice on **Estimates** at the

bottom of the equation window. We run the model by clicking on the **Start** button.

The model converges instantly.

Equations

$$\begin{aligned} \text{resp}_{1jki} &\sim N(XB, \Omega) \\ \text{resp}_{2jki} &\sim N(XB, \Omega) \\ \text{resp}_{3jki} &\sim N(XB, \Omega) \\ \text{resp}_{1jki} &= \beta_{0jki} \text{CONS.GTH1}_{ijki} \\ \beta_{0jki} &= 1.114(0.060) + f_{0i} + v_{0ki} + u_{0jki} \\ \text{resp}_{2jki} &= \beta_{1jki} \text{CONS.GTH2}_{ijki} \\ \beta_{1jki} &= 1.315(0.078) + f_{1i} + v_{1ki} + u_{1jki} \\ \text{resp}_{3jki} &= \beta_{2jki} \text{CONS.GTH3}_{ijki} \\ \beta_{2jki} &= 1.414(0.059) + f_{2i} + v_{2ki} + u_{2jki} \end{aligned}$$

$$\begin{bmatrix} f_{0i} \\ f_{1i} \\ f_{2i} \end{bmatrix} \sim N(0, \Omega_f) : \Omega_f = \begin{bmatrix} 0.012(0.017) & & \\ 0.021(0.021) & 0.030(0.027) & \\ 0.000(0.000) & 0.000(0.000) & 0.000(0.000) \end{bmatrix}$$

$$\begin{bmatrix} v_{0ki} \\ v_{1ki} \\ v_{2ki} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.051(0.025) & & \\ 0.044(0.026) & 0.035(0.032) & \\ 0.006(0.020) & 0.005(0.025) & 0.004(0.030) \end{bmatrix}$$

$$\begin{bmatrix} u_{0jki} \\ u_{1jki} \\ u_{2jki} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.161(0.020) & & \\ 0.159(0.025) & 0.338(0.044) & \\ 0.144(0.029) & 0.272(0.045) & 0.509(0.066) \end{bmatrix}$$

-2*loglikelihood(IGLS Deviance) = 604.258(455 of 465 cases in use)

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4.2 A Multivariate Time Series Model

We now want to add successively **TIME**, **TIMESQ** and **TIMECB** (see Formula 4.1). We click on **Add Term** and select the respective **variable** (one after the other) from the drop-down list and click on **add separate coefficients**. After having clicked on **More** the model converges without problems.

In order to predict responses before and after surgical root coverage in different jaws (mandible or maxilla) and taking into account the different situations of baseline gingival width, we want to add further variables. In **Data Manipulation**, we click on **recode** and select **By range**. We select **TOOTH2** in **Input columns** and **c141** in **Output columns**. **Values in range of 11 to 28** get the **new value** of 0. We click on **Add to action list** where the **Recode Specification** appears on the right side. **Values in range of 31 to 48** get the **new value** of 1. We click on **Execute** and change the name of **c141** to **JAW** (the reference will be teeth in the maxilla).

Baseline **GW** has to be repeated, or carried (see Chapter 3). We click on **Data Manipulation** and select **Split records**. We select in **Repeat (carried) Data** at the bottom the **Input column GW0** (i.e. baseline gingival width) and **c142** as **Output column**. (Note that, in order to execute the command, one has to **Stack** repeated data of a variable again, for instance **GIM0 ...GIM12**, **into** the variable **GIM**. So,

we enter 5 in **Number of occasions** and then **GIM0 ...GIM12** into **Occasion 1...5**.) We can then click on **Split** and on **No** in the appearing window when asked whether we want to save the worksheet now. We rename **c142** to **GWBASE**.

Now we enter **JAW** and **GWBASE** into the model together with respective interactions with **TIME**, **TIMESQ** and **TIMECB**. For the latter, after having clicked on **Add Term** at the bottom of the equation window we enter 1 next to **order** and, for instance **JAW** and **TIME** as variables. The interaction term will appear in the equation when having clicked on **add Separate coefficients**. We may click on **Zoom** at the bottom of the equation window and enter, for instance, 70 to reduce the font size. For **Estimation control**, we choose **RIGLS** (restricted iterative generalized least squares) which leads to unbiased estimates of random parameters. We check the box **suppress numeric warnings**, click on **done** and run the model by clicking on **More**. After a few iterations, the model had converged, see below.

```

Equations
respijk ~ N(XB, Ω)
respijk ~ N(XB, Ω)
respijk ~ N(XB, Ω)
respijk = β0ijkCONS.GTH1ijk + 0.757(0.094)TIME.GTH1ijk + -0.143(0.020)TIMESQ.GTH1ijk + 0.007(0.001)TIMECB.GTH1ijk + 0.215(0.160)JAW.GTH1ijk + -0.457(0.099)JAW.TIME.GTH1ijk +
0.087(0.021)JAW.TIMESQ.GTH1ijk + -0.004(0.001)JAW.TIMECB.GTH1ijk + 0.114(0.056)GWBASE.GTH1ijk + -0.117(0.034)GWBASE.TIME.GTH1ijk + 0.023(0.007)GWBASE.TIMESQ.GTH1ijk +
-0.001(0.000)GWBASE.TIMECB.GTH1ijk
β0ijk = 0.556(0.160) + f0i + v0jk + u0ik
respijk = β1ijkCONS.GTH2ijk + 1.092(0.126)TIME.GTH2ijk + -0.202(0.026)TIMESQ.GTH2ijk + 0.010(0.001)TIMECB.GTH2ijk + 0.142(0.200)JAW.GTH2ijk + -0.431(0.128)JAW.TIME.GTH2ijk +
0.082(0.027)JAW.TIMESQ.GTH2ijk + -0.004(0.001)JAW.TIMECB.GTH2ijk + 0.063(0.069)GWBASE.GTH2ijk + -0.154(0.044)GWBASE.TIME.GTH2ijk + 0.032(0.009)GWBASE.TIMESQ.GTH2ijk +
-0.002(0.000)GWBASE.TIMECB.GTH2ijk
β1ijk = 0.583(0.203) + f1i + v1jk + u1ik
respijk = β2ijkCONS.GTH3ijk + 0.965(0.161)TIME.GTH3ijk + -0.169(0.033)TIMESQ.GTH3ijk + 0.008(0.002)TIMECB.GTH3ijk + 0.086(0.220)JAW.GTH3ijk + 0.139(0.163)JAW.TIME.GTH3ijk +
-0.028(0.034)JAW.TIMESQ.GTH3ijk + 0.001(0.002)JAW.TIMECB.GTH3ijk + 0.025(0.075)GWBASE.GTH3ijk + -0.142(0.056)GWBASE.TIME.GTH3ijk + 0.026(0.012)GWBASE.TIMESQ.GTH3ijk +
-0.001(0.001)GWBASE.TIMECB.GTH3ijk
β2ijk = 0.675(0.217) + f2i + v2jk + u2ik

[ f0i ]
[ f1i ] ~ N(0, Ωf) : Ωf = [ 0.024(0.020)
[ f2i ] [ 0.026(0.020) 0.026(0.023)
[ 0.000(0.000) 0.000(0.000) 0.000(0.000) ]

[ v0jk ]
[ v1jk ] ~ N(0, Ωv) : Ωv = [ 0.055(0.022)
[ v2jk ] [ 0.067(0.025) 0.083(0.033)
[ 0.048(0.020) 0.066(0.025) 0.064(0.029) ]

[ u0ik ]
[ u1ik ] ~ N(0, Ωu) : Ωu = [ 0.089(0.011)
[ u2ik ] [ 0.039(0.011) 0.139(0.018)
[ 0.022(0.013) 0.041(0.017) 0.223(0.029) ]

-2*loglikelihood(TGLS Deviance) = 401.653(455 of 465 cases in use)
Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 70

```

We want to save worksheet and model as *dimension_05.wsz*.

Table 4.1a lists fixed effects of the above multivariate, 3-level (occasion, tooth, subject), time series, random intercept model of mucosal thickness at the gingival margin (GHT1), at the mucogingival border (GTH2), and of the alveolar lining mucosa (GHT3).

To calculate 95% confidence intervals we may click on **Model** in the main menu and **Intervals and tests**. We enter 1 in respective cells, click **Calc** at the bottom and get the respective 95% confidence intervals. Considerable linear increase in mucosal thickness with time of between 0.757 (0.573; 0.941) mm and 1.092 (0.846; 1.338) mm after implantation of a bio-absorbable membrane was accompanied by highly significant deceleration (between -0.143 and -0.202 mm x month squared), while the cubic term was highly significant as well.

Table 4.1a Fixed effects estimates (SE) of multivariate, three-level (occasion, tooth, subject) time series, random intercept model of mucosal thickness at the gingival margin (GTH1), at the mucogingival border (GTH2), and of the alveolar lining mucosa (GTH3)

	Estimate (SE)		
	GTH1	GTH2	GTH3
Intercept β_{mik}	0.556 (0.160)	0.583 (0.203)	0.675 (0.217)
t^a (months)	0.757 (0.094)	1.092 (0.126)	0.965 (0.161)
t^2	-0.143 (0.020)	-0.202 (0.026)	-0.169 (0.033)
t^3	0.007 (0.001)	0.010 (0.001)	0.008 (0.002)
JAW ^b	0.215 (0.160)	0.142 (0.200)	0.086 (0.220)
t x JAW	-0.457 (0.099)	-0.431 (0.128)	-0.139 (0.163)
t^2 x JAW	0.087 (0.021)	0.082 (0.027)	-0.028 (0.034)
t^3 x JAW	-0.004 (0.001)	-0.004 (0.001)	0.001 (0.002)
GW ^c	0.114 (0.056)	0.063 (0.069)	0.025 (0.075)
t x GW	-0.117 (0.034)	-0.154 (0.044)	-0.142 (0.056)
t^2 x GW	0.023 (0.007)	0.032 (0.009)	0.026 (0.012)
t^3 x GW	-0.001 (0.000)	-0.002 (0.000)	-0.001 (0.001)

^a Time (months)

^b Mandible = 1; maxilla = 0

^c Baseline gingival width (mm)

While mucosal thickness was not significantly greater at mandibular teeth in general, the interaction with time was negative and highly significant for gingival thickness at the gingival margin and at the mucogingival border (-0.457 and -0.431, respectively) with significant quadratic and cubic terms. Baseline gingival width was significantly associated with gingival thickness as measured at the gingival margin (0.114 mm). This influence decreased drastically with time after surgery (-0.117 mm), with quadratic and cubic terms being also significant.

Random effects of the model are listed in Table 4.1b.

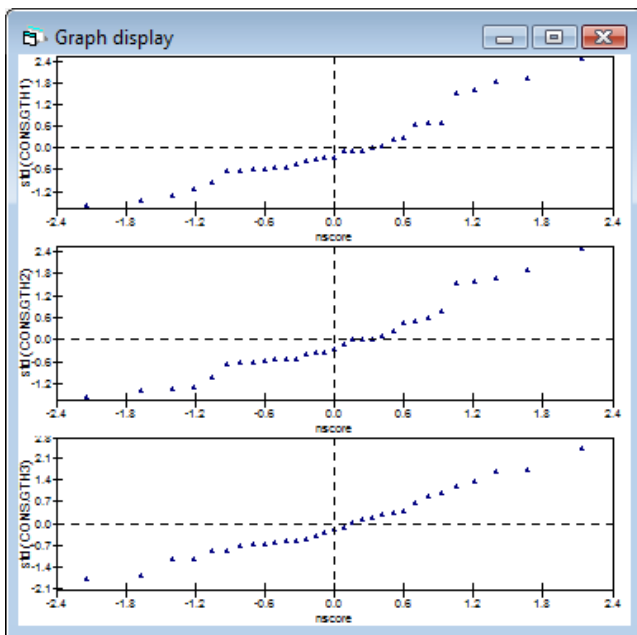
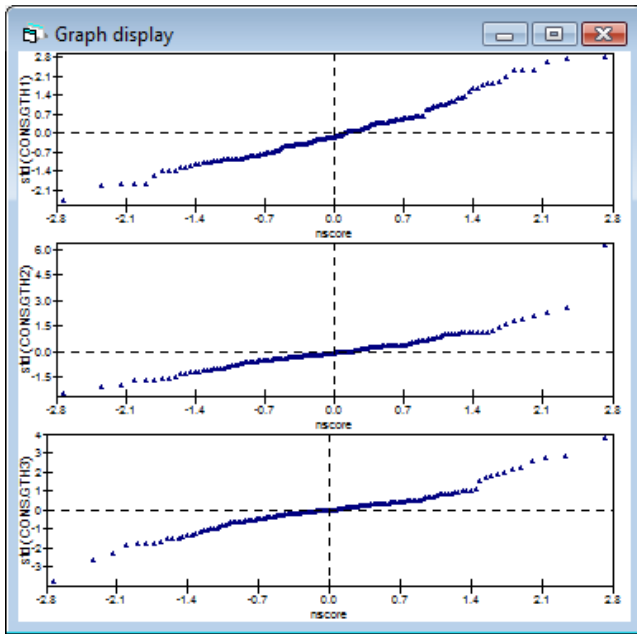
<i>Table 4.1b</i> Random effects estimates (SE) of multivariate, three-level (occasion, tooth, subject), time series, random intercept model of mucosal thickness at three locations				
		Estimate (SE)		
	Parameter	GTH1	GTH2	GTH3
Subject	$\sigma_{fl,m}^2$	0.024 (0.020)	0.026 (0.023)	
	$\sigma_{fl,m,m+1}$	0.026 (0.020)		
Tooth	$\sigma_{vkl,m}^2$	0.055 (0.022)	0.083 (0.033)	0.064 (0.029)
	$\sigma_{vkl,m,m+1}$	0.067 (0.020)	0.066 (0.025)	
	$\sigma_{vkl,m,m+2}$	0.048 (0.020)		
Occasion	$\sigma_{ujkl,m}^2$	0.089 (0.011)	0.139 (0.018)	0.223 (0.029)
	$\sigma_{ujkl,m,m+1}$	0.039 (0.011)	0.041 (0.017)	
	$\sigma_{ujkl,m,m+2}$	0.022 (0.013)		

Variations and covariances at the subject level were not significant. At the tooth level, the significant covariances for thickness at different locations, say m and n, yielded very high correlation coefficients as calculated by $r_{m,n} = \sigma_{m,n} / (\sqrt{\sigma_m^2 \times \sigma_n^2})$. *MLwiN* allows us to instantly check correlations from the covariance matrix. For that purpose we open **Estimate tables** in the **Model** menu in order to get estimates. We select **Level 3: TOOTH2_long** and check box **C** (for correlation).

	CONS.GTH1	CONS.GTH2	CONS.GTH3
CONS.GTH1	$\sigma_{v 0}^2$		
	0.055		
	(0.022)		
	0.055		
	Corr: 1.000		
CONS.GTH2	$\sigma_{v 0 1}$	$\sigma_{v 1}^2$	
	0.067	0.083	
	(0.025)	(0.033)	
	0.067	0.083	
	Corr: 0.983	Corr: 1.000	
CONS.GTH3	$\sigma_{v 0 2}$	$\sigma_{v 1 2}$	$\sigma_{v 2}^2$
	0.048	0.066	0.064
	(0.020)	(0.025)	(0.029)
	0.048	0.066	0.064
	Corr: 0.806	Corr: 0.902	Corr: 1.000

As can be seen in the window, correlations vary between 0.983 for GTH1 and GTH2, and 0.806 for correlations between GTH1 and GTH3. Thus, even thickness of lining mucosa was highly correlated with gingival thickness at both measurement locations. At the occasion level, correlations were essentially weaker, see below.

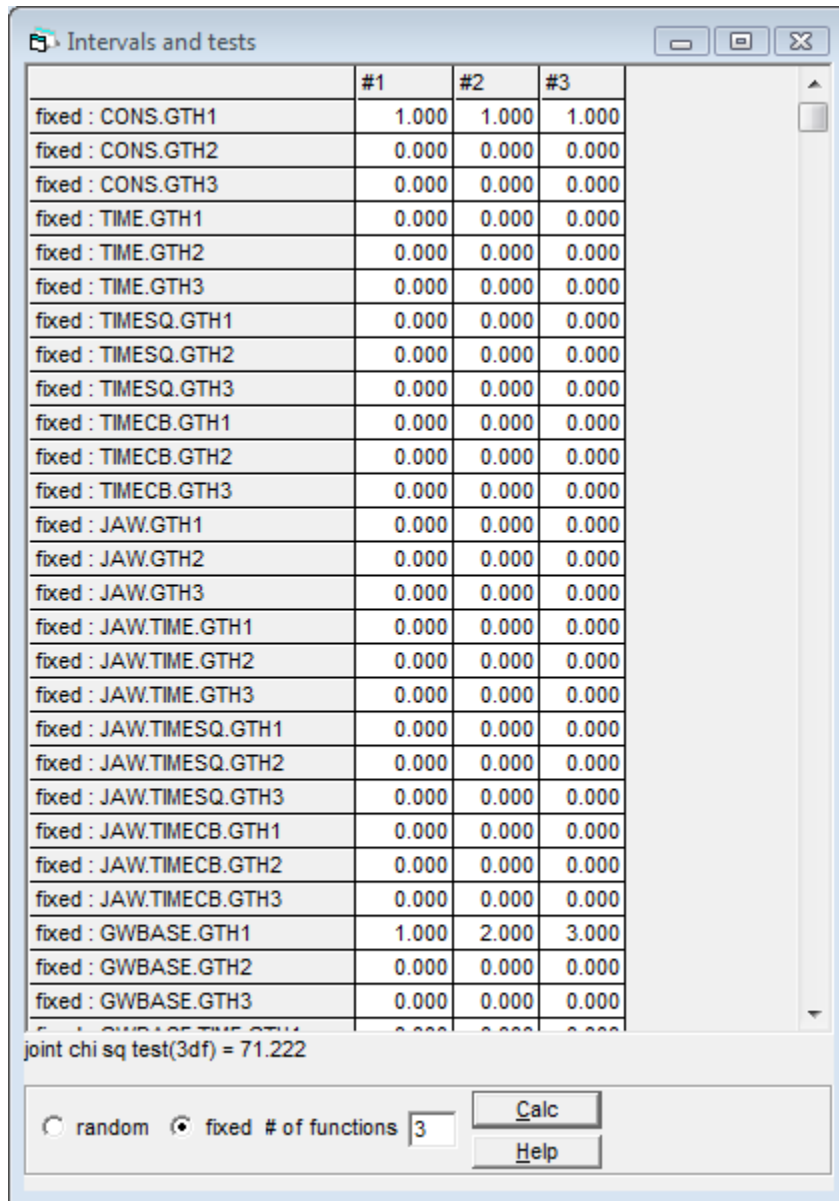
Before calculating predictions, we want to check whether estimated residuals follow a Normal distribution at each level. We want to have a look at the Normal probability plots, in which the ranked residuals are plotted against corresponding points on a Normal distribution curve. The points on a Normal plot should lie approximately on a straight line if the Normality assumption is valid. In the two plots below occasion level and tooth level estimates of residuals lie more or less on straight lines, not invalidating the Normality assumption.



4.3 Predictions

Predictions of mucosal thickness can easily be derived from the model. We open **Intervals and tests** from the **Model** menu, check **fixed** at the bottom and enter, say 3 in **# of functions**. We are interested in gingival thickness at the gingival

margin of maxillary teeth at baseline and how it relates to gingival width in 1-mm steps. So, we enter 1 for **CONS.GTH1** and 1, 2, or 3 for **GWBASE.GTH1**, respectively.



When we click on **Calc** we get the following results.

	#1	#2	#3
fixed : JAW.TIME.GTH1	0.000	0.000	0.000
fixed : JAW.TIME.GTH2	0.000	0.000	0.000
fixed : JAW.TIME.GTH3	0.000	0.000	0.000
fixed : JAW.TIMESQ.GTH1	0.000	0.000	0.000
fixed : JAW.TIMESQ.GTH2	0.000	0.000	0.000
fixed : JAW.TIMESQ.GTH3	0.000	0.000	0.000
fixed : JAW.TIMECB.GTH1	0.000	0.000	0.000
fixed : JAW.TIMECB.GTH2	0.000	0.000	0.000
fixed : JAW.TIMECB.GTH3	0.000	0.000	0.000
fixed : GWBASE.GTH1	1.000	2.000	3.000
fixed : GWBASE.GTH2	0.000	0.000	0.000
fixed : GWBASE.GTH3	0.000	0.000	0.000
fixed : GWBASE.TIME.GTH1	0.000	0.000	0.000
fixed : GWBASE.TIME.GTH2	0.000	0.000	0.000
fixed : GWBASE.TIME.GTH3	0.000	0.000	0.000
fixed : GWBASE.TIMESQ.GTH1	0.000	0.000	0.000
fixed : GWBASE.TIMESQ.GTH2	0.000	0.000	0.000
fixed : GWBASE.TIMESQ.GTH3	0.000	0.000	0.000
fixed : GWBASE.TIMECB.GTH1	0.000	0.000	0.000
fixed : GWBASE.TIMECB.GTH2	0.000	0.000	0.000
fixed : GWBASE.TIMECB.GTH3	0.000	0.000	0.000
constant(k)	0.000	0.000	0.000
function result(f)	0.670	0.784	0.898
f-k	0.670	0.784	0.898
chi sq, (f-k)=0. (1df)	30.316	60.947	69.653
+/- 95% sep.	0.239	0.197	0.211
+/- 95% joint	0.340	0.281	0.301

joint chi sq test(3df) = 71.222

random
 fixed # of functions

So, for maxillary teeth, gingival thickness at the gingival margin was estimated as 0.670 (95% confidence interval 0.431; 0.909) mm in case of 1-mm-wide gingiva, 0.784 (0.587; 0.981) mm at 2-mm wide gingiva, and 0.898 (0.687; 1.109) mm at 3-mm-wide gingiva. Consider mucosal thickness of lining mucosa 3 months after surgery at mandibular teeth where baseline gingival width was 1 mm.

	#1	#2	#3	#4
fixed : JAW.TIME.GTH1	0.000	0.000	0.000	0.000
fixed : JAW.TIME.GTH2	0.000	0.000	0.000	0.000
fixed : JAW.TIME.GTH3	0.000	0.000	0.000	3.000
fixed : JAW.TIMESQ.GTH1	0.000	0.000	0.000	0.000
fixed : JAW.TIMESQ.GTH2	0.000	0.000	0.000	0.000
fixed : JAW.TIMESQ.GTH3	0.000	0.000	0.000	9.000
fixed : JAW.TIMECB.GTH1	0.000	0.000	0.000	0.000
fixed : JAW.TIMECB.GTH2	0.000	0.000	0.000	0.000
fixed : JAW.TIMECB.GTH3	0.000	0.000	0.000	27.000
fixed : GWBASE.GTH1	1.000	2.000	3.000	0.000
fixed : GWBASE.GTH2	0.000	0.000	0.000	0.000
fixed : GWBASE.GTH3	0.000	0.000	0.000	1.000
fixed : GWBASE.TIME.GTH1	0.000	0.000	0.000	0.000
fixed : GWBASE.TIME.GTH2	0.000	0.000	0.000	0.000
fixed : GWBASE.TIME.GTH3	0.000	0.000	0.000	3.000
fixed : GWBASE.TIMESQ.GTH1	0.000	0.000	0.000	0.000
fixed : GWBASE.TIMESQ.GTH2	0.000	0.000	0.000	0.000
fixed : GWBASE.TIMESQ.GTH3	0.000	0.000	0.000	9.000
fixed : GWBASE.TIMECB.GTH1	0.000	0.000	0.000	0.000
fixed : GWBASE.TIMECB.GTH2	0.000	0.000	0.000	0.000
fixed : GWBASE.TIMECB.GTH3	0.000	0.000	0.000	27.000
constant(k)	0.000	0.000	0.000	0.000
function result(f)	0.670	0.784	0.898	2.343
f-k	0.670	0.784	0.898	2.343
chi sq, (f-k)=0. (1df)	30.316	60.947	69.653	277.072
+/- 95% sep.	0.239	0.197	0.211	0.276
+/- 95% joint	0.375	0.309	0.331	0.434

joint chi sq test(4df) = 349.514

random
 fixed # of functions

If one enters the product of the respective conditions into function #4, one gets an estimate (prediction) of 2.343 (2.067; 2.616). Ninety-five per cent confidence intervals were in general low, ± 0.2 - 0.3 mm at maxillary teeth and ± 0.4 - 0.5 mm at teeth in the mandible. In the maxilla mucosal thickness at all measurement locations peaked 3 months after surgery with negative correlations with baseline gingival width. Thereafter, thickness gradually decreased but remained higher (about 0.3-0.5 mm) than before surgery, while positive correlations with baseline

gingival width were re-established. At mandibular teeth, gingival thickness did not change so dramatically, while thickness of lining mucosa underwent similar changes as at maxillary teeth.

Fig. 4.1 displays mucosal thickness at three different locations (at the gingival margin (GTH1), at the mucogingival border (GTH2), and of the lining mucosa (GTH3) before and 3, 6, 9, and 12 months after surgical root coverage in relation to baseline gingival width (GW) and jaw. It has been created in PowerPoint after all predictions had been calculated.

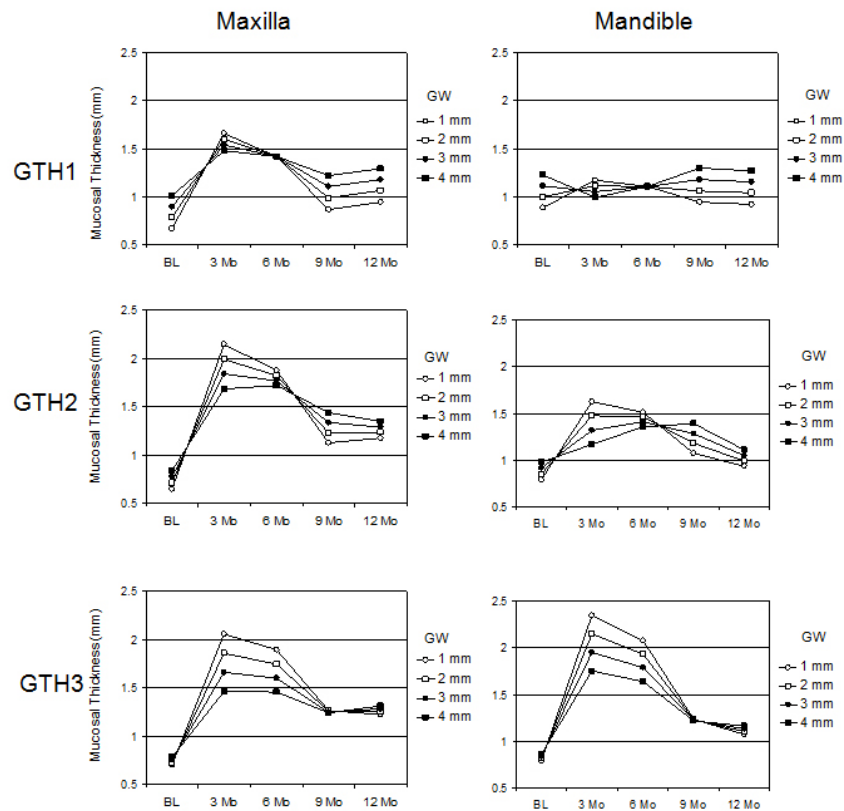


Fig. 4.1 Modeling longitudinal gingival/mucosal thickness in relation to preoperative gingival width (GW) at three locations (GTH1-3) after implantation of a bio-resorbable membrane for surgical root coverage (Müller 2008).

One may intuitively compare the multilevel model with a microscope here since raw data or presentation of means and standard deviations would hardly give a similarly elegant impression of what is actually going on after implantation of a bio-resorbable membrane for surgical root coverage employing guided tissue regeneration.

5 Logistic Models for Binary and Binomial Responses

In the previous chapters, continuous response variables had been considered in various variance components, random intercept, random coefficient, time series, and multivariate time series multilevel models. In this chapter, we want to look at binary or binomial (proportion) responses. We will mainly focus on the logit link function. As usual, we start with a single-level model and extend this to appropriately consider the three-level hierarchical structure. We also explore contextual effects here. Significance testing and model interpretation using odds ratios and variance partition coefficients are discussed.

5.1 Description of the Example Data Set

The data for an example are stored in an EXCEL file (*bop_pli01.xlsx*). The binary response variable here is presence or absence of bleeding on probing (BOP) at gingival units in 50 students at Kuwait University. All had plaque-induced gingival disease.

<i>Variable</i>	<i>Description</i>
ID	Subject's identifier (1-50)
GENDER	(0, 1)
AGE	In years
TOOTH_NO	FDI notation of teeth (11-48)
TYPE	Tooth type (1-16)

SITE	Tooth site (1-6)
PPD	Periodontal probing depth (mm)
CAL	Clinical attachment level (mm)
BOP	Bleeding on probing (0, 1)
PLI	Silness & Loe's plaque index (0-3)
CLS	Presence of calculus (0,1)

The cohort consisted of 16 male and 34 female dental students. They were between 19 and 28 years of age.

After we have opened a new worksheet in *MLwiN* by clicking on **File** in the main menu and **New worksheet**, we can easily import the EXCEL data just by copy them to the clipboard and paste them into *MLwiN*. For that we click on **Edit** in the main menu and **Paste**. We check the box **Use first row as names** in the new window and click **Paste**. We want to **Save the worksheet** in the **File** menu as *bop01.wsz*.

The main objective for the present analysis is to get an idea about the association between (supragingival) plaque and gingival bleeding after probing (BOP), a measure of gingival inflammation. Since the disease is called “plaque-induced”, we would expect a strong association. As a first step, let us tabulate BOP by ordinal scores describing the amount of supragingival plaque at the gingival margin, i.e. Silness and Loe's plaque index of 1963 (PLI). We click in **Basic Statistics** in the main menu and select **Tabulate**. Note that the default **Output**

mode is **Counts**. We type next to **Columns** **PLI**, check the **Rows** box and type **BOP**. We click on **Tabulate** and get the result below.

```

->TABulate 0 'PLI' 'BOP'

840 missing value(s)

Columns are levels of PLI
Rows are levels of BOP

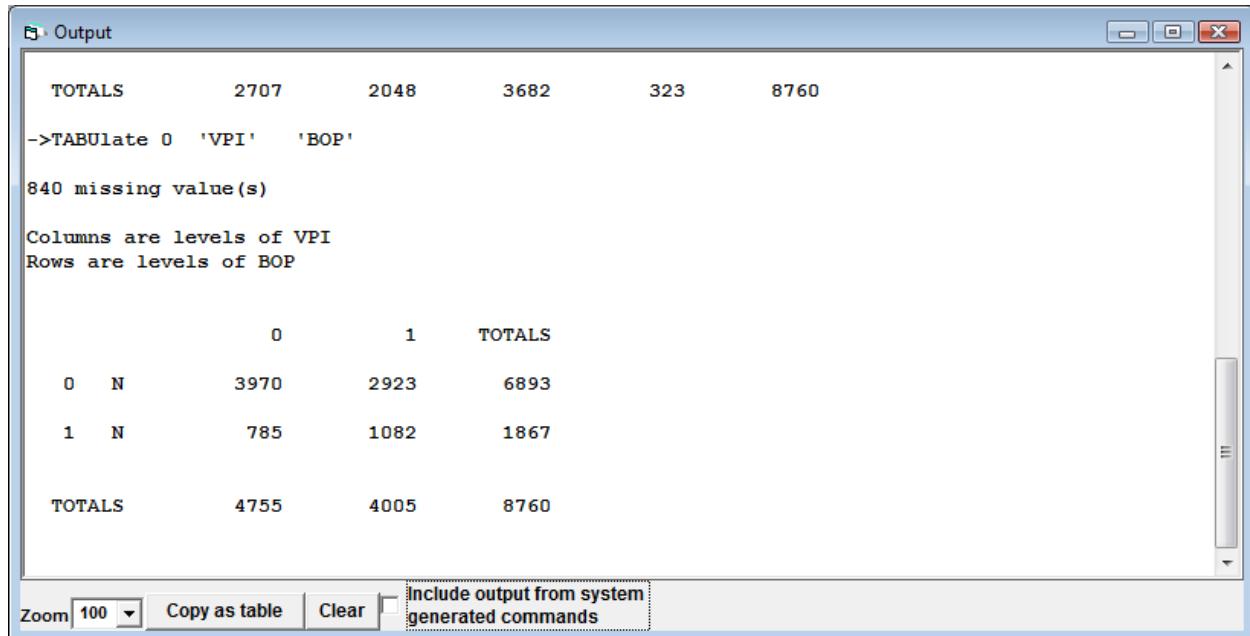
      0      1      2      3      TOTALS
0  N    2364   1606   2751   172    6893
1  N     343    442    931    151   1867
TOTALS 2707   2048   3682    323   8760

```

Zoom 100 Copy as table Clear include output from system generated commands

What has been expected is that most sites without plaque or small (invisible, if not disclosed with a dye) amounts of plaque (PLI scores of 0 or 1) do not bleed after probing. But the vast majority of sites with considerable plaque (PLI score of 2) and the majority of sites with even abundance of plaque (PLI score of 3) did not bleed upon probing either. In order to make things easier, we want to collapse plaque index scores of 0 and 1 (which is usually not visible) and plaque index scores of 2 and 3, and create a new variable, the visible plaque index (Ainamo and Bay 1975). We click on **recode** and **by range** in **Data Manipulation** of the main menu. We select **PLI** for **Input columns** and type next to the boxes of the **Recode specification** for values in range **0 to 1** and type **0** next to **new value**. In **Output**

columns we select **c12** and click on **Add to action list**. Next we assign **1** for **Values in range of 2 to 3** in the **to new value** box. We click on **Add to action list** and on **Execute** in the right window. We should rename column **c12** to **VPI** by clicking on **Name** in the **Column** menu. We now want to tabulate BOP by VPI.



The data suggest a moderate association. The odds ratio can be calculated as

$\frac{3970/785}{2923/1082} = 1.872$. An asymptotic approximation of the standard error of the log

odds ratio is $SE = \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{10}} + \frac{1}{n_{01}} + \frac{1}{n_{00}}} = 0.0528$. If L is the sample log odds

ratio, an approximate 95% confidence interval is $L \pm 1.96SE$. To obtain a 95%

confidence interval (CI) for the odds ratio, one has to take exponentials: $\exp(L-$

$1.96SE$), $\exp(L+1.96SE)$. In the present example, one gets $\exp(0.5235) = 1.6879$, and $\exp(0.7305) = 2.0761$, respectively.

5.2 The Logit Link Function

We want to see whether *MLwiN* can reproduce these estimates. Since all subjects had, as mentioned above, plaque-induced gingival disease, we start with assessing the association between visible plaque and gingival bleeding on probing by fitting a respective single-level logistic regression model. We intentionally omit the higher level, the subject.

The binary (0, 1) response, bleeding on probing, for the i th gingival unit is denoted as y_i . We denote the probability that y_i is 1 by π_i . A general model for binary response data is

$$f(\pi_i) = \beta_0 + \beta_1 x_1$$

where $f(\pi_i)$ is some transformation of π_i called the *link function*. We want to consider here the logit link $f(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right)$, where the quantity $\pi_i/(1-\pi_i)$ is the odds that y_i is 1. Thus, predicted probabilities $\hat{\pi}$ derived from the fitted model will lie between 0 and 1. Note that there are other link functions possible in *MLwiN*, such as the probit and log-log link which will not be dealt with in this chapter. The

logit transformation is most widely used since exponential coefficients from the logit model can be interpreted as odds ratios. So, the model takes the form

$$\text{logit}(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_i \quad (5.1)$$

or,

$$\frac{\pi_i}{1-\pi_i} = e^{\beta_0} \times e^{\beta_1 x_1} \quad (5.2)$$

If we increase x by 1 unit, we obtain

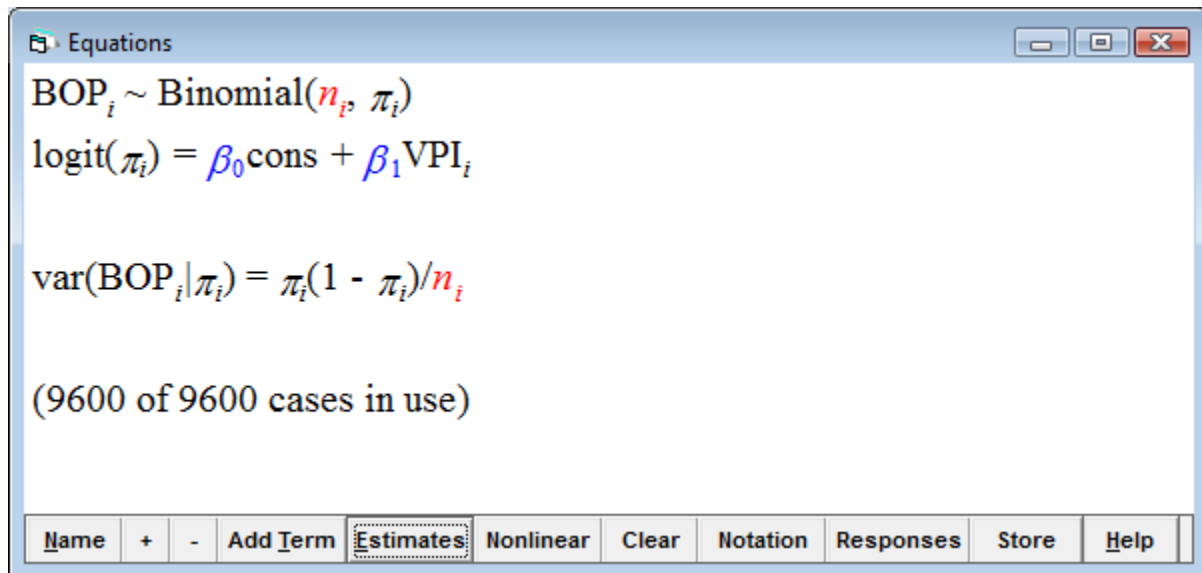
$$\frac{\pi_i}{1-\pi_i} = e^{\beta_0} \times e^{\beta_1(x_1+1)} = e^{\beta_0} \times e^{\beta_1 x_1} \times e^{\beta_1}$$

Thus, the exponential of β_1 is the *odds ratio* in case of binary response of x (0, 1), comparing the odds for units with $x = 1$ relative to the odds for units with $x = 0$. In case of continuous x , the exponential of β_1 is interpreted as multiplicative effect on the odds for a 1-unit increase in x . Formula 5.2 can be rearranged to obtain an expression of π_i :

$$\pi_i = \frac{\exp(\beta_0 + \beta_1)}{1 + \exp(\beta_0 + \beta_1)} = \frac{1}{1 + \exp(-(\beta_0 + \beta_1))} \quad (5.3)$$

5.3 A Single-level Logistic Regression Model

We shall now model this relationship by fitting a single-level model of the binary response variable BOP in *MLwiN*. From the **Model** menu, we select **Equations** and click on **y**. For **y**, we select from the drop-down menu of the **Y variable** window **BOP**, for **N-levels** we enter **1-i**, and for **Level 1(i)** we select **SITE** and click on **done**. Now we click on **N** in the **Equation window** and tag, in the **Response type** window, **Binomial**. We note that in the **Select link function** the default box **logit** is already checked. We click **Done**. We click on x_0 and select **cons** from the drop-down list of variables (*MLwiN* has created the **cons** variable already), and click **Done**. We click on **Add term**. From the variable drop-down list we select **VPI**, click **Done** and click on **Estimate** in the **Equation** window.

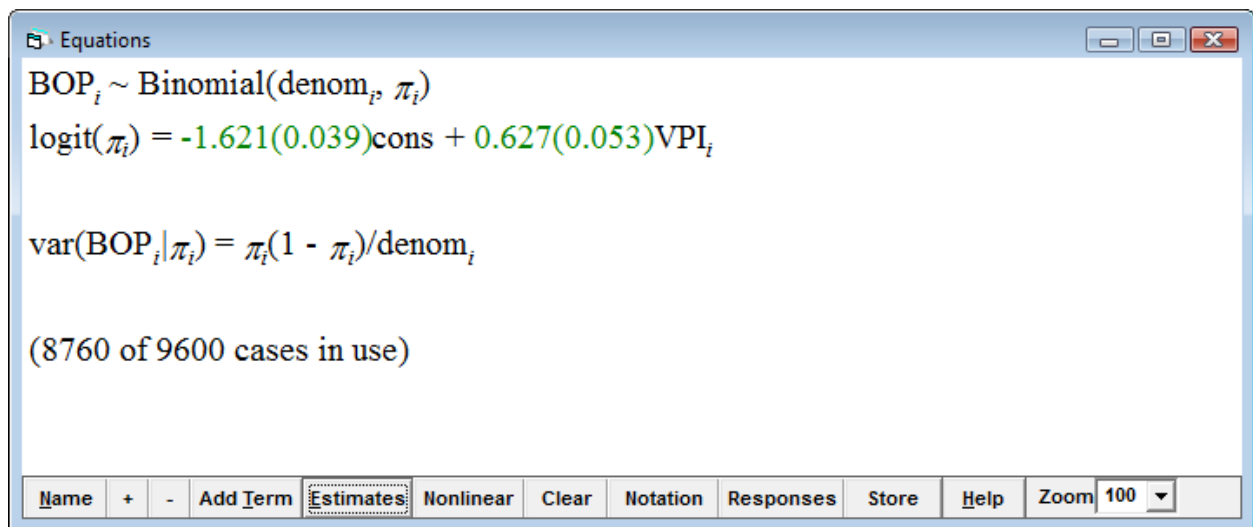


The first line states that the response variable follows a binomial distribution with parameters n_i and π_i . The parameter n_i is known as the denominator. In the case of binary data, n_i is equal to 1 for all units. We will now create n_i and call the new variable **denom**. From the **Data Manipulation** menu we select **Generate vector**. In the **Generate vector** window we select **c15**. Next to **Number of copies** we enter 9600, and 1 next to **Value**. Then, we **Generate** and rename **c15** to **denom** by clicking on **c15** and on the **Column Name** button. In the **Equations** window we click on n_i and select **denom**. (Note that if our data had been binomial, i.e. in the form of proportions, then n_i would be equal to the number of units on which the proportion is based; here, for instance, the number of sites where bleeding on probing had been assessed.)

The second line in the **Equations** window is the equation for the logit model which has the same form as (5.1) as can be shown by clicking on the **Name** button in the **Equations** window. We want to specify details about the estimation procedure to be used. We click on the **Nonlinear** button at the bottom of the **Equations** window and on **Use Defaults**. (We will discuss estimation choices when we come to fit multilevel models.)

Now we can run the model by clicking on the **Start** button in main menu. The model converges instantly and estimates can be seen after clicking on the **Estimates** button.

The last line in the **Equations** window states that the variance of the binomial response is $\pi_i(1 - \pi_i)/\text{denom}_i$, which, in the case of binary data, simplifies to $\pi_i(1 - \pi_i)$.



We want to **Save the worksheet** in the **File** menu as *bop02.wsz*.

5.4 Calculating Some Estimates Derived from the Model

Based on the fourfold table on frequencies of bleeding on probing by visible plaque (see 5.1) we had calculated an odds ratio of 1.872 (1.6879; 2.0761). The model above indicates an estimated coefficient for visible plaque of 0.627 with a

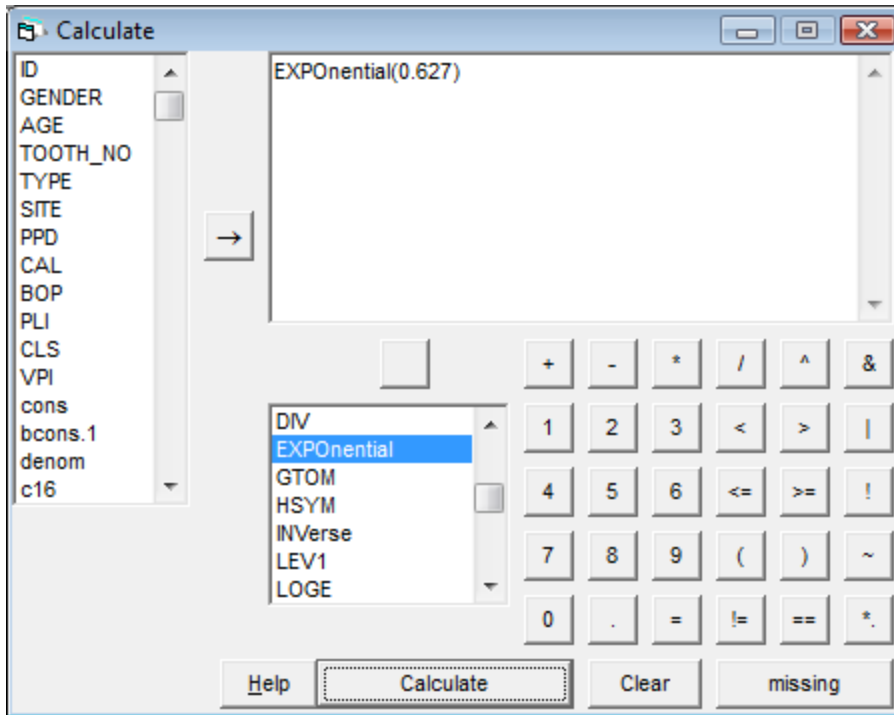
standard error of 0.053. We click on **Model** in the main menu and then on **Intervals and tests**. After having checked **fixed** at the bottom of the respective window we type **1** next to **fixed : VPI** and get a 95% CI for the coefficient estimate of ± 0.104 .

	#1
fixed : cons	0.000
fixed : VPI	1.000
constant(k)	0.000
function result(f)	0.627
f-k	0.627
chi sq, (f-k)=0. (1df)	140.826
+/- 95% sep.	0.104
+/- 95% joint	0.104

joint chi sq test(1df) = 140.826

random
 fixed # of functions

We may click on **Calculate** in the **Data manipulation** menu, select **EXPO** from the expressions at the bottom on the right side and click on the **button** to move it to the window at the top of the right side. We then type **(0.627)** and click on **Calculate**.



We get an odds ratio of 1.8720, exactly the same as the crude odds ratio derived from the four-fold table of frequencies. We then add and subtract 0.104 from 0.627 and get a very similar 95% CI of 1.6871 – 2.0772.

We can use the estimated coefficients to calculate predicted probabilities of bleeding on probing at a site with and without supragingival plaque by entering respective coefficient estimates into formula (5.3). Easier is to use again the **Calculate** window and take the **ALOGit** of -1.621 in case of no plaque, and of (-1.621 + 0.627) in case of plaque. The model estimates probabilities of 0.16507 and 0.27012, respectively. In order to get a 95% confidence interval for the latter, we type **1** next to **fixed : cons** and **1** next to **fixed : VPI** in the **Interval and tests** window, and click on **Calc**.

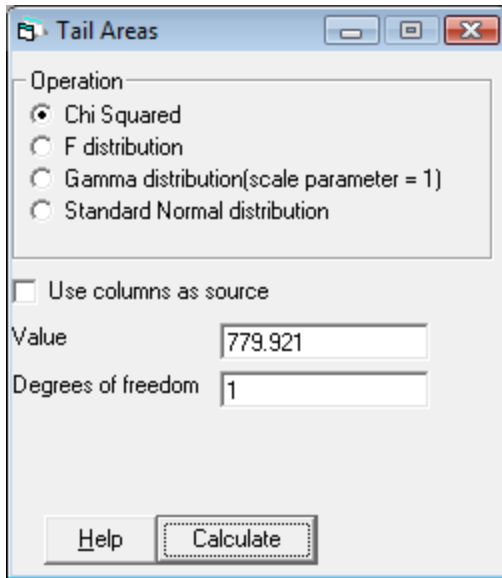
	#1
fixed : cons	1.000
fixed : VPI	1.000
constant(k)	0.000
function result(f)	-0.994
f-k	-0.994
chi sq, (f-k)=0. (1df)	779.921
+/- 95% sep.	0.070
+/- 95% joint	0.070

joint chi sq test(1df) = 779.921

random fixed # of functions

The $\text{logit}(\pi_i)$ estimate at sites with visible plaque ($\text{VPI} = 1$) has a 95% confidence interval of (-1.064; -0.924). **ALOGit** of these estimates yields a 95% CI of bleeding on probing in the presence of visible plaque of (0.25655; 0.28414). Likewise, the 95% CI for the probability of a site without visible plaque but bleeding on probing is (0.13147; 0.14957).

The joint chi square test for 1 degree of freedom is very large, about 800. Whether that is significant can be determined when clicking on **Tail Areas** in **Basic Statistics**. We select **Operation Chi Squared** and enter the **Value** of 799.921 and 1 for **Degrees of freedom**, then click on **Calculate**.



This yields a very low p -value, indicating that the Null hypothesis of no difference in the probability of bleeding on probing, regardless of whether visible plaque was present or not, has to be rejected.

5.5 A Two-level Random Intercept Model

We want to extend our model in (5.1) to allow for subject effects on the probability of bleeding on probing. Therefore, we begin with a random intercept (or variance components) model that allows the overall probability of bleeding on probing to vary across subjects. Our binary response is y_{ij} which equals 1 if bleeding on probing occurs at site i in subject j and 0 if bleeding did not occur. A j subscript is likewise added to the proportion so that $\pi_{ij} = \Pr(y_{ij} = 1)$. The model can then be written as,

$$\begin{aligned}\text{logit}(\pi_{ij}) &= \beta_{0j} + \beta_1 x_{ij} \\ \beta_{0j} &= \beta_0 + u_{0j}\end{aligned}\tag{5.4}$$

As in a random intercept model for continuous responses, the intercept consists of two terms, a fixed component β_0 and a subject-specific component, the random effect u_{0j} . As before, we assume that the u_{0j} follow a Normal distribution with mean zero and variance σ_{u0}^2 .

We first need to declare that the data have a two-level hierarchical structure with subject at the higher level and then allow the intercept β_0 to vary randomly across subjects. We click on **BOP_i** in the **Equations** window and select **2-ij** for **N levels** in the **Y variable** window. For **level 2(j)** we select **ID** and for **level 1(i)** **SITE**, and click on **done**. We then click on the estimated coefficient for **cons** in the **X variable window**, check the box for **j(ID)** and click on **Done**.

We click on **Estimates** and get the window below. The model follows equation (5.4). In particular, an additional line states that the random effects u_{0j} follow a Normal distribution with mean zero and covariance matrix Ω_u , which, for a random intercept model, consists of a single term σ_{u0}^2 .

Equations

$$\text{BOP}_{ij} \sim \text{Binomial}(\text{denom}_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = \beta_{0j}\text{cons} + \beta_1\text{VPI}_{ij}$$

$$\beta_{0j} = \beta_0 + u_{0j}$$

$$[u_{0j}] \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma_u^2 \end{bmatrix}$$

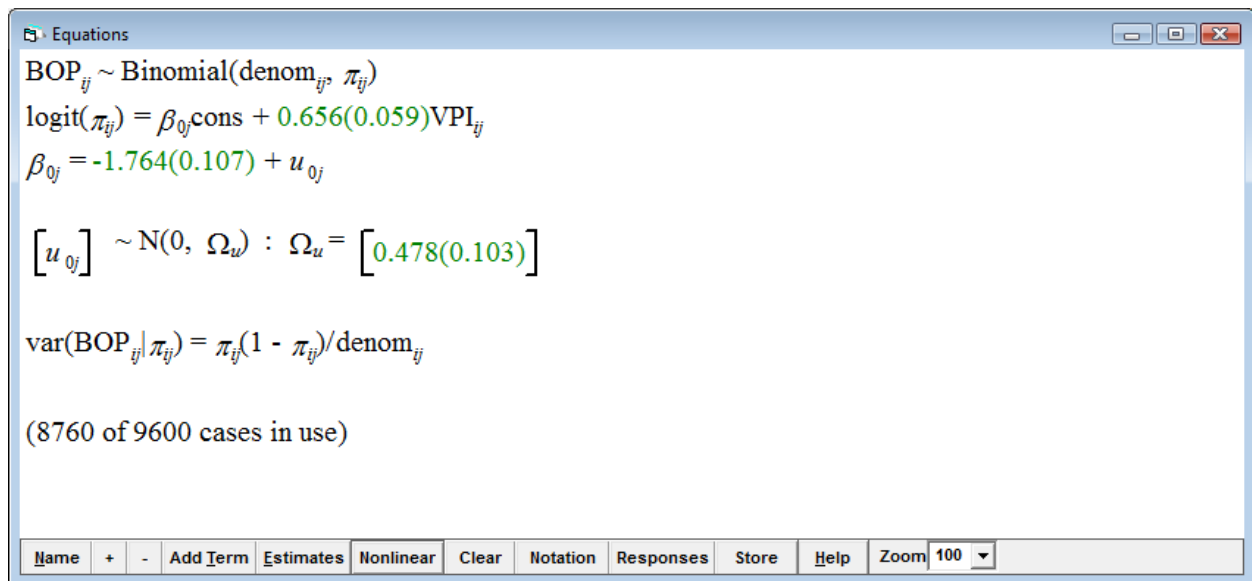
$$\text{var}(\text{BOP}_{ij} | \pi_{ij}) = \pi_{ij}(1 - \pi_{ij})/\text{denom}_{ij}$$

Name + - Add Term **Estimates** Nonlinear Clear Notation Responses Store Help

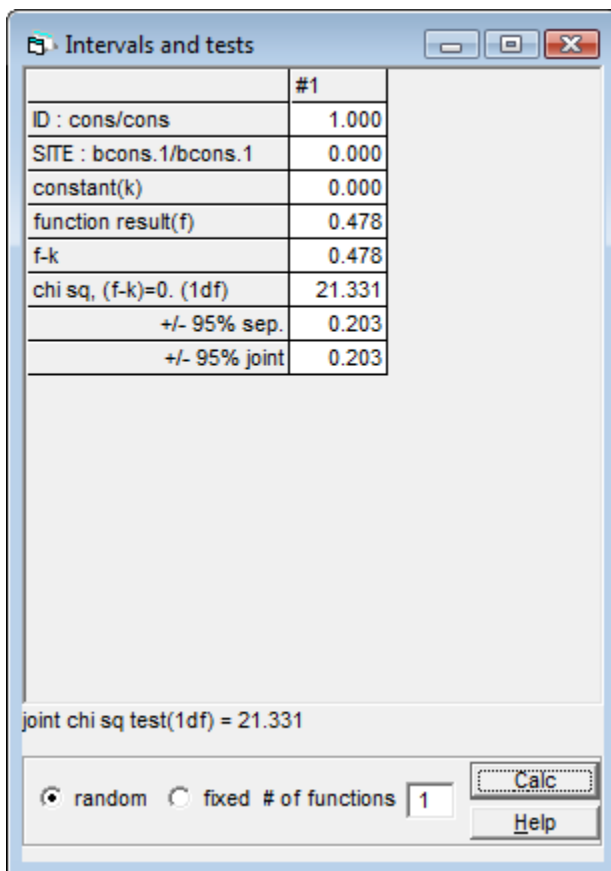
Before running the model we have to specify estimation procedures, see Rasbash et al. (2015), p. 125 and, in particular Goldstein (2003). *MLwiN* has implemented quasi-likelihood methods using a linearization method based on a Taylor series expansion which transforms a discrete response model to a continuous response model. After applying the linearization, the model is then estimated using iterative generalized least squares (IGLS) or reweighted IGLS (RIGLS), see Goldstein (2003) for further details. The types of approximation available in *MLwiN* are marginal quasi-likelihood (MQL) and penalized quasi-likelihood (PQL). Both of these methods can include either 1st order terms or up to 2nd order terms of the Taylor series expansion. The 1st order MQL procedure offers the crudest approximation and may lead to estimates that are biased downwards, particularly if sample sizes within higher level units are small or the response proportion is extreme. An improved approximation procedure is 2nd order PQL. Note that this

method is less stable and may encounter convergence problems. Thus, it is advisable to start the analysis beginning with the 1st order MQL procedure to obtain starting values for the 2nd order PQL procedure. Intermediate choices, for instance, 1st order PQL and 2nd order MQL are also often useful.

We can check that the default estimation procedure is selected. By clicking on **Estimation** in the main menu and **IGLS** we see that this method is already selected. In the **Equation** window, we click on **Nonlinear** at the bottom and see that the **Distribution assumption** (binomial), **Linearisation** (1st order) and **Estimation type** (MQL) are tagged. We click on **Done** and run the model by clicking on **Start**. We can have a look at estimates by clicking twice on **Estimates**. We click on **Nonlinear** again and specify 2nd order **Linearisation** and PQL **Estimation type**, and click on **Done** and **More**.



The intercept for subject j is $-1.764 + u_{0j}$ where the variance of u_{0j} is estimated as 0.478 (SE = 0.103). Whether the latter estimate is significant may be assessed by a Wald test. But note that this is an approximation since variance parameters are not Normally distributed. The preferred approach is to construct interval estimates for variance parameters using bootstrap or MCMC methods, see Chapter 3 in Goldstein (2003) and Chapter 4 in Browne (2003). To carry out just a Wald test in *MLwiN* we click on **Intervals and tests** in the **Model** menu, check **random** at the bottom of the **Intervals and tests** window, type **1** next to **ID : cons/cons** (this refers to the parameter $\sigma_{u_0}^2$) and click on **Calc**.



The joint chi square test yields a test statistic of 21.331 which we may compare to a chi-squared distribution on 1 degree of freedom. We type the respective values in the **Tails area** window (in **Basic statistics** in the main menu) and click on **Calc**. The p -value is very low, so we conclude that differences between subjects are highly significant.

5.5.1 Addition of further covariates

In plaque-induced gingival disease, the development of gingival pockets which may bleed on probing is rather typical. Thus, increased periodontal probing depth (PPD) might be related to bleeding on probing independent of presence of visible plaque. Likewise, presence of calculus might lead to increased bleeding tendency of the gingiva. We may first **Tabulate** (in **Basic Statistics**) PPD by clinical attachment loss (CAL) and notice that both are ordered categorical variables comprising only non-negative integers, despite the fact that they are interpreted as continuous measurements. Most attachment loss was related to shallow PPD (indicating gingival recession). Most sites with increased PPD >3 mm had not undergone attachment loss (indicating what is sometimes called pseudopockets). We may want to enter PPD in the model centered on the mean value (which is 2.30 mm as can be calculated in the **Basic Statistics** menu).

Output

```

->TABULATE 0 'PPD' 'CAL'

834 missing value(s)

Columns are levels of PPD
Rows are levels of CAL

```

		1	2	3	4	5	6	TOTALS
0	N	3019	4623	1017	65	19	2	8745
1	N	3	0	0	0	0	0	3
2	N	11	1	0	0	0	1	13
3	N	2	2	1	0	0	0	5
TOTALS		3035	4626	1018	65	19	3	8766

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We click on **Add term** in the equation window and select **variable PPD** in the drop-down list. As there are no zero or negative measurements for PPD, we want to enter the variable centered around 2 mm. In the **Specify term** window, we check **around value** and type **2** next to it. We click on **Done**. We then add CLS from the drop-down menu and click on **Done** and on **More** in the main menu. As discussed before, after having obtained starting values we now want to select the 2nd order penalized quasi-likelihood procedure. We click on **Nonlinear** at the bottom of the **Equation** window, and check **2nd order** for **Linearisation** and **PQL** for **Estimation** type.

Equations

$$BOP_{ij} \sim \text{Binomial}(\text{denom}_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = \beta_{0j}\text{cons} + 0.509(0.061)VPI_{ij} + 0.561(0.043)(PPD-2)_{ij} + 0.285(0.170)CLS_{ij}$$

$$\beta_{0j} = -1.623(0.106) + u_{0j}$$

$$[u_{0j}] \sim N(0, \Omega_u) : \Omega_u = [0.459(0.101)]$$

$$\text{var}(BOP_{ij} | \pi_{ij}) = \pi_{ij}(1 - \pi_{ij}) / \text{denom}_{ij}$$

(8760 of 9600 cases in use)

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As expected, PPD-2 is as strongly associated with BOP as is VPI. With each mm increase the odds of bleeding increases by a factor of 1.7524 (95% CI 1.6112; 1.9060). A Wald test yields a large joint chi squared test statistic of 172.888 for 1 df. Also calculus was associated with BOP. If present, the odds of gingival bleeding on probing is increased by a factor of 1.3298 (0.95211; 1.8571). The joint chi squared test statistic of 2.802 for 1 df relates to a p -value of 0.094147. We want to save worksheet and model as *bop03.wsz*.

5.5.2 Variance partition coefficient

In Chapter 2 we had partitioned the total variance for a two-level random intercept model and expressed the proportion of total residual variance which is attributable

to level 2, the so-called variance partition coefficient (VPC), $\sigma_{u0}^2 / (\sigma_{u0}^2 + \sigma_e^2)$. For a

random intercept model fitted to continuous data, the VPC is equal to the intra-class correlation, which is the correlation between two level 1 units in the same level 2 unit. For random coefficient models, VPC and intraclass correlation are not equivalent, see Goldstein et al. (2002). In case of binary and other discrete response models, there is also no single VPC measure since the level 1 variance is a function of the mean which depends on the values of the explanatory variables in the model. Nevertheless, Snijder & Bosker (1999) give an approximate VPC as

$\sigma_{u0}^2 / (\sigma_{u0}^2 + \pi^2/3)$. For the above model we can calculate an approximate VPC of

0.123.

Goldstein et al. (2002) propose a simulation method using the macro *vpc.txt* in *MLwiN*. It consists of the following steps:

1. From the fitted model simulate M (for instance 5000) values for the level 2 residual from the distribution $N(0, \sigma_{u0}^2)$, using the sample estimate of the variance, $u_{0j}^{(m)}$ ($m = 1, 2, \dots, M$)

- For a given value of x_{ij} , say x^* compute the m corresponding values of $\pi_j^{*(m)}$

$$\pi_j^{*(m)} = \frac{\exp(\widehat{\beta}_0 + \widehat{\beta}_1 x^* + u_{0j}^{(m)})}{1 + \exp(\widehat{\beta}_0 + \widehat{\beta}_1 x^* + u_{0j}^{(m)})}. \text{ Also compute the level 1 variance } v_{1j}^{*(m)} =$$

$$\pi_j^{*(m)}(1 - \pi_j^{*(m)})$$

- The level 1 variance is then calculated as the mean of the $v_{1j}^{*(m)}$ ($m = 1, 2, \dots, M$), and the level 2 variance is the variance of the $\pi_j^{*(m)}$.

Before running the macro, we need to do the following:

- set values for explanatory variables and store these in **c151**, and
- set values for the explanatory variables which have random coefficients at level 2 and store these in **c152**. (This will be a subset of **c151**.)

In the above model, there are four explanatory variables (including **cons**). We will begin computing the VPC for a site with neither visible plaque nor calculus, and a periodontal probing depth of 1 mm. Remember that the variable PPD is centered around 2 mm. We therefore want to enter the values (1, 0, -1, 0) in **c151**. Since the model is a random intercept model, only **cons** has a random coefficient. We thus want to input the value **1** in **c152**. To create these two columns, we select **View or edit data** from the **Data Manipulation** menu, click on **view**, select **c151** and **c152**, and click **OK**. We then input 1, 0, -1, and 0, respectively into the first five rows of **c151**, and 1 in the first row of **c152**.

	c151(4)	c152(1)
1	1.000	1.000
2	0.000	-
3	-1.000	-
4	0.000	-
5	-	-
6	-	-
7	-	-
8	-	-
9	-	-
10	-	-

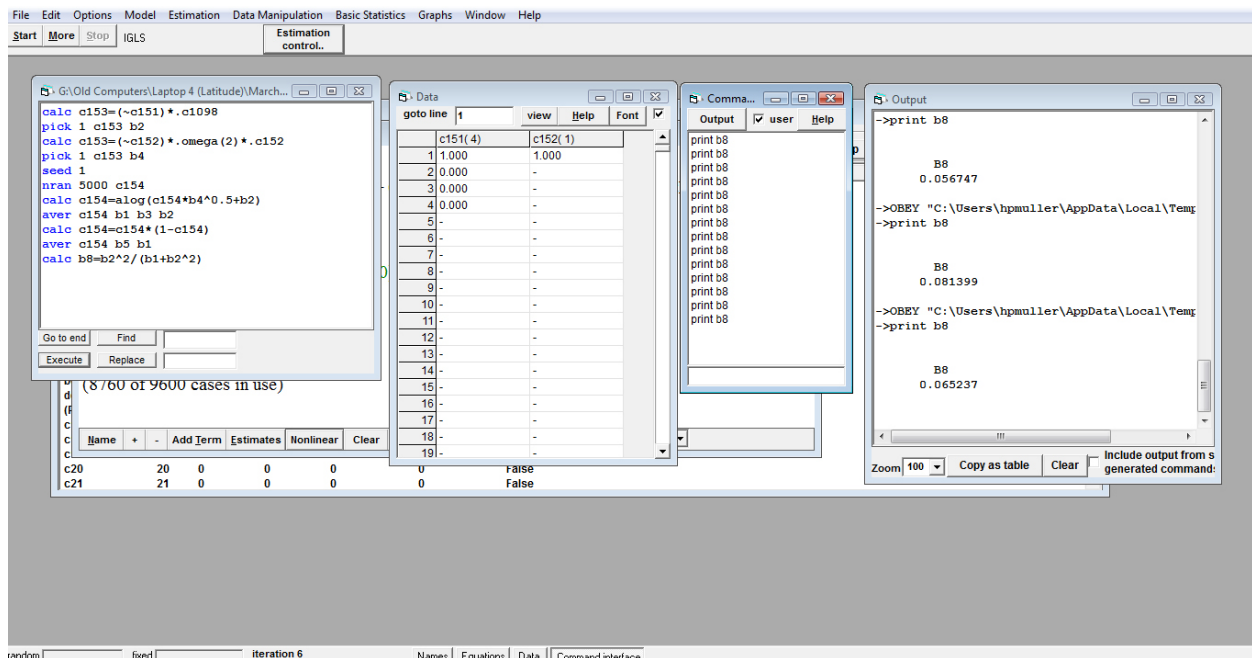
We can open the macro which contains a sequence of *MLwiN* commands by selecting **Open Macro** from **File**. We double click on *vpc.txt*. In the window which shows, and click on the **Execute** button.

```

calc c153=(~c151)*.c1098
pick 1 c153 b2
calc c153=(~c152)*.omega(2)*.c152
pick 1 c153 b4
seed 1
nran 5000 c154
calc c154=log(c154*b4^0.5+b2)
aver c154 b1 b3 b2
calc c154=c154*(1-c154)
aver c154 b5 b1
calc b8=b2^2/(b1+b2^2)

```

The result of running the macro, namely the VPC, will be stored in a worksheet box called B8. To print the contents of the box, we select from the **Data Manipulation** menu **Command interface** and type in the space at the bottom of the window **print b8**. We then press **Enter**. We can get the value by clicking on **Output**. For this particular site, the VPC is about 0.048. Thus, among sites with no plaque or calculus and a probing depth of 1 mm, 4.8% of the residual variation is attributable to differences between subjects. At 3 mm deep sites (we need to enter 1 in the 3rd line of column **c151**) with plaque and calculus, 9.6% of the unexplained variation can be attributed to subject differences.



The VPC for various clinical conditions is tabulated in *Table 5.1*.

<i>Table 5.1</i> Variance partition coefficients for different combinations of covariates based on the simulation method				
PPD/mm	VPI=0/CLS=0	VPI=0/CLS=1	VPI=1/CLS=0	VPI=1/CLS=1
1	0.049	0.057	0.064	0.072
2	0.065	0.074	0.080	0.087
3	0.081	0.088	0.092	0.096

5.6 Two-level Random Coefficient Models

So far, we have allowed bleeding on probing to vary across subjects, but we have assumed that the effects of explanatory variables (VPI, PPD-2, and CLS) are the same for each subject. We will now modify the assumption by allowing the bleeding differences between sites with and without plaque and sites with various periodontal probing depths to vary across subjects by introducing random coefficients. (Tabulating CLS reveals that the vast majority of sites, 8534 out of 8766 sites assessed in the 50 subjects, were not covered by calculus. Moreover, calculus was not observed in 19 subjects at all. Due to anticipated conversion problems, at the moment we do not want to assume the coefficient of CLS vary across subjects.) We click, in turn, on the respective coefficient in the equation, check **j(ID)** and click on **Done**. It is recommended to start the models with the default estimation procedure 1st order linearization and MQL estimation (checked in **Nonlinear** at the bottom of the **Equation** window), then change to 2nd order PQL and click **More** and, after conversion of the model, on **Estimates**.

Equations

$$BOP_{ij} \sim \text{Binomial}(\text{denom}_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = \beta_{0j}\text{cons} + \beta_{1j}\text{VPI}_{ij} + \beta_{2j}(\text{PPD-2})_{ij} + \beta_3\text{CLS}_{ij}$$

$$\beta_{0j} = \beta_0 + u_{0j}$$

$$\beta_{1j} = \beta_1 + u_{1j}$$

$$\beta_{2j} = \beta_2 + u_{2j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & \\ \sigma_{u01} & \sigma_{u1}^2 & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 \end{bmatrix}$$

$$\text{var}(BOP_{ij} | \pi_{ij}) = \pi_{ij}(1 - \pi_{ij}) / \text{denom}_{ij}$$

(8760 of 9600 cases in use)

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Note that a j subscript has been added to the coefficients of VPI and PPD-2 indicating that the coefficients depend on the subject. The average effects of VPI and PPD-2 are β_1 and β_2 , respectively, but the effects for subject j are $\beta_{1j} = \beta_1 + u_{1j}$ and $\beta_{2j} = \beta_2 + u_{2j}$, respectively, where u_{1j} and u_{2j} are Normally distributed random effects with mean zero and variances σ_{u1}^2 and σ_{u2}^2 , respectively. Allowing the coefficients to vary across subjects has also introduced parameters σ_{u01} , σ_{u02} , and σ_{u12} , which are the covariances between u_{0j} and u_{1j} , u_{0j} and u_{2j} ; and u_{1j} and u_{2j} , respectively.

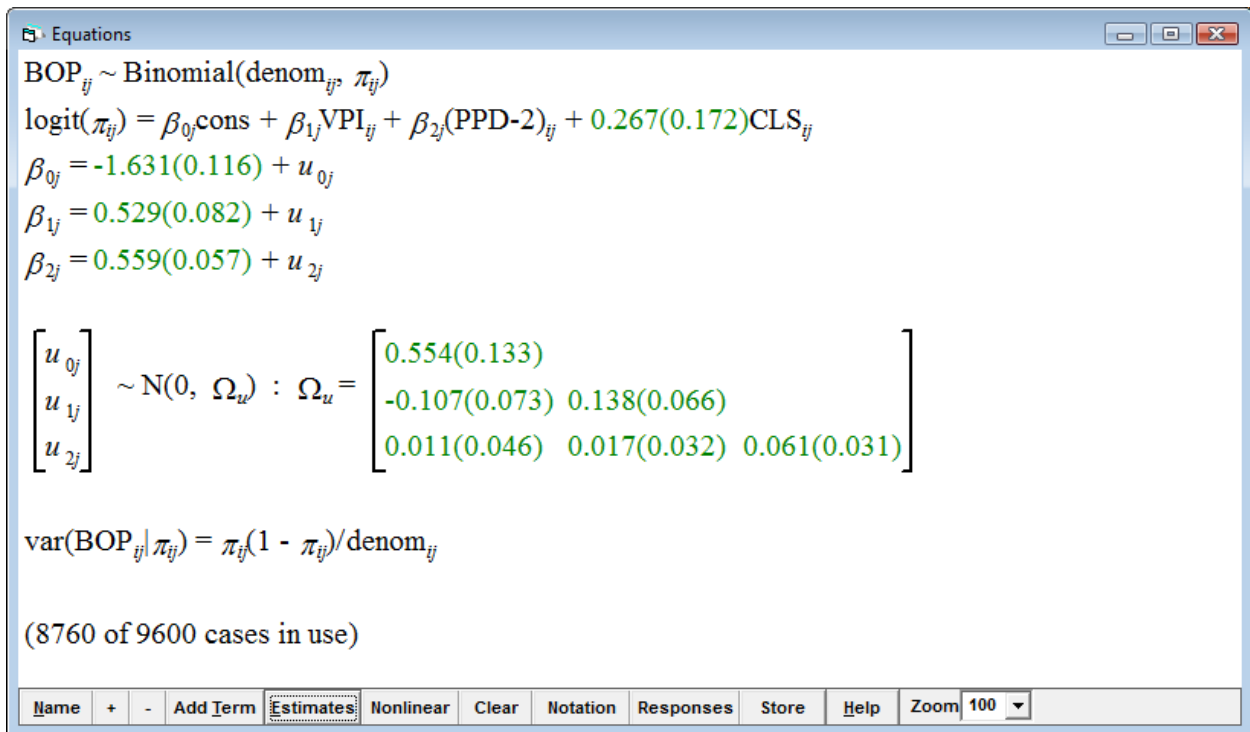
As for continuous response random coefficient models, the level 2 variance is a function of the explanatory variables that have random coefficients. For the model

specified above, the residual variance between subjects is a function of VPI and PPD-2:

$$\begin{aligned} \text{var}(u_{0j} + u_{1j}\text{VPI}_{ij} + u_{2j}\text{PPD} - 2_{ij}) &= \text{var}(u_{0j}) + 2\text{cov}(u_{uj}, u_{1j})\text{VPI} + \\ \text{var}(u_{1j})\text{VPI}^2 + 2\text{cov}(u_{0j}, u_{2j})\text{PPD} - 2 &+ 2\text{cov}(u_{1j}, u_{2j})\text{VPI} * \text{PPD} - 2 + \\ \text{var}(u_{2j})\text{PPD} - 2^2 & \end{aligned} \quad (5.5)$$

(Note that because VPI is a (0, 1) variable, $\text{VPI}^2 = \text{VPI}$).

In order to fit the random coefficient model, we click on **More** and on **Estimate**.



We can test the significance of the added parameters σ_{u10}^2 , σ_{u20}^2 , σ_{u01} , σ_{u02} , and σ_{u12} , using Wald tests. From the **Model** menu, we select **Intervals and tests**,

choose **random** in the new window, type **5** next to **# of functions**, and type **1** in each of the boxes **ID : VPI/cons**, **ID : VPI/VPI**, **ID: PPD/cons**, **ID : VPI/PPD**, and **ID : PPD/PPD**. When clicking on **Calc**, we note, for instance, that the separate chi squared test statistics for 1 df were 4.415 for VPI and 3.806 for PPD yielding *p*-values of 0.036 and 0.051, respectively. The joint chi square test statistic for 5 df is 8.807 which yields a *p*-value of 0.117.

	#1	#2	#3	#4	#5
ID : cons/cons	0.000	0.000	0.000	0.000	0.000
ID : VPI/cons	1.000	0.000	0.000	0.000	0.000
ID : VPI/VPI	0.000	1.000	0.000	0.000	0.000
ID : (PPD-2)/cons	0.000	0.000	1.000	0.000	0.000
ID : (PPD-2)/VPI	0.000	0.000	0.000	1.000	0.000
ID : (PPD-2)/(PPD-2)	0.000	0.000	0.000	0.000	1.000
SITE : bcons.1/bcons.1	0.000	0.000	0.000	0.000	0.000
constant(k)	0.000	0.000	0.000	0.000	0.000
function result(f)	-0.107	0.138	0.011	0.017	0.061
f-k	-0.107	0.138	0.011	0.017	0.061
chi sq, (f-k)=0. (1df)	2.143	4.415	0.060	0.262	3.806
+/- 95% sep.	0.143	0.129	0.091	0.063	0.061
+/- 95% joint	0.242	0.219	0.154	0.108	0.103

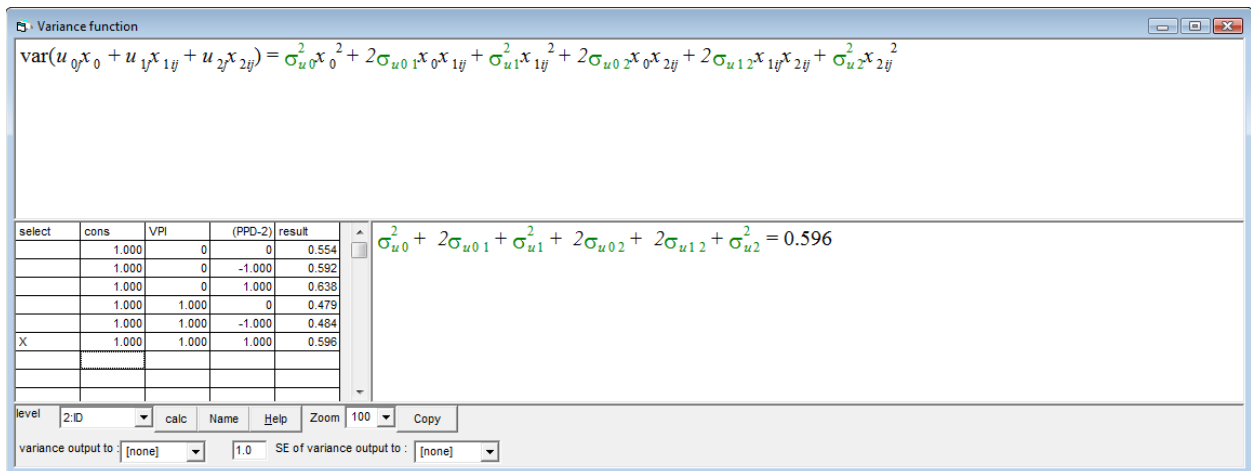
joint chi sq test(5df) = 8.807

random
 fixed # of functions

So, we may conclude that, at least at the 10% level, effects of VPI and PPD do in fact vary across subjects. While on average, the log odds is 0.529 times higher at

sites with visible plaque and the odds ratio is $\exp(0.529) = 1.6972$, depending on the value of u_{1j} , the odds ratio may be larger or smaller in different subjects. For each 1-mm increase in periodontal probing depth the odds of bleeding on probing will be increased by $\exp(0.559) = 1.7489$, on average, but depending on u_{2j} , this varies across subjects.

By substituting estimates of σ_{u10}^2 , σ_{u20}^2 , σ_{u01} , σ_{u02} , and σ_{u12} into (5.5), we may obtain estimates of residual subject-level variation. In the **Model** menu, we choose **Variance function** and select for **level 2: ID**. We can edit the table in the lower left corner for different clinical situations and get estimates of residual variance at the subject level. We want to **Save the worksheet** in the **File** menu as *bop04.wsz*.



Since Silness and Loe's plaque index are scores on an ordinal scale we want to add PLI as categorical variable. In the **Names** window, we therefore click on **PLI** and on **Toggle Categorical**. We delete the **VPI** term from the model by clicking on it

and on **Delete Term**, then clicking on **Done**, and add **PLI** in the equation. Note that in the **Specify term** window, the default reference category (**ref cat**), **PLI_0** appears. (We may change the reference category if we want.) When clicking on done, we see that now 3 terms of PLI appear in the equation, **PLI_1**, **PLI_2**, and **PLI_3**, meaning that the 4 PLI scores are defined by 3 dummy variables. We allow coefficients of PLI scores vary across subjects by checking the respective boxes for **j(ID)**. We make sure that in **Nonlinear** the default settings are selected. We then click on **Start** and, after the model has converged, change to **2nd order PQL**.

We want to **Save the worksheet** in the **File** menu as *bop05.wsz*.

Equations

$BOP_y \sim \text{Binomial}(\text{denom}_y, \pi_y)$

$\text{logit}(\pi_y) = \beta_0 \text{cons} + \beta_1 \text{PLI}_1_y + \beta_2 \text{PLI}_2_y + \beta_3 \text{PLI}_3_y + \beta_4 (\text{PPD}-2)_y + 0.246(0.174) \text{CLS}_y$

$\beta_0 = -1.930(0.130) + u_{0j}$

$\beta_1 = 0.571(0.125) + u_{1j}$

$\beta_2 = 0.776(0.117) + u_{2j}$

$\beta_3 = 1.520(0.194) + u_{3j}$

$\beta_4 = 0.550(0.056) + u_{4j}$

$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \\ u_{4j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.581(0.164) & & & & \\ -0.124(0.121) & 0.347(0.150) & & & \\ -0.201(0.121) & 0.246(0.120) & 0.329(0.133) & & \\ -0.424(0.201) & 0.033(0.173) & 0.094(0.165) & 0.493(0.313) & \\ 0.024(0.051) & -0.019(0.048) & 0.002(0.045) & 0.021(0.071) & 0.050(0.029) \end{bmatrix}$

$\text{var}(BOP_y | \pi_y) = \pi_y(1 - \pi_y) / \text{denom}_y$

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While on average, the log odds of bleeding on probing is 0.571 times higher at sites with a plaque index score of 1, 0.776 time higher at sites with a plaque index

score of 2, and 1.520 times higher at sites with a score of 3 as compared to sites with no plaque (corresponding to odds ratios of $\exp(0.571) = 1.7700$, $\exp(0.776) = 2.1728$, and $\exp(1.520) = 4.5722$, respectively), depending on the values of u_{1j} , u_{2j} , and u_{3j} , odds ratios may be larger or smaller in different subjects.

We can test the significance of the added parameters using a Wald test. As regards the addition of PLI scores in the model, the joint chi square test statistic for 12 df is 18.275 which yields a p -value of 0.10759.

5.7 Modeling Binomial Data

So far, we have considered logistic models for binary response data. The same models can be used for binomial data, i.e. where the response is a proportion. Only for illustration, we want to model the subject-level *proportion* of sites bleeding on probing as a function of the subject's mean periodontal probing depth, the proportion of sites covered by visible plaque (or the mean plaque index), and the proportion of sites with calculus. As a caveat, note that any site-specific information and, in particular, the association between site-specific observations is lost in this case. As has been detailed in the Introduction chapter, we have to keep in mind that any inferences from this model will be prone to the ecological fallacy of associations of aggregate data which may be spurious. If site-level data are

available, they should therefore be analyzed as such. In many cases, however, one may have only access to aggregate data.

5.8.1 Modeling subject-level variation with subject-level proportions

Our response variable y_j will be the sample proportion of sites bleeding on periodontal probing in subject j . After aggregating the data to the subject level, the only other change to the previous model is that the denominator n_j will no longer equal 1 as for binary data but will be equal to the number of sites assessed in subject j . Although our response variable is now at the subject level, we can still fit a two-level random intercept model of the form:

$$\begin{aligned}\text{logit}(\pi_{ij}) &= \beta_{0j} + \beta_1 \text{propVPI}_j + \beta_2 \text{avePPD}_j + \beta_3 \text{propCLS}_j \\ \beta_{0j} &= \beta_0 + u_{0j}.\end{aligned}$$

where π_{ij} is the probability of a site i bleeding on probing for subject j as before. avePPD_j denotes the average PPD in subject j , and propVPI_j and propCLS_j the proportions of sites with visible plaque and calculus, respectively.

When we specify the model, we will use the aggregate subject ID as the identifier for both level 1 and level 2. This implies a model with 50 level 2 units (subjects), each with one level 1 observation. (Note the tremendous loss of information here.)

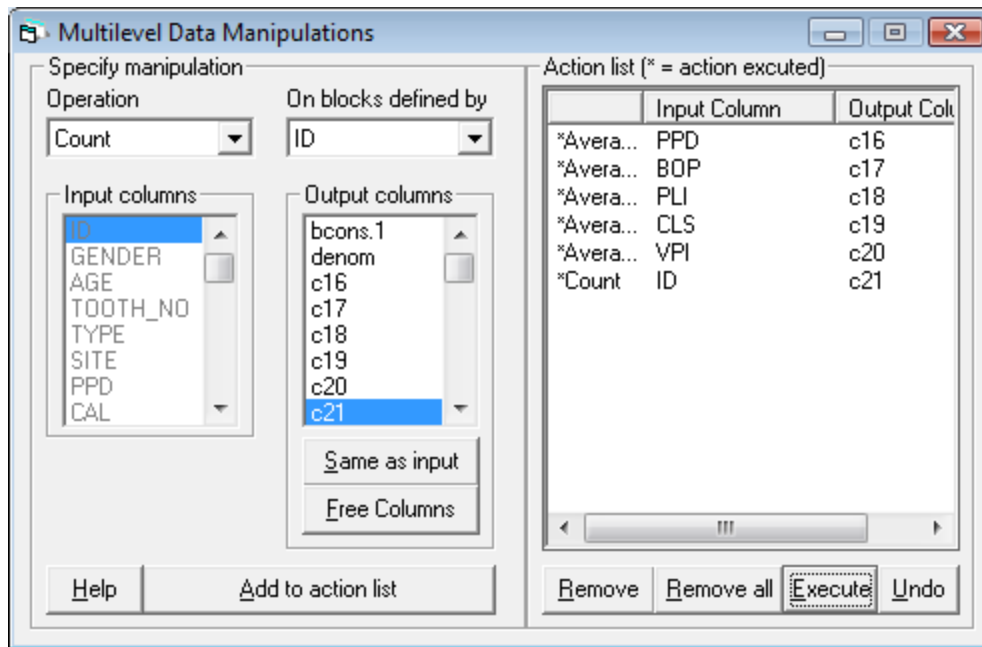
Since each level 1 unit has an associated denominator n_j , which is the number of

gingival units assessed in subject j , and since the level 1 variance depends on the explanatory variables, the model is not confounded.

5.7.2 Creating a subject-level data set

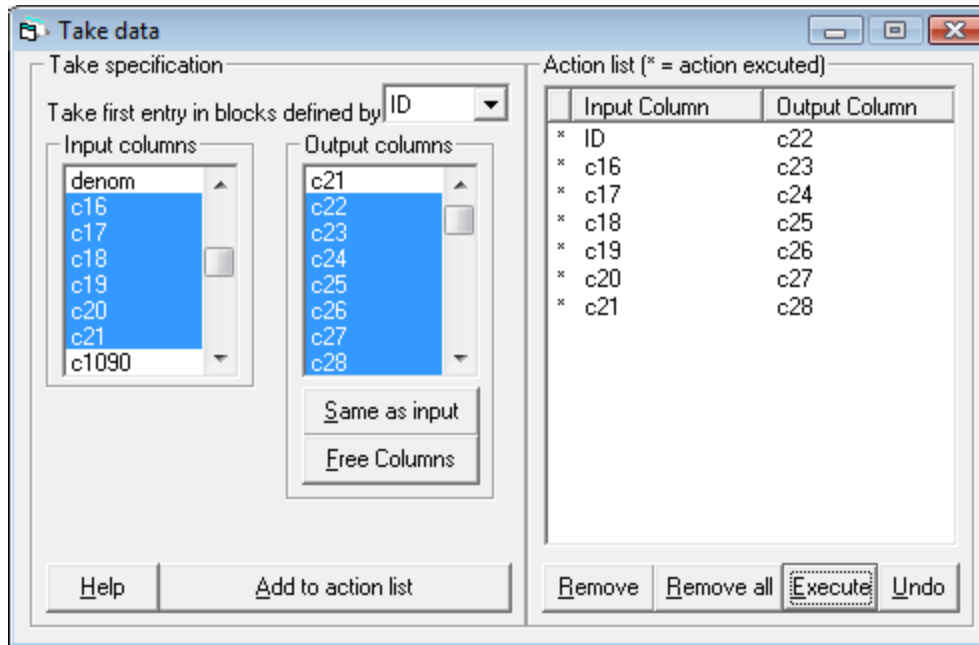
We open *bop02.wsz* and create a subject-level data set. We start with creating the response variable y_j and the denominator n_j .

We select from the **Data Manipulation** menu **Multilevel data manipulations**. In the respective window, under **Operation**, we select **Average**. For **On blocks defined by**, we select **ID**. For **Input columns**, we select **PPD, BOP, PLI, CLS** and **VIP** for **Output columns c16-c20**. We click on **Add to action list** and **Execute**. We then change **Operation** to **Count** and select **c24** for **Output column**. We **Add to action list** and **Execute**.



Columns **c16-c20** and **c21** now contain the response and explanatory variables, and denominator, respectively. However, they still contain a record for each site where the values for sites in the same subject are replicated. To see this, we select **View or edit data** from **Data Manipulation**. We have therefore to convert **c16-c21** so that they have only one record per subject.

From the **Data Manipulation** menu, we select **unreplicate** to open the **Take data** window. For **Take first entry in blocks defined by**, we select **ID** from the drop-down list. For **Input columns**, we select variables **ID**, and **c16-c21** (using ctrl-click). For **Output columns**, we select **c22-c28**. We **Add to action list** and **Execute**.



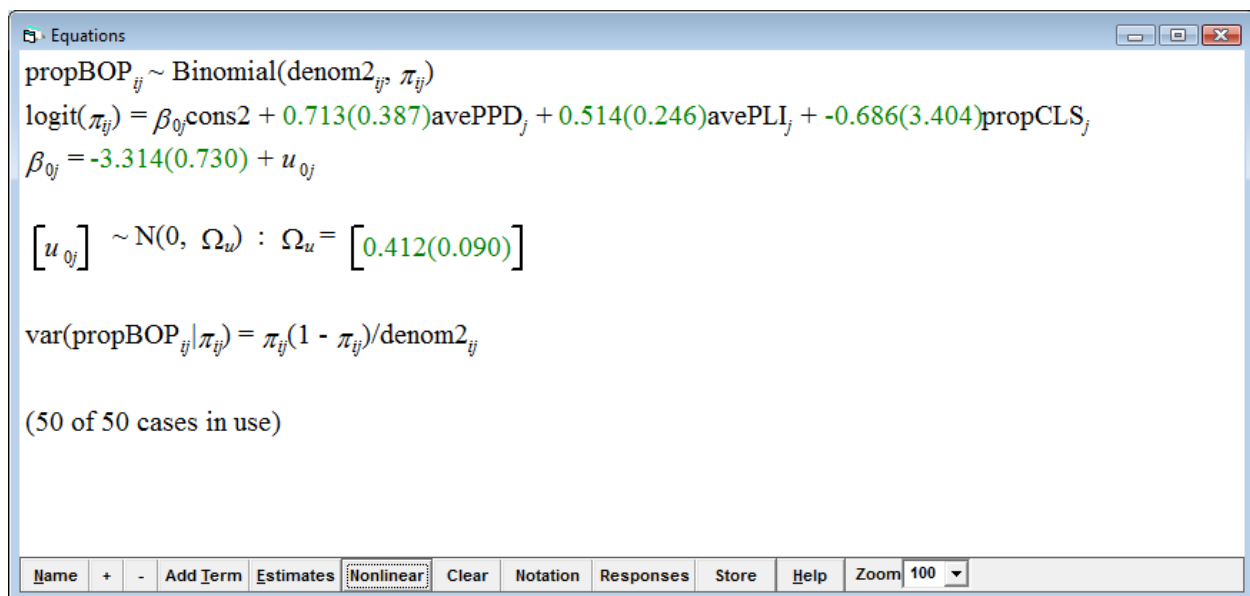
We want to rename **c22-c28** (in order): **ID2, avePPD, propBOP, avePLI, propCLS** and **propVPI**, and **denom2**. The final step in setting up the subject-level data set is to create a **cons** variable by clicking on **Generate vector** (in the **Data Manipulation** menu). We check **Constant vector**, select **c29** from the **Output column** drop-down list and type 50 next to **Number of copies**, and 1 next to **Value**. We then **Generate** and finally change the **Name** of **c29** into **cons2**.

5.8.3 Fitting the model

We can now set up the model. In the **Model** menu, we select **Equations** and click on **Clear**. We then click on **y**. In the **Y variable** window, we select **propBOP** from the drop-down list. For **N levels**, we select **2-ij** and enter **ID1** next to both **level**

2(j) and **level 1(i)**. We click on **done**. By clicking on **N**, we now **Select distribution Binomial** and **Select the link function, logit**, then click on **Done**. We click on n_{ij} and, in the **specify denominator** window, we select **denom2**. We click on x_0 and select **cons** from the **X variable** drop-down list. We check both **Fixed Parameter** and **j(ID1)**. We click on **Done**. We add **avePPD**, **avePLI**, and **propCLS**; Use defaults in the **Nonlinear Estimation** window and click on **Start** in the main menu.

Now we change to 2nd order PQL using the **Nonlinear** button and click on **More**.



The model indicates positive effects of mean probing depth and plaque index on the proportion of gingival units bleeding on periodontal probing. A Wald test yields a joint chi squared of 9.207 for 2 degrees of freedom which corresponds to a p -value of about 0.01. (Note that the standard error of calculus is five times as

large as its coefficient estimate. We may want to remove CLS from the equation).

We can conclude that, at the 1% level, both mean periodontal probing depth and plaque index is significantly related to the proportion of gingival units bleeding on probing. We may want to save the worksheet as *bop_prop.wsz*.

6 Repeated Measures Models for Binary Outcomes

In Chapter 3, we had described simple, and quite complex, repeated measures time series models in which continuous outcomes, for instance, gingival thickness or gingival recession, were modeled over time after the implantation of a bio-resorbable membrane, when it had to be assumed that the responses were nonlinear and non-monotonic.

In this chapter we want to model the binary outcome, bleeding on gingival probing, in subjects with mild plaque-induced gingival disease over time. While participants of the 1999 Workshop on Periodontal Diseases and Conditions had realized that most gingival inflammation is indeed dental plaque-induced, there seem to be numerous intrinsic and extrinsic factors which may modify the response. For instance, a common toothpaste compound, Triclosan, seems to dampen gingival inflammation in the presence of dental plaque (Müller et al. 2006). One may also ask whether the so-called interleukin-1 genotype, a combination of two single polymorphisms in the IL-1 gene, i.e. a haplotype, which had been associated with increased susceptibility for destructive periodontal disease (Kornman et al. 1997), has a clinically discernable influence on the inflammatory response on dental plaque.

Consider, for instance, a clinical experiment in a steady-state plaque environment where participants were asked not to alter their oral hygiene habits. So, after a 4-wk preparatory phase, 17 control subjects and 17 test subjects with mild gingival disease were properly randomized and given fluoride containing toothpastes without and with 0.3% Triclosan, respectively. They were then examined every other week for six weeks. Post hoc genetic testing revealed that the above mentioned IL-1 genotype was more or less evenly distributed among control and test subjects. The presence (six sites per tooth) of dental plaque, as described by the Silness & Loe plaque index (PI) on a four scores scale (Silness and Loe 1964), and bleeding on probing (BOP) were assessed. The cumulative topographical distribution of both PI and BOP during the 6-wk experiment is displayed in *Fig. 6.1* (mean PI and BOP at a given point of time with 4-wk as baseline after the preparatory period is plotted on top of each other).

One might argue that there were not really relevant differences except for BOP in Test subjects who were IL-1 genotype positive. While plaque amount and distribution were similar to other groups, BOP seems to be attenuated. One may immediately ask the question, Can that be modeled with multilevel modeling?

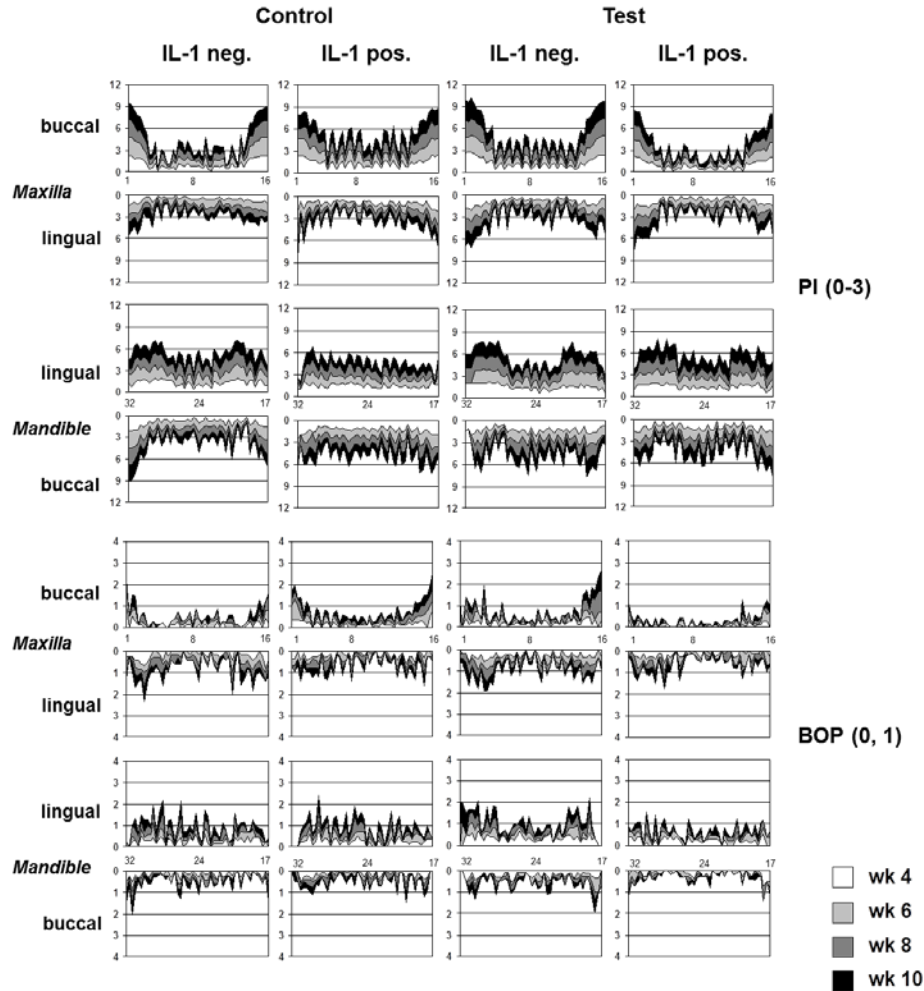


Fig. 6.1 Topographical distribution (see, for orientation, tooth numbers 1, 8, 16 in the maxilla, and 17, 24, and 32 in the mandible; three sites were assessed on the buccal aspect, and three sites on the lingual aspect of each tooth) of the Silness & Loe plaque index (PI) and bleeding on probing in subjects receiving fluoride containing toothpaste without (Control) and with 0.3% triclosan (Test) as regards IL-1 genotype (negative or positive). Mean scores (0-3) for PI and (0, 1) for BOP at week 4, 6, 8, and 10 were plotted on top of each other.

We want to postpone this analysis for a moment and start with a simpler case. Fifty subjects had been genotyped and again examined every other week. They were

allowed to choose their preferred toothpaste and continue with oral hygiene habits but were asked to avoid any triclosan-containing paste.

6.1 Description of the Example Data Set

The data for our example are stored in an EXCEL file (*ILI_bop.xlsx*). The binary response variable here is again presence or absence of bleeding on probing (BOP) at gingival units in the above cohort of 50 dental students at Kuwait University, 16 male and 34 female. They were between 19 and 28 years of age.

<i>Variable</i>	<i>Description</i>
NO	Subject's identifier (1-50)
GENDER	(0, 1)
ILGT	Interleukin 1 genotype (0, 1)
AGE	In years
TOOTH_NO	FDI notation of teeth (11-48)
TYPE	Tooth type (1-16)
SITE	Tooth site (1-6)
PPD	Periodontal probing depth (mm)
CAL	Clinical attachment level (mm)
BOP	Bleeding on probing (0, 1)
PLI	Silness & L�oe's plaque index (0-3)
CLS	Presence of calculus (0, 1)

Clinical variables PPD, CAL, BOP, PLI and CLS have each been assessed three times every other week.

After we have opened a new worksheet in *MLwiN* by clicking on **File** in the main menu and **New worksheet**, we can import the EXCEL data by copy them to the clipboard and paste them into *MLwiN*. For that we click on **Edit** in the main menu and **Paste**. We check the box **Use first row as names** in the new window and click **Paste**. We want to **Save the worksheet** in the **File** menu as *IL1_01.wsz*.

6.2 Separate Two-level Random Intercept Logistic Models

Our main interest lies in the longitudinal association between site-specific BOP and site-specific amount of supragingival plaque, and how this is influenced by subject-related IL-1 genotype. We can tabulate baseline BOP by PLI scores in IL-1 genotype negatives by clicking on **Tabulate** in **Basic Statistics**. We type next to **Columns PLI1**, check the **Rows** box and type **BOP1**. We then check the **Where values in** box, type **ILGT** and **are between 1 and 1**. When we click on **Tabulate**, we get the table below.

Output

```

->TABULATE 0 'PLI1' 'BOP1' 'ILGT' 1 1

840 missing value(s)

Columns are levels of PLI1
Rows are levels of BOP1

ILGT          = 1

```

		0	1	2	3	TOTALS
0	N	1296	911	1484	35	3726
1	N	186	193	447	26	852

Zoom 100 Copy as table Clear Include output from system generated commands

A respective table for IL-1 genotype negatives can easily be generated as well.

Output

```

840 missing value(s)

Columns are levels of PLI1
Rows are levels of BOP1

ILGT          = 0

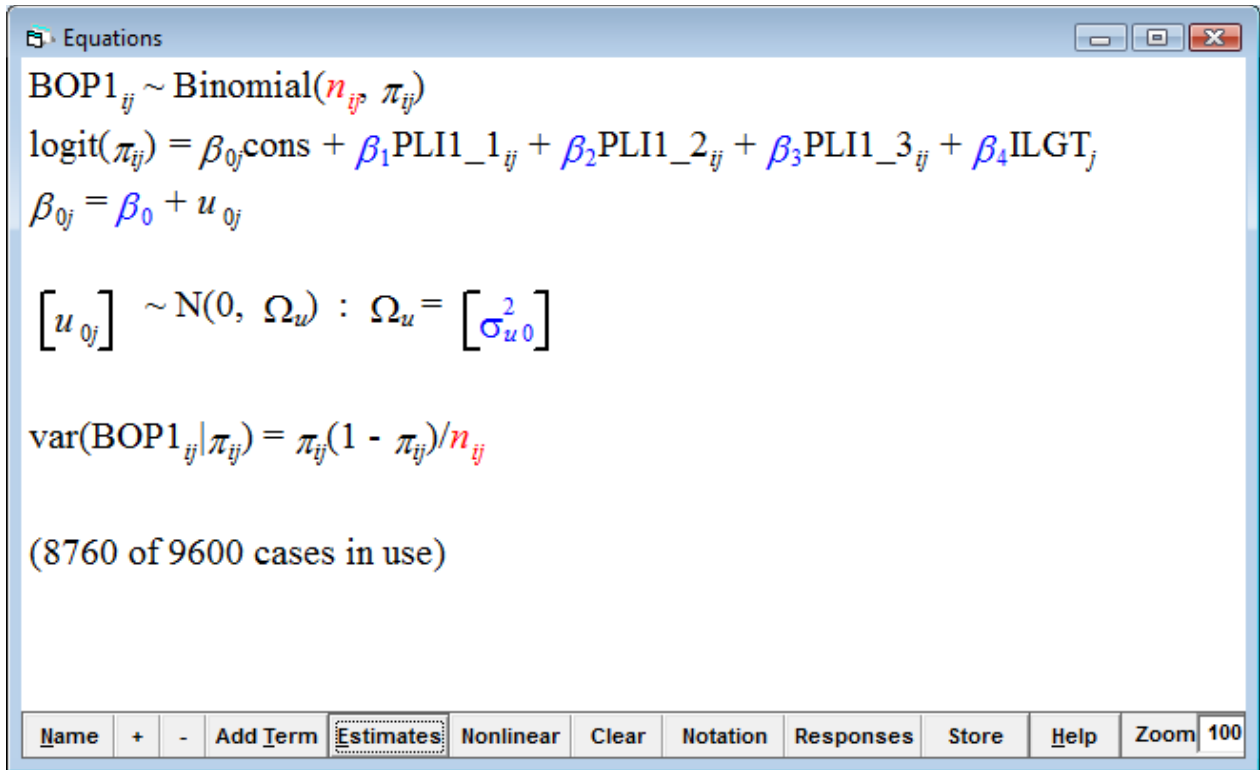
```

		0	1	2	3	TOTALS
0	N	1068	695	1267	137	3167
1	N	157	249	484	125	1015
TOTALS		1225	944	1751	262	4182

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Since PLI is categorical, we mark PLI1, PLI2, and PLI3 successively and click each time on **Toggle Categorical**.

We can first assess the association in three separate two-level random intercept models where we allow for subject effects on the probability of the binary response bleeding on probing. From the **Model** menu, we select **Equations** and click on **y**. For **y**, we select from the drop-down menu of the **Y variable** window **BOP1**, for **N-levels** we enter **2-ij**. For **Level 2(j)** we select **NO**, for **Level 1(i)** we select **SITE** and click on **done**. We now click on **N** in the **Equation window** and tag, in the **Response type** window, **Binomial**. In the **Select link function** the default box **logit** is already checked. We click on **Done**. We click on x_0 and select **cons** from the drop-down list of variables (*MLwiN* has created the **cons** variable already), check the box **j(NO)** and click on **Done**. We click on **Add term**. From the variable drop-down list we select **PLI1** (with reference category PLI1_0) and click on **Done**. We want to add IL-1 genotype by clicking on **Add Term** and choosing **variable** ILGT. We click on **Estimates** in the **Equation** window.



As before (Chapter 5), the first line states that the response variable follows a binomial distribution with parameters n_i and π_i . The parameter n_i , the denominator, is, in the case of binary data equal to 1 for all units. We create n_i and call the new variable **denom**. From the **Data Manipulation** menu we select **Generate vector**. In the **Generate vector** window we select **c28**. Next to **Number of copies** we enter 9600, and 1 next to **Value**. Then, we **Generate** and rename **c28** to **denom** by clicking on **c28** and on the **Column Name** button. In the **Equations** window we click on n_i and select **denom**.

The second line in the **Equations** window is the equation for the logit model which has the same form as (5.4) as can be shown by clicking on the **Name** button in the

Equations window. The three scores (1-3) of the PLI1 are entered into the model with PLI1 score of 0 as reference. We specify details about the estimation procedure to be used by clicking on the **Nonlinear** button at the bottom of the **Equations** window and on **Use Defaults**. Now we can run the model by clicking on the **Start** button in main menu. The model converges and estimates can be seen after clicking on the **Estimates** button again.

The screenshot shows the 'Equations' window with the following content:

$$\text{BOP1}_{ij} \sim \text{Binomial}(\text{denom}_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = \beta_{0j} \text{cons} + 0.598(0.081)\text{PLI1_1}_{ij} + 0.871(0.073)\text{PLI1_2}_{ij} + 1.466(0.138)\text{PLI1_3}_{ij} + -0.258(0.176)\text{ILGT}_j$$

$$\beta_{0j} = -1.785(0.137) + u_{0j}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.349(0.077) \end{bmatrix}$$

$$\text{var}(\text{BOP1}_{ij} | \pi_{ij}) = \pi_{ij}(1 - \pi_{ij}) / \text{denom}_{ij}$$

(8760 of 9600 cases in use)

At the bottom, there is a toolbar with buttons: Name, +, -, Add Term, **Estimates**, Nonlinear, Clear, Notation, Responses, Store, Help, Zoom, 100.

The last line in the **Equations** window states that the variance of the binomial response is $\pi_{ij} (1 - \pi_{ij}) / \text{denom}_{ij}$, which, in the case of binary data, simplifies to $\pi_{ij} (1 - \pi_{ij})$.

The intercept for subject j is $-1.785 + u_{0j}$ where the variance of u_{0j} is estimated as 0.349 (SE = 0.077). By calculating **ALOGit** of the former, one gets 0.14369 for the intercept. Whether the latter (variance of u_{0j}) is significant may approximately be assessed by a Wald test (see Chapter 5). To carry out a Wald test in *MLwiN* we click on **Intervals and tests** in the **Model** menu, check **random** at the bottom of the **Intervals and tests** window, type **1** next to **ID : cons/cons** (this refers to the parameter $\sigma_{u_0}^2$) and click on **Calc**. The joint chi square test yields a test statistic of 20.573 which we may compare to a chi-squared distribution on 1 degree of freedom. We type the respective values in the **Tails area** window (in **Basic statistics** in the main menu) and click on **Calc**. The p -value is very low, 5.7400e-6. So, we can conclude that differences between subjects are highly significant.

As expected, PLI1 at all scores significantly increased the odds for BOP1. The above model indicates estimated coefficients for PLI1 scores 1-3 of 0.598 (standard error 0.081), 0.871 (0.073), and 1.466 (0.138), respectively. In order to calculate odds ratios, we click on **Model** in the main menu and then on **Intervals and tests**. After having checked **fixed** at the bottom of the respective window we type **1** next to **fixed : PLI1_1** and get a 95% CI for the coefficient estimate of ± 0.160 . We then click on **Calculate** in the **Data manipulation** menu, select **EXPONENTIAL** from the expressions at the bottom on the right side and click on the **button** to move it to the window at the top of the right side. We type **(0.598)** and click on **Calculate**. We

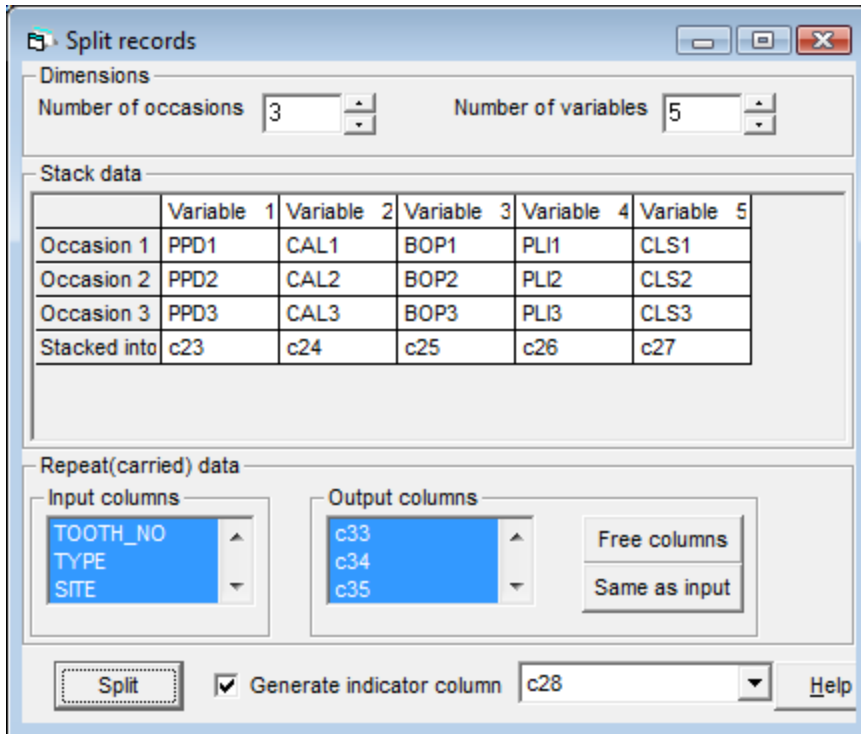
get an odds ratio of 1.8185. We then add and subtract 0.160 and get a 95% CI of 1.5496 – 2.1340. We can repeat the calculation for PLI1_2, PLI1_3, and ILGT. It may be useful to **Save the worksheet** in the **File** menu as *ILI_02.wsz*. We may then model BOP2 and BOP3. Respective results are displayed in *Table 6.1*.

<i>Table 6.1</i> Odds ratios (95% confidence interval) of three separate two-level random intercept logistic models			
	Model 1 (BOP1)	Model 2 (BOP2)	Model 3 (BOP3)
PLI_1	1.8185 (1.5496-2.1340)	1.7212 (1.4434-2.0524)	1.7950 (1.4978-2.1511)
PLI_2	2.3893 (2.0689-2.7594)	2.6912 (2.3117-3.1330)	2.4157 (2.0730-2.8151)
PLI_3	4.3319 (3.3036-5.6803)	4.4106 (3.2904-5.9121)	3.5716 (2.5472-5.0078)
ILGT	0.77260 (0.54717-1.0909)	0.75730 (0.53687-1.0682)	0.65312 (0.45566-0.93613)

As expected, BOP was consistently associated with plaque index. The association became stronger with higher scores. The IL-1 genotype was, in general, negatively associated with BOP. However, parameter estimates do not allow us to draw any firm conclusions about the relative weight of amount of plaque (as described by PLI scores) and the IL-1 genotype on BOP at various examination occasions. In order to avoid the drawbacks of the separate models we can pool the data from each examination occasion into a single, three-level repeated measures model.

6.3 Repeated Measures Multilevel Repeated Measures Models

The models described so far are separate, two-level, models ignoring repeat observations made at sites in subjects. An instantly conceived model which would better describe the structure of the data would be the standard multilevel repeated measures logistic model. As has been described in Chapter 3, we need to transform site data records into separate records (or rows) for each occasion. Thus, we want to split the records in the worksheet *IL1_01.wsz*. We click on **Data manipulation** in the main menu and select **Split records**. Since data were recorded three times, we set 3 in **Number of occasions**. The **Number of variables** to be split is set 5. In the **Stack data** grid we click on **Variable 1** and select in the drop-down the three variables PPD1, PPD2, and PPD3 and click on **Done**. We repeat the two above steps for **Variable 2** (CAL1 ..., CAL3), and all the other variables to be stacked. We want to stack the data into free columns c23 to c28. For that purpose we click in the **Stacked into** row of the **Stack data** grid and select in the appearing drop-down lists the respective columns c23 ... c27. We tick the **Generate indicator** column check box and select, in the neighboring drop-down list, c28 for the five occasions. Seven variables have to be repeated (carried data). In the **Repeat (carried data)** frame, we select NO, GENDER, ILGT, AGE, TOOTH_NO, TYPE, and SITE as input columns and assign to them c29 ...c35 as the respective outputs.



We click on the **Split button** to execute the changes. Before saving the worksheet, we want to first assign names to columns c23 ... c35 and thus select **No** when being asked whether we want to save the worksheet. We still need to create a constant column (cons) and denominator column (denom) by generating respective vectors of value 1 in free columns. Since PLI is categorical, we mark it and click on **Toggle Categorical**. After having renamed respective columns, the worksheet should be saved under a different name, for instance *IL1_03.wsz*.

Name	Cn	n	missing	min	max	categorical	description
BOP3	16	9600	840	0	1	False	
PLI1	17	9600	834	0	3	False	
PLI2	18	9600	834	0	3	False	
PLI3	19	9600	828	0	3	False	
CLS1	20	9600	833	0	1	False	
CLS2	21	9600	834	0	1	False	
CLS3	22	9600	834	0	1	False	
PPD	23	28800	2502	1	6	False	
CAL	24	28800	2502	0	3	False	
BOP	25	28800	2508	0	1	False	
PLI	26	28800	2496	0	3	True	
CLS	27	28800	2501	0	1	False	
OCC	28	28800	0	1	3	True	
ID	29	28800	0	1	50	False	
GEN	30	28800	0	0	1	False	
IL1	31	28800	0	0	1	False	
AGE2	32	28800	0	19	28	False	
TOOTH	33	28800	0	11	48	False	
TYPE2	34	28800	0	1	16	False	
SITE2	35	28800	0	1	6	False	
cons	36	28800	0	1	1	False	

We treat examination occasion (OCC) as the repetition at level 1 (indicated by t) nested within sites (indicated by i), which are nested in subjects (j). Let z_t be the vector of indicator variables for $t=1, 2, 3$ (or BL, 2 wk, 4 wk) respectively,

$$\left. \begin{aligned} z_{1ij} &= 1 && \text{if } t = 1 \\ z_{2ij} &= 1 && \text{if } t = 2 \\ z_{3ij} &= 1 && \text{if } t = 3 \end{aligned} \right\} \text{ and 0 otherwise.}$$

We can create dummy variables z_1 - z_3 in the usual way by selecting **recode (by range)** in the **Data Manipulation** menu. We select OCC in **Input columns** and some free columns in **Output columns**. We type respective **Values in range ... to** and assign respective values 1 or 0 **to new values, Add to action list** and **Execute**, then rename the columns. Since examination occasion is now level 1, the notation reflects this with t being the index for the first subscript.

We can write a model for the probability of a positive response bleeding on probing, π_{tij} as follows,

$$\text{logit}(\pi_{tij}) = \sum_{t=1}^3 \beta_{0,t} z_{tij} + \sum_{t=1}^3 \sum_{h=1}^4 \beta_{h,t} z_{tij} x_{h,tij} \sum_{t=1}^3 v_{tj} z_{tij} + u_{tij} z_{tij}$$

$$v_{tj} \sim N(0, \Omega_v), \quad u_{tij} \sim N(0, \Omega_u)$$

$$\Omega_v = \begin{pmatrix} \sigma_{v1}^2 & & \\ \sigma_{v12} & \sigma_{v2}^2 & \\ \sigma_{v13} & \sigma_{v23} & \sigma_{v3}^2 \end{pmatrix}, \quad \Omega_u = \begin{pmatrix} \sigma_{u1}^2 & & \\ \sigma_{u12} & \sigma_{u2}^2 & \\ \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 \end{pmatrix}$$

(6.1)

Where v_{ij} and u_{tij} are the residual terms at the subject and site level, respectively, associated with the intercept for each examination occasion t . We can set up a three-level random intercept model (with OCC as level 1), adding (categorical) PLI and IL1 at each examination by typing 1 next to **order**, and **variables** PLI and z_1 , z_2 , and z_3 as well as IL1 and z_1 , z_2 , and z_3 , respectively.

$BOP_{ijk} \sim \text{Binomial}(\text{denom}_{ijk}, \pi_{ijk})$
 $\text{logit}(\pi_{ijk}) = \beta_{0jk}z1_{ijk} + \beta_{1jk}z2_{ijk} + \beta_{2jk}z3_{ijk} + \beta_3z1.PLI_1_{ijk} + \beta_4z1.PLI_2_{ijk} + \beta_5z1.PLI_3_{ijk} + \beta_6z2.PLI_1_{ijk} + \beta_7z2.PLI_2_{ijk} + \beta_8z2.PLI_3_{ijk} + \beta_9z3.PLI_1_{ijk} + \beta_{10}z3.PLI_2_{ijk} + \beta_{11}z3.PLI_3_{ijk} + \beta_{12}IL1.z1_{ijk} + \beta_{13}IL1.z2_{ijk} + \beta_{14}IL1.z3_{ijk}$
 $\beta_{0jk} = \beta_0 + v_{0k} + u_{0jk}$
 $\beta_{1jk} = \beta_1 + v_{1k} + u_{1jk}$
 $\beta_{2jk} = \beta_2 + v_{2k} + u_{2jk}$

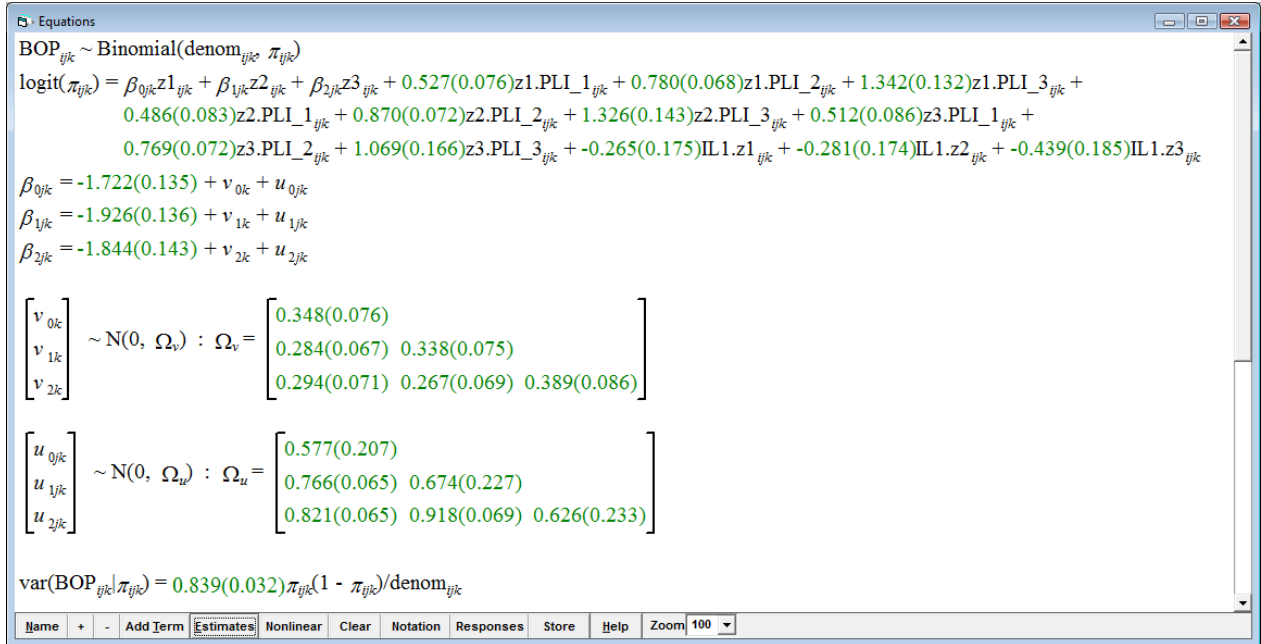
$$\begin{bmatrix} v_{0k} \\ v_{1k} \\ v_{2k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} \sigma_{v0}^2 & & \\ \sigma_{v01} & \sigma_{v1}^2 & \\ \sigma_{v02} & \sigma_{v12} & \sigma_{v2}^2 \end{bmatrix}$$

$$\begin{bmatrix} u_{0jk} \\ u_{1jk} \\ u_{2jk} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & \\ \sigma_{u01} & \sigma_{u1}^2 & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 \end{bmatrix}$$

$\text{var}(BOP_{ijk} | \pi_{ijk}) = \alpha \pi_{ijk} (1 - \pi_{ijk}) / \text{denom}_{ijk}$

The last line in the **Equations** window states that the variance of the binomial response is $\pi_i (1 - \pi_i) / \text{denom}_i$, which, in case of binary data, simplifies to $\pi_i (1 - \pi_i)$. Note the extrabinomial, so-called scale factor α , which can be estimated as well. If α is significantly greater than 1, this would imply overdispersion of the data at level 1 in the model. This is often the case when the model misses an important explanatory variable, or unaccounted clustering at higher level is present. If α is significantly less than 1, this implies underdispersion, possibly due to strong correlation between outcomes after controlling for higher level effects (Griffiths et al. (2004)). In either case, the assumption of conditionally independent Bernoulli trials is violated. α may therefore be used as valuable diagnostic in that regard when considering the model. So far, we have constrained the extrabinomial parameter. In order to unconstrain, we click on **Nonlinear** in the equation window

and check **extra Binomial**. We then click on **Done** and run the model by clicking on **Start**. The model converges after 8 iterations.



Only the MQL plus first-order approximation procedure provided converged estimates. However, there are definitely serious problems with this model.

Correlations between occasions at the site level are generally much greater than 1.

We can check that by clicking on **Estimate tables** in the **Model** menu. In the **Estimates** window, we select **Level 2:Site 2** and check the **C** box for correlations.

Moreover, since the scale factor is well below 1, there is definitely underdispersion in the model. A considerable proportion of sites had the same bleeding status on all examination occasions which can be assessed by tabulating BOP status at all three occasions: 302/8766 (3%) were consistently bleeding, but 5244/8766 (60%) were

consistently not bleeding. So we reasonably may suppose that for a large majority their probabilities are in fact 0.

```
846 missing value(s)
Columns are levels of BOP1
Rows are levels of BOP2
BOP3          = 1
              0      1      TOTALS
0  N          659    327    986
1  N          287    302    589
TOTALS        946    629    1575
->TABULATE 0 'BOP1' 'BOP2' 'BOP3' 0 0
846 missing value(s)
Columns are levels of BOP1
Rows are levels of BOP2
BOP3          = 0
              0      1      TOTALS
0  N          5244   893   6137
1  N           702   340   1042
TOTALS        5946  1233   7179
```

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We do not consider this model but want to save the worksheet under *IL1_04.wsz*.

6.4 Multivariate Multilevel Repeated Measures Models

We may use the same notation as in (6.1) to set up a general multivariate logistic model,

$$y_{tij} = \text{bin}(1, \pi_{tij})$$

$$\text{logit}(\pi_{tij}) = \sum_{t=1}^m \beta_{0,t} z_{tij} + \sum_{t=1}^m \sum_{h=1}^n \beta_{h,t} z_{tij} x_{h,tij} \sum_{t=1}^3 u_{tj} z_{tij}$$

$$u_{tj} \sim N(0, \Omega_u)$$

(6.2)

where m occasions and n covariates were considered. We make the same assumption as for the repeated measures model. Residual terms at the subject level associated with the intercept for each examination are designated u_{tk} . There is no level 1 (occasion) variation, because at level 2 (site), binomial variates among occasions are allowed to covary within sites. At this level, a covariance structure is estimated in which diagonal terms are constrained to having binomial variance, and off-diagonal terms are estimated. Thus, the dependence of observations at this level is fully accounted for. Unconstraining level 2 variance by introducing a scale factor a then allows assessment of extrabinomial variation (Müller and Barrieshi-

Nusair 2010). This is a convenient and efficient model for formulating a multivariate multilevel model (Yang et al. 2000).

6.4.1 A three-level repeated measures multivariate logistic variance components model

In order to set up the above model, we want to start with a variance components model without covariates. We open the worksheet saved in *IL1_02.wsz*, open the **Equations** window and click on **Clear**. In the **Responses** drop-down list, we select BOP1, BOP2, and BOP3. As before, we click on **N** in the **Equation window** and tag, in the **Response type** window, **Binomial**. In the **Select link function** the default box **logit** is already checked. We click on **Done**. We click on x_0 and select **cons** from the drop-down list of variables and select the box **Add Separate coefficients**. We now click on **resp** and select in **N levels 3-ijk** after which we specify the levels: **level 3(k)**: NO_long; **level 2(j)**: SITE_long (note that *MLwiN* has created these variables containing all 28800 observations automatically); **level 1 (i)**: resp_indicator. We then click on **Done**. We need to **Generate vector** denom in the **Data Manipulation** menu in the usual way. We click in turn on cons.BOP1, cons.BOP2, and cons.BOP3 in the Equations window and check for each the box

k(NO_long). Our simple multivariate model (without covariates) has now the desired form, and the respective worksheet may be saved under *ILI_05.wsz*.

Equations

$$\text{resp}_{2jk} \sim \text{Binomial}(\text{denom}_{2jk}, \pi_{2jk})$$

$$\text{resp}_{3jk} \sim \text{Binomial}(\text{denom}_{3jk}, \pi_{3jk})$$

$$\text{logit}(\pi_{1jk}) = \beta_{0k} \text{cons.BOP1}_{ijk}$$

$$\beta_{0k} = \beta_0 + v_{0k}$$

$$\text{logit}(\pi_{2jk}) = \beta_{1k} \text{cons.BOP2}_{ijk}$$

$$\beta_{1k} = \beta_1 + v_{1k}$$

$$\text{logit}(\pi_{3jk}) = \beta_{2k} \text{cons.BOP3}_{ijk}$$

$$\beta_{2k} = \beta_2 + v_{2k}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \\ v_{2k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} \sigma_{v0}^2 & & \\ \sigma_{v01} & \sigma_{v1}^2 & \\ \sigma_{v02} & \sigma_{v12} & \sigma_{v2}^2 \end{bmatrix}$$

$$\text{cov} \begin{bmatrix} \text{resp}_{1jk} | \pi_{1jk} \\ \text{resp}_{2jk} | \pi_{2jk} \\ \text{resp}_{3jk} | \pi_{3jk} \end{bmatrix} = \begin{bmatrix} g(\pi_{1jk}) & & \\ \rho [g(\pi_{1jk})g(\pi_{2jk})]^{0.5} & g(\pi_{2jk}) & \\ \rho [g(\pi_{1jk})g(\pi_{3jk})]^{0.5} & \rho [g(\pi_{2jk})g(\pi_{3jk})]^{0.5} & g(\pi_{3jk}) \end{bmatrix}$$

$$g(\pi) = \pi(1 - \pi)/n$$

(26292 of 28800 cases in use)

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 75

We want to run the model by clicking on **Start** in the main menu. It converges after 6 iterations. By clicking on **Estimates**, we get the following:

Equations

$$\text{resp}_{ijk} \sim \text{Binomial}(\text{denom}_{ijk}, \pi_{ijk})$$

$$\text{logit}(\pi_{ijk}) = \beta_{ik} \text{Cons.BOP1}_{ijk}$$

$$\beta_{0k} = -1.308(0.093) + v_{0k}$$

$$\text{logit}(\pi_{2jk}) = \beta_{1k} \text{Cons.BOP2}_{ijk}$$

$$\beta_{1k} = -1.472(0.096) + v_{1k}$$

$$\text{logit}(\pi_{3jk}) = \beta_{2k} \text{Cons.BOP3}_{ijk}$$

$$\beta_{2k} = -1.516(0.109) + v_{2k}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \\ v_{2k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.401(0.087) & & \\ 0.358(0.082) & 0.421(0.092) & \\ 0.390(0.091) & 0.407(0.094) & 0.559(0.120) \end{bmatrix}$$

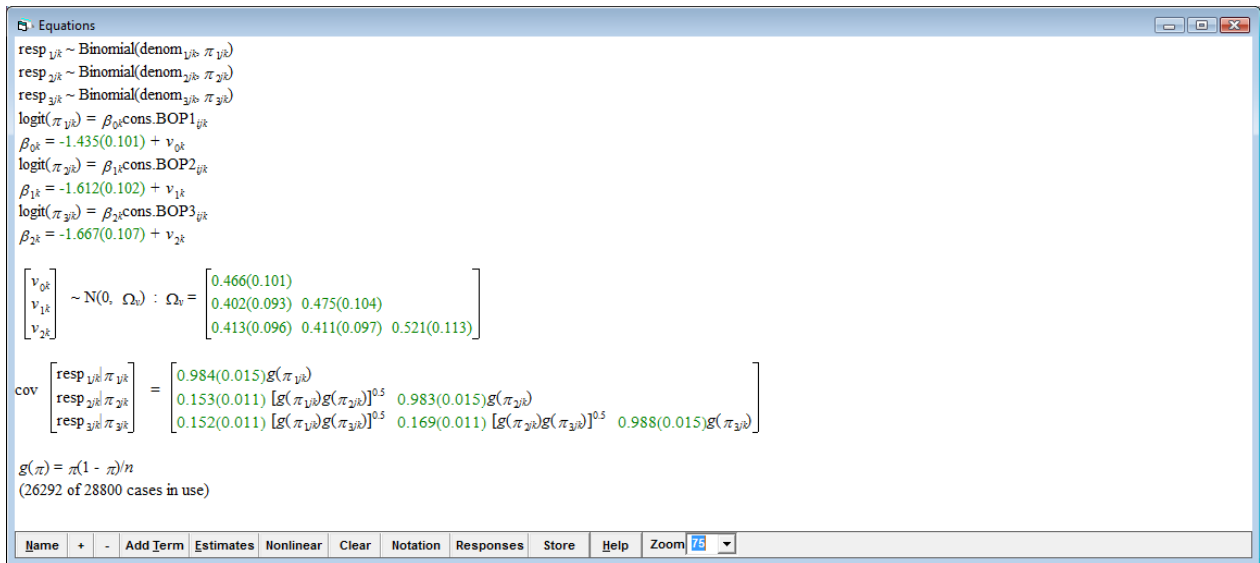
$$\text{cov} \begin{bmatrix} \text{resp}_{ijk}/\pi_{ijk} \\ \text{resp}_{2jk}/\pi_{2jk} \\ \text{resp}_{3jk}/\pi_{3jk} \end{bmatrix} = \begin{bmatrix} g(\pi_{1jk}) & & \\ 0.179(0.010) [g(\pi_{1jk})g(\pi_{2jk})]^{0.5} & g(\pi_{2jk}) & \\ 0.180(0.010) [g(\pi_{1jk})g(\pi_{3jk})]^{0.5} & 0.193(0.010) [g(\pi_{2jk})g(\pi_{3jk})]^{0.5} & g(\pi_{3jk}) \end{bmatrix}$$

$$g(\pi) = \pi(1 - \pi)/n$$

(26292 of 28800 cases in use)

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 75

The predicted proportions of BOP, ALOGit (β_k) at examination occasions 1-3, are 0.213, 0.187, and 0.180, which are identical with the raw proportions. In order to assess extrabinomial variation, we want to unconstrain the level 2 variance and introduce scale factors α . We click on **Nonlinear** in the **Equations** window, check **extra Binomial** in **Distributional assumptions** select **2nd order Linearisation** and **Estimation type PQL**, and click on **Done**. After clicking on **More**, the model converges after a few iterations.



At the site level, extrabinomial parameters are all close to 1, indicating that the assumption of binomial error distribution for each examination occasion is adequate. The three biserial covariances between examination occasions are 0.153 (OCC1:OCC2), 0.152 (OCC1:OCC3), and 0.169 (OCC2:OCC3). As before (see chapter 5), correlation coefficients $r_{m,n}$ for occasions m and n can be calculated by $r_{m,n} = \sigma_{m,n}/(\sqrt{\sigma_m^2 \times \sigma_n^2})$. By clicking on **Estimate tables** in the **Model** menu, selecting **Level 2:SITE_long** and checking **C** (for correlations), we see that the biserial covariances correspond to correlations between examinations occasions of 0.155-0.171. They are rather small as compared with correlations at the subject level, which are considerably higher ranging between 0.826 and 0.854. High intercorrelations at the subject level were actually expected since subjects had been asked not to change their oral hygiene habits in order to study bleeding on probing in a steady-state plaque environment. On the other hand, intercorrelations at the

site level were rather low pointing to the interesting observation of low degree of predictability of bleeding on probing in the presence of supragingival plaque.

6.4.2 A three-level repeated measures multivariate logistic model with covariates

We want to add covariates (of categorical) PLI and ILGT to the model by forming interaction terms between the explanatory variables and the examination occasion indicators to fit main effects for each occasion in the fixed part according to equation (6.2). We click on **Add term** in the **Equations** window, select in turn PLI1, PLI2, PLI3 as well as ILGT and click on **add Separate coefficients**. (Note that, if we are only interested in PLI on the same occasion as BOP was assessed, we need to delete PLI for the other occasions). We run the model which converges after a few more iterations.

```

Equations
resp1jk ~ Binomial(denom1jk, π1jk)
resp2jk ~ Binomial(denom2jk, π2jk)
resp3jk ~ Binomial(denom3jk, π3jk)
logit(π1jk) = β0kcons.BOP1jk + 0.546(0.081)PLI1_1.BOP1jk + 0.825(0.073)PLI1_2.BOP1jk + 1.435(0.135)PLI1_3.BOP1jk + -0.242(0.193)ILGT.BOP1jk
β0k = -1.873(0.149) + v0k
logit(π2jk) = β1kcons.BOP2jk + 0.474(0.088)PLI2_1.BOP2jk + 0.893(0.076)PLI2_2.BOP2jk + 1.399(0.141)PLI2_3.BOP2jk + -0.294(0.188)ILGT.BOP2jk
β1k = -2.042(0.146) + v1k
logit(π3jk) = β2kcons.BOP3jk + 0.511(0.092)PLI3_1.BOP3jk + 0.791(0.079)PLI3_2.BOP3jk + 1.145(0.165)PLI3_3.BOP3jk + -0.427(0.192)ILGT.BOP3jk
β2k = -1.977(0.150) + v2k

[ v0k ]
[ v1k ] ~ N(0, Ωv) : Ωv = [ 0.423(0.093)
[ v2k ] [ 0.339(0.081) 0.395(0.088)
[ 0.344(0.082) 0.306(0.078) 0.413(0.092) ]

cov [ resp1jk | π1jk ] = [ 0.978(0.015)g(π1jk)
[ resp2jk | π2jk ] [ 0.121(0.011) [g(π1jk)g(π2jk)]0.5 0.976(0.015)g(π2jk)
[ resp3jk | π3jk ] [ 0.129(0.011) [g(π1jk)g(π3jk)]0.5 0.144(0.011) [g(π2jk)g(π3jk)]0.5 0.983(0.015)g(π3jk) ]

g(π) = π(1 - π)n
(26286 of 28800 cases in use)

```

Estimates of all parameters are rather similar for each examination occasion. We may anyway want to carry out a joint approximate Wald test to compare, for instance, the estimate of PLI score 3 at occasion 1 (1.435, SE 0.135) with that at occasion 3 (1.145, SE 0.165). In the **Model** menu, we select **Intervals and tests** and check at the bottom **fixed** effects. We type 1 next to PLI1_3.BOP1 and -1 next to PLI3_3.BOP3 and click on **Calc**. We yield a chi square of 1.951 for 1 degree of freedom. In **Basic statistics** we may check **Tail areas** by typing the value and degrees of freedom next to the respective fields. We make sure that **Chi Squared** is checked and yield a p value of 0.16248 meaning that there is no good reason to assume that the estimates differ substantially. We note that extrabinomial parameters at the site level again are all close to 1 (~0.98) pointing to the correct assumption of conditionally independent Bernoulli trials.

6.4.3 Some contextual effects

In the above model we noticed that the ILGT had a consistently negative impact on our response variable, BOP. In order to address, for instance, the important question, How does the ILGT influence the bleeding response of gingiva to different amounts of supragingival plaque?, we need to modify our model further.

We want to add interaction terms of ILGT and PLI for each examination occasion.

In the **Specify term** window we type 1 next to **order** and choose **variables** ILGT and in turn PLI1, PLI2 and PLI3. We click add Separate coefficients (and have to delete all interaction terms with PLI of different occasions, see above). We run the model which converges after a few further iterations.

```

Equations
resp1jk ~ Binomial(denom1jk, π1jk)
resp2jk ~ Binomial(denom2jk, π2jk)
resp3jk ~ Binomial(denom3jk, π3jk)
logit(π1jk) = β0kcons.BOP1jk + 0.779(0.116)PLI1_1.BOP1jk + 0.946(0.106)PLI1_2.BOP1jk + 1.512(0.161)PLI1_3.BOP1jk + -0.015(0.220)ILGT.BOP1jk +
-0.458(0.162)ILGT.PLI1_1.BOP1jk + -0.231(0.147)ILGT.PLI1_2.BOP1jk + -0.011(0.323)ILGT.PLI1_3.BOP1jk
β0k = -1.993(0.160) + v0k
logit(π2jk) = β1kcons.BOP2jk + 0.322(0.124)PLI2_1.BOP2jk + 0.838(0.106)PLI2_2.BOP2jk + 1.270(0.165)PLI2_3.BOP2jk + -0.425(0.218)ILGT.BOP2jk +
0.303(0.176)ILGT.PLI2_1.BOP2jk + 0.100(0.152)ILGT.PLI2_2.BOP2jk + 0.431(0.341)ILGT.PLI2_3.BOP2jk
β1k = -1.973(0.156) + v1k
logit(π3jk) = β2kcons.BOP3jk + 0.398(0.127)PLI3_1.BOP3jk + 0.709(0.108)PLI3_2.BOP3jk + 1.059(0.193)PLI3_3.BOP3jk + -0.569(0.225)ILGT.BOP3jk +
0.233(0.185)ILGT.PLI3_1.BOP3jk + 0.168(0.158)ILGT.PLI3_2.BOP3jk + 0.181(0.389)ILGT.PLI3_3.BOP3jk
β2k = -1.907(0.159) + v2k

[ v0k
  v1k
  v2k ] ~ N(0, Ωv) : Ωv = [ 0.423(0.093)
                             0.337(0.080) 0.394(0.088)
                             0.342(0.082) 0.307(0.078) 0.416(0.093) ]

cov [ resp1jk π1jk
      resp2jk π2jk
      resp3jk π3jk ] = [ 0.977(0.015)g(π1jk)
                        0.122(0.011) [g(π1jk)g(π2jk)]0.5 0.976(0.015)g(π2jk)
                        0.129(0.011) [g(π1jk)g(π3jk)]0.5 0.143(0.011) [g(π2jk)g(π3jk)]0.5 0.984(0.015)g(π3jk) ]

g(π) = π(1 - π)n
(26286 of 28800 cases in use)

```

With this model set-up, we might calculate odds ratios, for the different examination occasions, for BOP at sites with varying amounts of plaque, and PLI score 0 in ILGT negatives as reference. We click **Intervals and tests** in the **Model** menu and check **fixed**. We want to assess, for example, first sites with a PLI score of 1 at examination occasion 1. For ILGT negatives, we type 1 next to **fixed:PLI1_1.BOP1** and click on **Calc**. The expected estimate from the model equation is 0.779 with 95% confidence interval of 0.226. The odds ratio can be calculated in the **Data Manipulation** menu by taking the EXPOnential(0.779). It is

2.1793 with a 95% confidence interval of 1.7385 to 2.7319. That means that, at examination occasion 1, the odds of bleeding on probing in ILGT negatives was more than two times higher at sites covered by plaque with a PLI1 score of 1. We can calculate odds ratios for PLI1 scores 2 and 3 accordingly. In case of PLI1 score of 0 in ILGT positives, we type 1 next to **fixed: ILGT.BOP1** in the **Interval and tests** window and get an estimate of -0.015 with a 95% confidence interval of 0.431. The odds ratio (with a PLI1 score of 0 in ILGT negatives) is 0.98511 (0.64018-1.5159). For sites with a PLI1 score of 1 in ILGT positives, we need to type 1 next to **fixed:PLI1_1.BOP1**, **fixed: ILGT.BOP1**, and **fixed: ILGT.PLI1_1.BOP1**. The odds ratio is 1.3580 (0.88161-2.0917).

	#1
fixed : cons.BOP3	0.000
fixed : PLI1_1.BOP1	1.000
fixed : PLI1_2.BOP1	0.000
fixed : PLI1_3.BOP1	0.000
fixed : PLI2_1.BOP2	0.000
fixed : PLI2_2.BOP2	0.000
fixed : PLI2_3.BOP2	0.000
fixed : PLI3_1.BOP3	0.000
fixed : PLI3_2.BOP3	0.000
fixed : PLI3_3.BOP3	0.000
fixed : ILGT.BOP1	1.000
fixed : ILGT.BOP2	0.000
fixed : ILGT.BOP3	0.000
fixed : ILGT.PLI1_1.BOP1	1.000
fixed : ILGT.PLI1_2.BOP1	0.000
fixed : ILGT.PLI1_3.BOP1	0.000
fixed : ILGT.PLI2_1.BOP2	0.000
fixed : ILGT.PLI2_2.BOP2	0.000
fixed : ILGT.PLI2_3.BOP2	0.000
fixed : ILGT.PLI3_1.BOP3	0.000
fixed : ILGT.PLI3_2.BOP3	0.000
fixed : ILGT.PLI3_3.BOP3	0.000
constant(k)	0.000
function result(f)	0.306
f-k	0.306
chi sq, (f-k)=0. (1df)	1.925
+/- 95% sep.	0.432
+/- 95% joint	0.432

joint chi sq test(1df) = 1.925

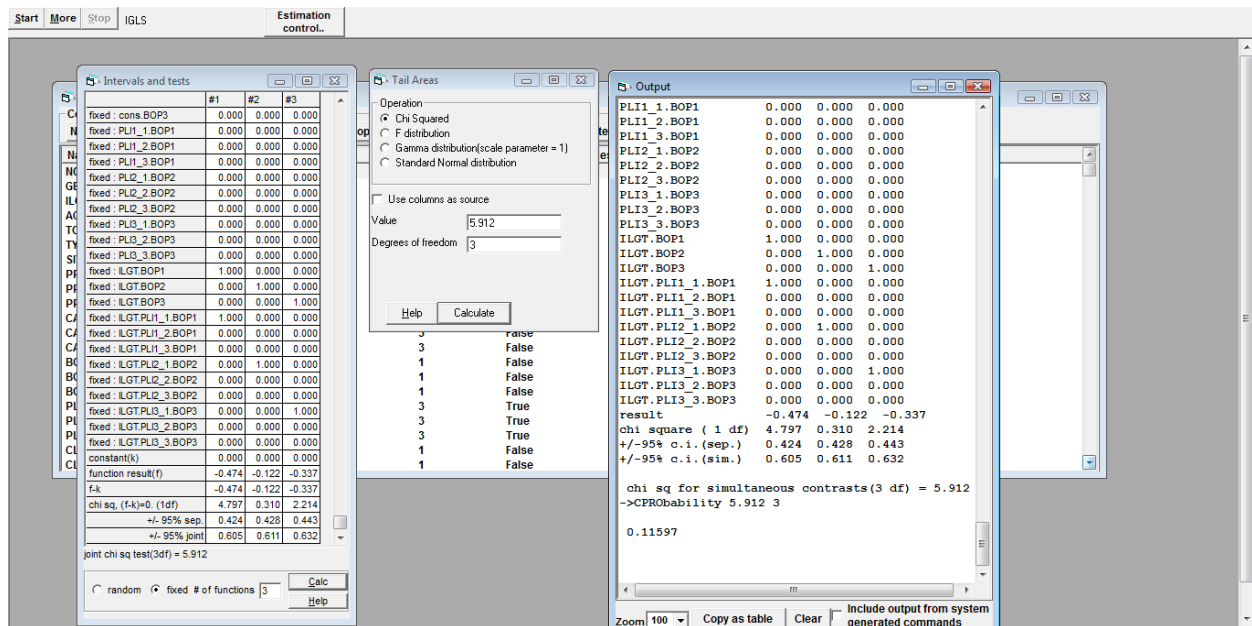
random
 fixed # of functions

We may want to calculate respective odds ratios for examination occasion 2 and 3 as well. They are tabulated in *Table 6.2*.

Table 6.2 Odds ratios (95% confidence intervals) of BOP with ILGT negative individuals at sites with a PLI score of 0 as reference at the three examination occasions

OCC_1		
ILGT_0	PLI_0	Reference
	PLI_1	2.18 (1.74-2.73)
	PLI_2	2.58 (2.09-3.17)
	PLI_3	4.54 (3.31-6.22)
ILGT_1	PLI_0	0.99 (0.64-1.52)
	PLI_1	1.36 (0.88-2.09)
	PLI_2	2.01 (1.33-3.05)
	PLI_3	4.42 (2.28-8.55)
OCC_2		
ILGT_0	PLI_0	Reference
	PLI_1	1.38 (1.08-1.76)
	PLI_2	2.31 (1.88-2.84)
	PLI_3	3.56 (2.58-4.92)
ILGT_1	PLI_0	0.65 (0.43-1.00)
	PLI_1	1.22 (0.80-1.87)
	PLI_2	1.67 (1.11-2.51)
	PLI_3	3.58 (1.81-7.09)
OCC_3		
ILGT_0	PLI_0	Reference
	PLI_1	1.49 (1.16-1.91)
	PLI_2	2.03 (1.64-2.51)
	PLI_3	2.88 (1.97-4.21)
ILGT_1	PLI_0	0.57 (0.36-0.88)
	PLI_1	1.06 (0.68-1.66)
	PLI_2	1.36 (0.90-2.06)
	PLI_3	1.96 (0.93-4.13)

It seems so that odds ratios were lower in ILGT positives, in particular at sites with low plaque levels. Thus, associations between small amounts of supragingival plaque and bleeding on probing may be dampened in ILGT positives. We can carry out joint tests (approximate Wald tests) to substantiate this hypothesis. We select 3 in # of functions in the **Interval and tests** window. For PLI scores 0, we only need to enter 1 next to **fixed:ILGT.BOP1**, **fixed:ILGT.BOP2**, and **fixed:ILGT.BOP3**. After clicking on **Calc**, we see that the joint chi square test with 3 degrees of freedom is 11.781. The p -value, which can be obtained by entering respective values in the **Tail Areas** window of the **Basic Statistics** menu is 0.008. For the case of PLI scores of 1, we need to enter 1 in addition to **fixed:ILGT.PLI1_1.BOP1**, **fixed:ILGT.PLI2_1.BOP2**, and **fixed:ILGT.PLI3_1.BOP3**. The joint chi sq test(3df) is 5.912, and the respective p -value 0.11597.



Results of all joint chi square tests are displayed in Table 6.3.

Table 6.3 Joint chi square tests for contrasts of BOP estimates in IL1 genotype positives and negatives

	Chi squared (3df)	<i>p</i>
PLI_0	11.781	0.00817
PLI_1	5.912	0.11597
PLI_2	4.474	0.21462
PLI_3	0.956	0.81190

It can be concluded that bleeding tendency at sites without or with only small amounts of supragingival plaque (PLI scores 0 or 1) was significantly lower in individuals with positive interleukin genotype as compared to ILGT negatives.

Results of further multivariate multilevel logistic regression models using this data set can be found in Müller and Barrieshi-Nusair (2010).

6.4.4A four-level repeated measures multivariate logistic model

A question remains whether the model can be improved by introducing another level, the tooth. By clicking on the responses, we can define **NO_long** as level 4, and **TOOTH_NO_long** as level 3 (note that the program has created a respective column already). **SITE_long** is, as before, level 2 and the multivariate structure of responses level 1. We need to click on intercepts and check the boxes **I(NO_long)** and **k(TOOTH_NO_long)**. We should first run the model by using defaults for **Nonlinear Estimation**. After converging, we check **extra Binomial** and later **2nd order PQL**.

Equations

```

resp1ki ~ Binomial(denom1ki, π1ki)
resp2ki ~ Binomial(denom2ki, π2ki)
resp3ki ~ Binomial(denom3ki, π3ki)
logit(π1ki) = β01cons.BOP1ki + 0.825(0.117)PLI1_1.BOP1ki + 0.990(0.108)PLI1_2.BOP1ki + 1.566(0.165)PLI1_3.BOP1ki + 0.002(0.228)ILGT.BOP1ki +
-0.479(0.163)ILGT.PLI1_1.BOP1ki + -0.284(0.149)ILGT.PLI1_2.BOP1ki + -0.049(0.333)ILGT.PLI1_3.BOP1ki
β01 = -2.088(0.166) + f0 + v01
logit(π2ki) = β12cons.BOP2ki + 0.351(0.125)PLI2_1.BOP2ki + 0.891(0.107)PLI2_2.BOP2ki + 1.363(0.171)PLI2_3.BOP2ki + -0.420(0.227)ILGT.BOP2ki +
0.328(0.177)ILGT.PLI2_1.BOP2ki + 0.065(0.154)ILGT.PLI2_2.BOP2ki + 0.300(0.361)ILGT.PLI2_3.BOP2ki
β12 = -2.094(0.162) + f1 + v12
logit(π3ki) = β23cons.BOP3ki + 0.433(0.128)PLI3_1.BOP3ki + 0.731(0.111)PLI3_2.BOP3ki + 1.106(0.202)PLI3_3.BOP3ki + -0.613(0.238)ILGT.BOP3ki +
0.243(0.187)ILGT.PLI3_1.BOP3ki + 0.174(0.162)ILGT.PLI3_2.BOP3ki + 0.344(0.409)ILGT.PLI3_3.BOP3ki
β23 = -2.033(0.169) + f2 + v23

```

$$\begin{bmatrix} f_{01} \\ f_{12} \\ f_{23} \end{bmatrix} \sim N(0, \Omega_f) : \Omega_f = \begin{bmatrix} 0.453(0.101) & & \\ 0.365(0.088) & 0.426(0.097) & \\ 0.375(0.092) & 0.342(0.088) & 0.468(0.107) \end{bmatrix}$$

$$\begin{bmatrix} v_{01} \\ v_{12} \\ v_{23} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.311(0.052) & & \\ 0.124(0.039) & 0.362(0.057) & \\ 0.152(0.042) & 0.101(0.044) & 0.475(0.064) \end{bmatrix}$$

$$\text{cov} \begin{bmatrix} \text{resp}_{1ki} | \pi_{1ki} \\ \text{resp}_{2ki} | \pi_{2ki} \\ \text{resp}_{3ki} | \pi_{3ki} \end{bmatrix} = \begin{bmatrix} 0.897(0.015)g(\pi_{1ki}) & & \\ 0.100(0.010) [g(\pi_{1ki})g(\pi_{2ki})]^{0.5} & 0.875(0.014)g(\pi_{2ki}) & \\ 0.104(0.010) [g(\pi_{1ki})g(\pi_{3ki})]^{0.5} & 0.121(0.010) [g(\pi_{2ki})g(\pi_{3ki})]^{0.5} & 0.862(0.014)g(\pi_{3ki}) \end{bmatrix}$$

$g(\pi) = \pi(1 - \pi)^n$
(26286 of 28800 cases in use)

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As can easily be seen, a significant part of variation of BOP scores can be found at the tooth level. Biserial correlations between examination occasions are displayed in the window below. They are moderate (0.244-0.395) when compared with correlations at the subject level (0.766-0.831) which, as has been noted before, may reflect the steady-state plaque environment. At the site level, they were again low (0.113-0.140). What is of concern, however, is extrabinomial parameters which significantly differ from 1.

	cons.BOP1	cons.BOP2	cons.BOP3
cons.BOP1	$\sigma_{v 0}^2$		
	0.311		
	(0.052)		
	0.344		
	Corr: 1.000		
cons.BOP2	$\sigma_{v 0 1}$	$\sigma_{v 1}^2$	
	0.124	0.362	
	(0.039)	(0.057)	
	0.424	0.362	
	Corr: 0.369	Corr: 1.000	
cons.BOP3	$\sigma_{v 0 2}$	$\sigma_{v 1 2}$	$\sigma_{v 2}^2$
	0.152	0.101	0.475
	(0.042)	(0.044)	(0.064)
	0.462	0.404	0.476
	Corr: 0.395	Corr: 0.244	Corr: 1.000

Sparseness at the lower level has been suggested as possible reason for underdispersion by Wright (1997). In our case, for instance, there are lots of teeth with just 6 observations of gingival bleeding/no bleeding on probing. There is little information about distributional characteristics for the tooth and in particular little that can be said about tooth level variance. So, we prefer the previous, three-level multivariate model.

7 Ordered Categorical Response Models

In several chapters so far we have addressed modeling a binary response variable, for instance gingival bleeding upon periodontal probing, which has only two expressions, yes or no (or 1, 0). Many kinds of response variables are ordered categorical. For instance, the Silness & Loe plaque index, which assesses the amount of supragingival plaque at a certain tooth surface adjacent to the gingival margin, comprises clinically defined situations on a scale of scores from 0 to 3 (Table 7.1).

Score	Description
0	No plaque
1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen <i>in situ</i> only after application of disclosing solution or by using the probe on the tooth surface
2	Moderate accumulation of soft deposits within the gingival pocket, or on the tooth and gingival margin which is can be seen with the naked eye
3	Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin

Very often, these scores are statistically treated as if they were measurements on a continuous scale. Then given averages have a number of shortcomings. For instance, values in-between scores are clinically not defined and have to be

reinterpreted as frequencies of integer scores. The differences in the amount of plaque of scores 0 and 1 are certainly smaller than those between scores 1 and 2. Moreover, both inter- and intra-examiner reliability of scoring may differ across different scores.

An alternative approach of dealing with this kind of data is to retain the categories throughout the analysis. The example analyses in the present chapter show how this can be accomplished.

7.1 Description of the Example Data Set

The data for our example, derived from the above cohort of 50 dental students at Kuwait University, are stored in an EXCEL file (*IL1_clearedbop.xlsx*). Missing observations (for instance missing teeth) had been removed.

<i>Variable</i>	<i>Description</i>
NO	Subject's identifier (1-50)
GENDER	(0, 1)
ILGT	Interleukin 1 genotype (0, 1)
AGE	In years
TOOTH_NO	FDI notation of teeth (11-48)
TYPE	Tooth type (1-16)
SITE	Tooth site (1-6)
PPD	Periodontal probing depth (mm)
CAL	Clinical attachment level (mm)
BOP	Bleeding on probing (0, 1)
PLI	Silness & L�oe's plaque index (0-3)

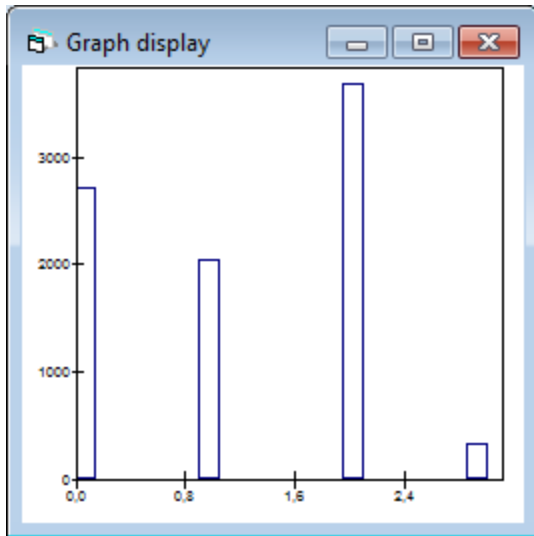
CLS	Presence of calculus (0, 1)
------------	-----------------------------

Recall that clinical variables PPD, CAL, BOP, PLI and CLS have each been assessed three times every other week. We copy and paste the data into a new worksheet in *MLwiN* as before and save it in the new file *ILI_cleared01.wsz*.

7.2 An Analysis Using a Traditional Approach

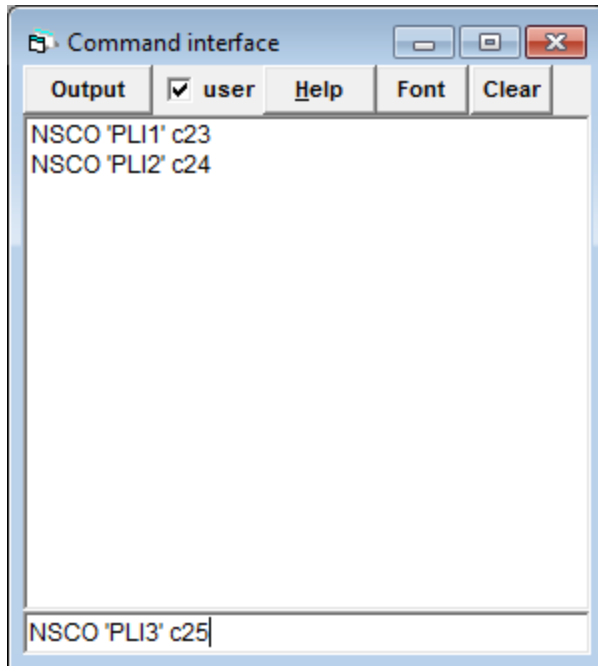
Our main interest lies in the plaque index which is so far considered as a continuous variable. However, as mentioned before, only integer scores 0-3 are properly defined. Note that the following analysis is done only to provide a comparison for the categorical response model that follows. Thus, we will begin by fitting a single-level model of plaque index that treats the response variable as if it was measured on a continuous scale.

We can illustrate the distribution by creating a histogram of PLA1. From the **Graph** menu we select **Customized graphs**. We select **PLI1** for **y** and **histogram** for **plot type** and click on **Apply**.



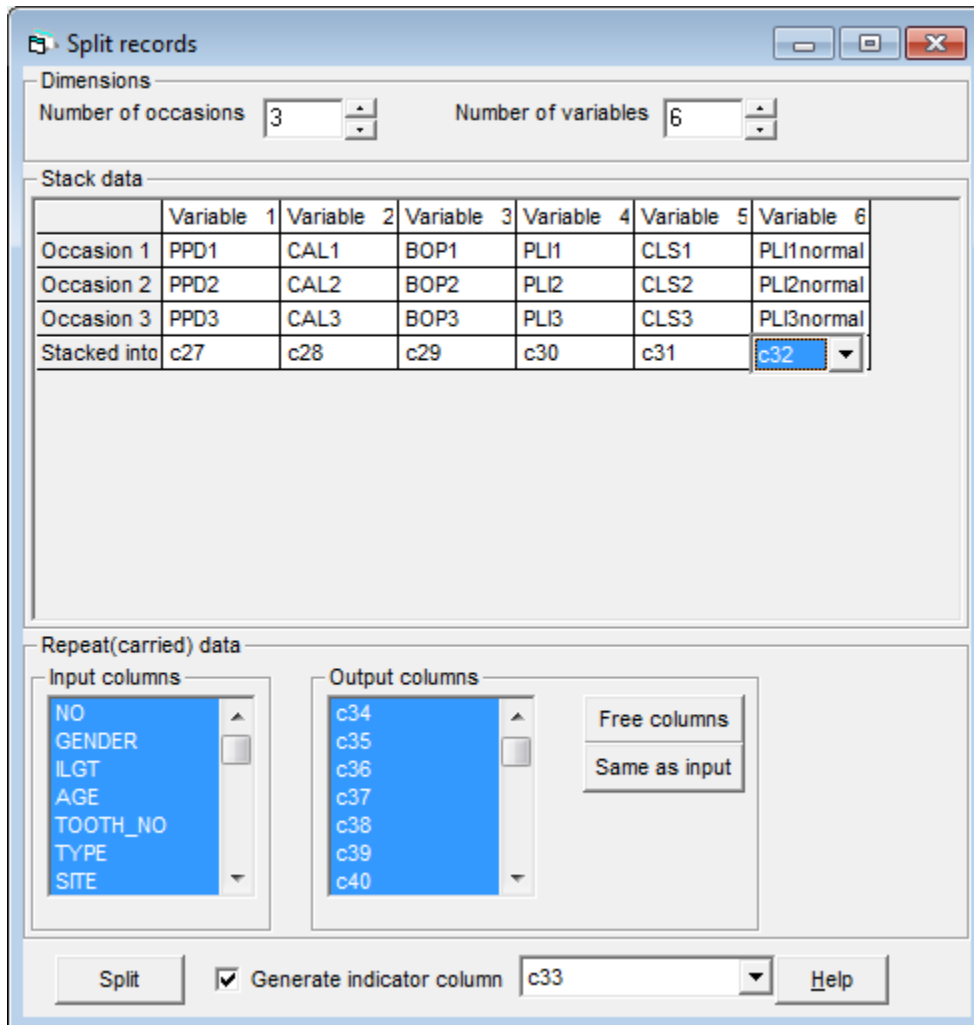
7.2.1 Setting up the data structure

As it is obvious that the distribution of PLA1 is certainly not Normal, we may transform it to Normal scores. To each response category, this transformation assigns the value from the inverse of the standard (0, 1) Normal cumulative distribution for the estimated proportion of sites from the response variable's original distribution. We can use *MLwiN*'s **NSCO** command to create new response variables for PLI at all three examination occasions. In the **Data Manipulation** menu we select **Command interface**. In the bottom box of the **Command interface** window, we type NSCO 'PLI1' c23 and press the return key, and so on. We have then to rename the columns as **PLI1normal**, **PLI2normal** and **PLI3normal**.



In order to transform site data record into separate records (or rows) for each occasion, we want to split the records as described in Chapter 3. Thus, in the main menu we click on **Data manipulation** and select **Split records**. Since data were recorded three times, we set 3 in **Number of occasions**. The **Number of variables** to be split is set 6. In the **Stack data** grid we click on **Variable 1** and select in the drop-down the five variables PPD1, PPD2, and PPD3. Then we click **Done**. We repeat the two above steps for **Variable 2** (CAL1 ...CAL2), and all the other variables to be stacked. Eventually we want to stack the data into free columns c27 to c32. We tick the **Generate indicator** column check box and select, in the neighboring drop-down list, c33 for the three occasions.

Seven variables have to be repeated (carried data). In the **Repeat (carried data)** frame, we select NO, GENDER, ILGT, AGE, TOOTH_NO, TYPE, and SITE as input columns and assign to them c34 ...c40 as the respective outputs.

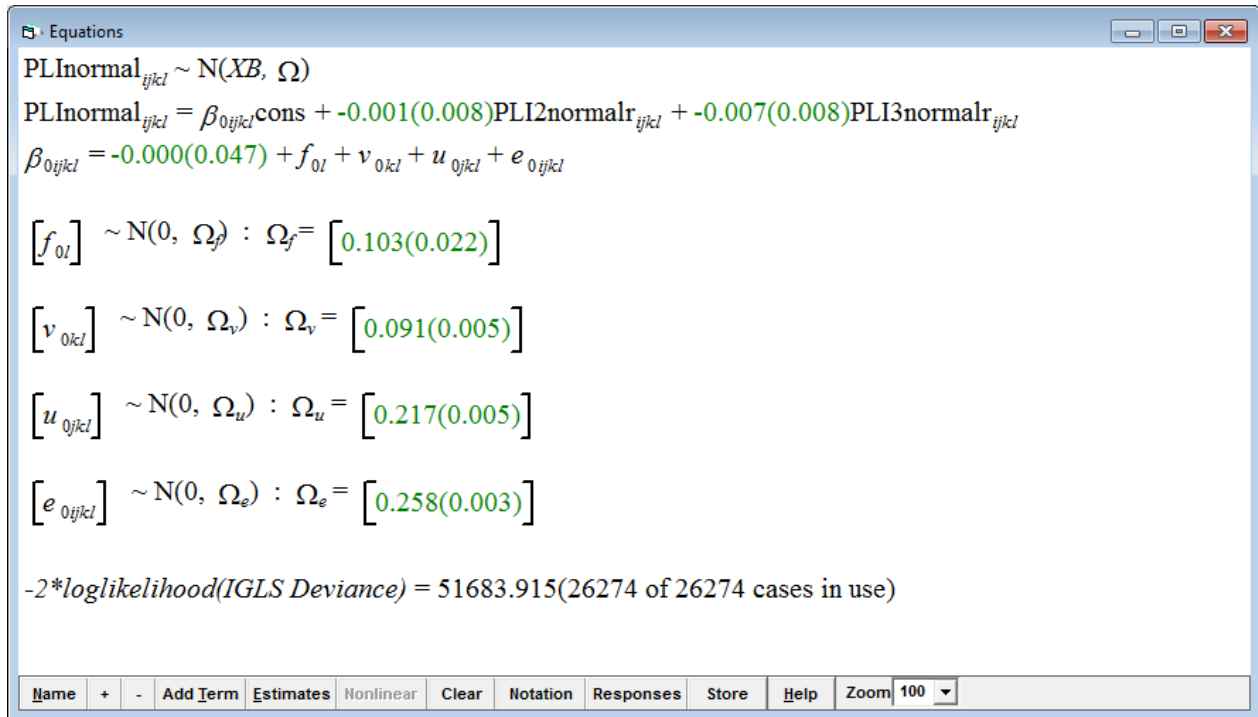


We then click the **Split** button to execute the changes. Before saving the worksheet, we want to first assign names to columns c27 ... c40 and thus select **No** when being asked whether we want to save the worksheet. We want to rename the respective columns. Before setting up simple variance components model we have

to create a constant column (CONS). We access the **Generate Vector** window via the **Data Manipulation** menu. We select c26 as **Output column**, fill in 26274 in **Number of copies** and assign the **Value** of 1 to them. We click on **Generate** and rename the column as before, **cons**. Now we want to save the worksheet, for instance as *ILI_cleared02.wsz*.

7.2.2 A four-level repeated measures model of plaque index considered as continuous response

We will now treat **PLInormal** at the different occasions as a continuous response variable. We start by seeing how the total variance of **PLInormal** is partitioned into four components, between subjects, teeth, sites and occasions within sites. Thus, we fit a four-level model involving the intercept term and OCC. In the **Equations** window we define **PLInormal** as response variable (with a Normal error distribution), and set up a four-level model with **NO2** as level 1, **TOOTH_NO2** as level 2 and **SITE2** as level 3 and **OCC** as level 4 identifier. We define the variable **cons** and add **OCC** as explanatory variable. We click on β_0 and check in the **X variable** window the boxes **l(NO2)**, **k(TOOTH_NO2)**, **j(SITE2)**, and **i(OCC)**, then click on **Done**. We run the model by clicking on **Start**.



Equations

$$\text{PLInormal}_{ijkl} \sim N(XB, \Omega)$$

$$\text{PLInormal}_{ijkl} = \beta_{0ijkl} \text{cons} + -0.001(0.008) \text{PLI2normalr}_{ijkl} + -0.007(0.008) \text{PLI3normalr}_{ijkl}$$

$$\beta_{0ijkl} = -0.000(0.047) + f_{0l} + v_{0kl} + u_{0jkl} + e_{0ijkl}$$

$$[f_{0l}] \sim N(0, \Omega_f) : \Omega_f = [0.103(0.022)]$$

$$[v_{0kl}] \sim N(0, \Omega_v) : \Omega_v = [0.091(0.005)]$$

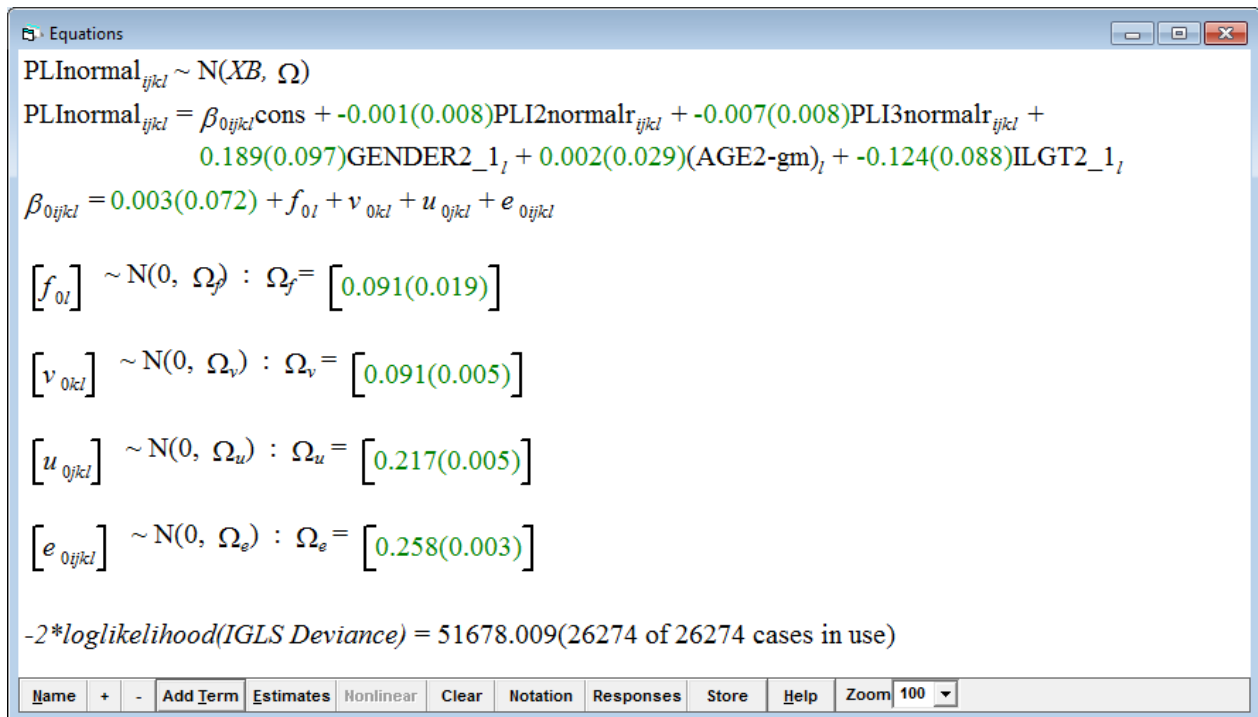
$$[u_{0jkl}] \sim N(0, \Omega_u) : \Omega_u = [0.217(0.005)]$$

$$[e_{0ijkl}] \sim N(0, \Omega_e) : \Omega_e = [0.258(0.003)]$$

$-2 * \log \text{likelihood}(\text{IGLS Deviance}) = 51683.915 (26274 \text{ of } 26274 \text{ cases in use})$

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As expected in a steady-state plaque environment, both coefficients of transformed to Normal scores PLI at occasion 2 and occasion 3 are not very much different from 0. Variances at the subject level and tooth levels were considerable, but those at the site and occasion level were considerably larger (32 and 39% of total variance). In the **Names** window, we **Toggle Categorical** GENDER2 (female 0, male 1), ILGT2, TOOTH_NO2, TYPE2, and SITE2. We first want to assess the effect of GENDER2, ILGT2, and AGE2 (centered on the **Grand mean**) on PLI and add respective terms into the model, which converges instantly after clicking on **More**.



Equations

$$\text{PLInormal}_{ijkl} \sim N(XB, \Omega)$$

$$\text{PLInormal}_{ijkl} = \beta_{0ijkl} \text{cons} + -0.001(0.008) \text{PLI2normalr}_{ijkl} + -0.007(0.008) \text{PLI3normalr}_{ijkl} + 0.189(0.097) \text{GENDER2_1}_i + 0.002(0.029) (\text{AGE2-gm})_i + -0.124(0.088) \text{ILGT2_1}_i$$

$$\beta_{0ijkl} = 0.003(0.072) + f_{0i} + v_{0kl} + u_{0ijkl} + e_{0ijkl}$$

$$\begin{bmatrix} f_{0i} \end{bmatrix} \sim N(0, \Omega_f) : \Omega_f = \begin{bmatrix} 0.091(0.019) \end{bmatrix}$$

$$\begin{bmatrix} v_{0kl} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} 0.091(0.005) \end{bmatrix}$$

$$\begin{bmatrix} u_{0ijkl} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} 0.217(0.005) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ijkl} \end{bmatrix} \sim N(0, \Omega_e) : \Omega_e = \begin{bmatrix} 0.258(0.003) \end{bmatrix}$$

$-2 * \log \text{likelihood}(\text{IGLS Deviance}) = 51678.009(26274 \text{ of } 26274 \text{ cases in use})$

Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

Apparently, males had more plaque than females. To do an approximate Wald test to get an idea of whether this was of significance we check **fixed in Intervals and tests** and type 1 next to **fixed:GENDER2_1** and click on **Calc**. Chi-squared on 1 degree of freedom is 3.762 which corresponds to a p -value of 0.052430. Centered (on the grand mean) age was not of importance whereas ILGT positives had slightly less plaque. Since all added covariates are subject-related, only the (unexplained) variance at the subject level has been reduced to 0.091 (SE 0.019).

We now want to assess tooth type as covariate and add categorically toggled TYPE2 which encodes teeth in the maxilla (central and lateral incisors, canines, first and second premolars, first, second and third molars, 1-8) and the mandible (9-16). The reference is a central incisor in the maxilla.

```

Equations
PLInormalijkl ~ N(XB, Ω)
PLInormalijkl = β0ijklcons + -0.001(0.008)PLI2normalijkl + -0.007(0.008)PLI3normalijkl + 0.181(0.096)GENDER2_1l + 0.002(0.029)(AGE2-gm)l +
-0.121(0.087)ILGT2_1l + 0.041(0.039)TYPE2_2kl + 0.063(0.039)TYPE2_3kl + -0.024(0.040)TYPE2_4kl + 0.090(0.039)TYPE2_5kl +
0.354(0.039)TYPE2_6kl + 0.642(0.039)TYPE2_7kl + 0.877(0.047)TYPE2_8kl + 0.352(0.039)TYPE2_9kl + 0.346(0.039)TYPE2_10kl +
0.395(0.039)TYPE2_11kl + 0.492(0.040)TYPE2_12kl + 0.487(0.039)TYPE2_13kl + 0.535(0.039)TYPE2_14kl + 0.670(0.039)TYPE2_15kl +
0.700(0.050)TYPE2_16kl
β0ijkl = -0.345(0.076) + f0l + v0kl + u0ijkl + e0ijkl
[f0l] ~ N(0, Ωf) : Ωf = [0.091(0.019)]
[v0kl] ~ N(0, Ωv) : Ωv = [0.025(0.003)]
[u0ijkl] ~ N(0, Ωu) : Ωu = [0.217(0.005)]
[e0ijkl] ~ N(0, Ωe) : Ωe = [0.258(0.003)]
-2*loglikelihood(IGLS Deviance) = 50782.097(26274 of 26274 cases in use)
Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

```

Apparently, plaque at maxillary lateral incisor, canines and premolars did not differ much from that at central incisors, while molars and all teeth in the mandible harbored considerably more plaque. Unexplained variance at the tooth level was considerably decreased. The model contains 15 more variables and we might assess whether it fits the data better by calculating the likelihood ratio statistic $51678.009 - 50782.097 = 895.912$ which is compared to a chi-squared distribution on 15 degrees of freedom. We conclude that the model with the tooth type covariate explains variation in PLInormal scores significantly better. A further improvement can be achieved by adding toggled categorical SITE2 (mesiobuccal, midbuccal, distobuccal, distolingual, midlingual, mesiolingual, 1-6) to the model with SITE2_1 as reference.


```

Equations
PLInormalijkl ~ N(XB, Ω)
PLInormalijkl = β0ijklcons + -0.001(0.008)PLI2normalijkl + -0.007(0.008)PLI3normalijkl + 0.181(0.096)GENDER2_1l + 0.002(0.029)(AGE2-gm)l +
-0.121(0.087)ILGT2_1l + 0.041(0.039)TYPE2_2kl + 0.063(0.039)TYPE2_3kl + -0.024(0.040)TYPE2_4kl + 0.090(0.039)TYPE2_5kl +
0.354(0.039)TYPE2_6kl + 0.642(0.039)TYPE2_7kl + 0.877(0.047)TYPE2_8kl + 0.352(0.039)TYPE2_9kl + 0.346(0.039)TYPE2_10kl +
0.395(0.039)TYPE2_11kl + 0.492(0.040)TYPE2_12kl + 0.487(0.039)TYPE2_13kl + 0.535(0.039)TYPE2_14kl + 0.670(0.039)TYPE2_15kl +
0.700(0.050)TYPE2_16kl + -0.313(0.020)SITE2_2jkl + 0.089(0.020)SITE2_3jkl + -0.075(0.020)SITE2_4jkl + -0.247(0.020)SITE2_5jkl +
-0.015(0.020)SITE2_6jkl
β0ijkl = -0.251(0.077) + f0l + v0kl + u0ijkl + e0ijkl
[f0l] ~ N(0, Ωf) : Ωf = [0.091(0.019)]
[v0kl] ~ N(0, Ωv) : Ωv = [0.029(0.003)]
[u0ijkl] ~ N(0, Ωu) : Ωu = [0.193(0.005)]
[e0ijkl] ~ N(0, Ωe) : Ωe = [0.258(0.003)]
-2*loglikelihood(IGLS Deviance) = 50178.994(26274 of 26274 cases in use)
Name + - Add Term Estimates Nonlinear Clear Notation Responses Store Help Zoom 100

```

We will now turn to a multinomial model of PLI scores which retains the response variable's original grade categories.

7.3 A Single-level Model with an Ordered Categorical Response Variable

We specify that our original response has t categories, indexed by s ($s = 1, \dots, t$) and we want to choose the highest category t as the reference category. Suppose that the probability of site i having a response variable value of s is $\pi_i^{(s)}$.

We want to base our model upon *cumulative* response probabilities rather than the response probabilities for each separate category. We define the cumulative response as,

$$E\left(y_i^{(s)}\right) = \gamma_i^{(s)} = \sum_{h=1}^s \pi_i^{(h)}, \quad s = 1, \dots, t-1 \quad (7.1)$$

Here, $y_i^{(s)}$ are the observed cumulative proportions (out of a total n_i observations – actually 3 in our example, but we first want to model just the first observation) for the i th site. Expressing the category probabilities in terms of the cumulative probabilities, we have,

$$\begin{aligned} \pi_i^{(h)} &= \gamma_i^{(h)} - \gamma_i^{(h-1)}, 1 < h < t \\ \pi_i^{(1)} &= \gamma_i^{(1)}; \gamma_i^{(t)} = 1 \end{aligned} \quad (7.2)$$

A common model choice is the *proportional odds* model with a logit link, namely,

$$\gamma_i^{(s)} = \{1 + \exp - [\alpha^{(s)} + (X\beta)_i]\}^{-1}$$

or

$$\text{logit}(\gamma_i^{(s)}) = \alpha^{(s)} + (X\beta)_i \quad (7.3)$$

This implies that increasing values of the linear component are associated with increasing probabilities as s increases.

If we assume an underlying multinomial distribution for the category probabilities, the cumulative proportions have a covariance matrix given by,

$$\text{cov}(y_i^{(s)}, y_i^{(r)}) = \gamma_i^{(s)}(1 - \gamma_i^{(r)})/n_i, \quad s \leq r \quad (7.4)$$

We can fit models to these cumulative proportions (or counts conditional on a fixed total) in the same way as with a regular multinomial response vector, substituting this covariance matrix (see, for further discussion, Yang 2001).

We start by clicking on **Clear** the **Equations** window and **Toggle Categorical PPD1 to PDD3** in the **Names** window. In order to set up the new model for just PPD1, we click on y in the **Equations** window and select **PPD1, 1-i** for **N levels** and **SITE** for **level 1(i)**. We click on **done**. We click on N in the **Equations** window and select **Multinomial**. Under **Multinomial options**, we select **Ordered proportional odds** and the default **link function, logit**. Next to **ref category**, we select **PLI1_3** and click **Done**, then on **Estimates** in the **Equations** window.

```

Equations
respij ~ Ordered Multinomial( $n_j$ ,  $\pi_{ij}$ )
 $\gamma_{0j} = \pi_{0j}$ ;  $\gamma_{1j} = \pi_{0j} + \pi_{1j}$ ;  $\gamma_{2j} = \pi_{0j} + \pi_{1j} + \pi_{2j}$ ;  $\gamma_{3j} = 1$ 
logit( $\gamma_{0j}$ ) =
logit( $\gamma_{1j}$ ) =
logit( $\gamma_{2j}$ ) =

cov( $y_{sj}, y_{tj}$ ) =  $\gamma_{sj}(1 - \gamma_{tj})/n_j$  s <= t
(26274 of 26274 cases in use)

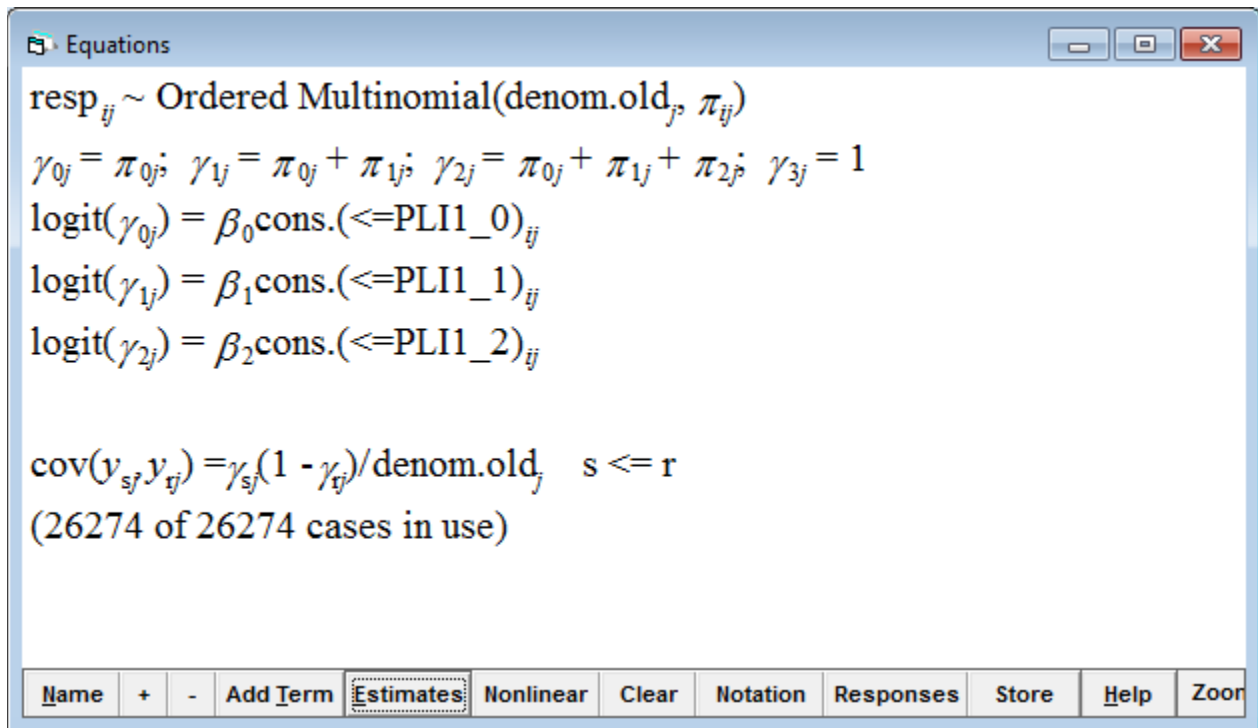
```

The model has now a form similar to the one presented in equations (7.1) to (7.4). Note, however, that y has been replaced by **resp**, and that subscripts i and j are used on this and the π and γ terms. *MLwiN* has created a two-level formulation of

the original single-level. Each site, now a level two unit, has three (number of categories s minus 1) response variables (level 1 units). We may check this by clicking on **resp** in the **Equations** window. If we look at the **Names** window, several new variables have been created by *MLwiN*. Which appear in vacant columns, for instance **resp_indicator** and **SITE_long**. (Remember that the suffix **_long** is created by *MLwiN* to distinguish each new variable created automatically in an expanded data set.) Each of these new columns has a length of 26274 (3 x 8758) because there are 3 responses per site.

We have not yet selected explanatory variables to be included in the model. We would interpret $\text{logit}(\gamma_{2j})$ as the logit of the expected probability that a plaque index (on first examination) of 2 or 3 at site j would have been scored. In order to further set up the model we need to define the denominator vector. We want to address only the plaque index score on occasion 1, so the value of n_j is always 1. We choose **c45** for a column of 1s as the denominator by choosing **Generating vector** in **Data Manipulation** which we rename to **denom_old**.

We can now start adding explanatory variables by clicking on the **Add term** button and selecting **cons**. As before, we fit a separate intercept for each of the three response variables by clicking on **add Separate coefficients**.



The naming of the explanatory variables indicates that we are fitting an ordered proportional odds model as given in equations (7.1) to (7.4). We chose **Use Defaults** in the **Nonlinear** menu and click **Done**. We now run the model by clicking on **Start** in the main menu. After a few iterations, the model converges. By clicking twice on **Estimates**, we get the following.

```

Equations
respij ~ Ordered Multinomial(denom.oldj, πij)
γ0j = π0j; γ1j = π0j + π1j; γ2j = π0j + π1j + π2j; γ3j = 1
logit(γ0j) = -0.805(0.023)cons.(≤PLI1_0)ij
logit(γ1j) = 0.171(0.021)cons.(≤PLI1_1)ij
logit(γ2j) = 3.262(0.057)cons.(≤PLI1_2)ij

cov(ysj, ytj) = γsj(1 - γtj)/denom.oldj  s ≤ r
(26274 of 26274 cases in use)

```

Name	+	-	Add Term	Estimates	Nonlinear	Clear	Notation	Responses	Store	Help	Zoom
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If we take the antilogit (in **Data manipulation**, click **Calculate** and select **ALOGit** of -0.805) of the first coefficient (-0.805), we get 0.30896, the estimated probability that a site has a plaque index score of 0. The proportion of sites with a plaque index score of 0 or 1 is the antilogit of 0.171, i.e. 0.54265; and that of either 0, 1 or 2 is antilogit of 3.262, namely 0.96310. These proportions agree with the proportions we can obtain directly from the data using the **Tabulate** window.

Output window showing the command: `->TABULATE 1 'PLI1'`

	PLI1_0	PLI1_1	PLI1_2	PLI1_3	TOTALS
N	2706	2047	3682	323	8758
%	30.9	23.4	42.0	3.7	100.0

Zoom: 100 Copy as table Clear Include output from system generated commands

7.4 A Two-level Model

The two-level ordered category response model is a generalization of the single-level model, as shown in the following set of corresponding model equations.

$$E(y_{ij}^{(s)}) = \gamma_{ij}^{(s)} = \sum_{h=1}^s \pi_{ij}^{(h)}, \quad s = 1, \dots, t-1$$

$$\gamma_{ij}^{(s)} = \{1 + \exp - [\alpha^{(s)} + (X\beta)_{ij} + Z_{ij}u_j]\}^{-1}$$

$$\text{cov}(y_{ij}^{(s)}, y_{ij}^{(r)}) = \gamma_{ij}^{(s)}(1 - \gamma_{ij}^{(r)})/n_{ij}, \quad s \leq r \quad (7.5)$$

or

$$\text{logit}(\gamma_{ij}^{(s)}) = \alpha^{(s)} + (X\beta)_{ij} + Z_{ij}u_j$$

$$\pi_{ij}^{(h)} = \gamma_{ij}^{(h)} - \gamma_{ij}^{(h-1)}, \quad 1 < h < t$$

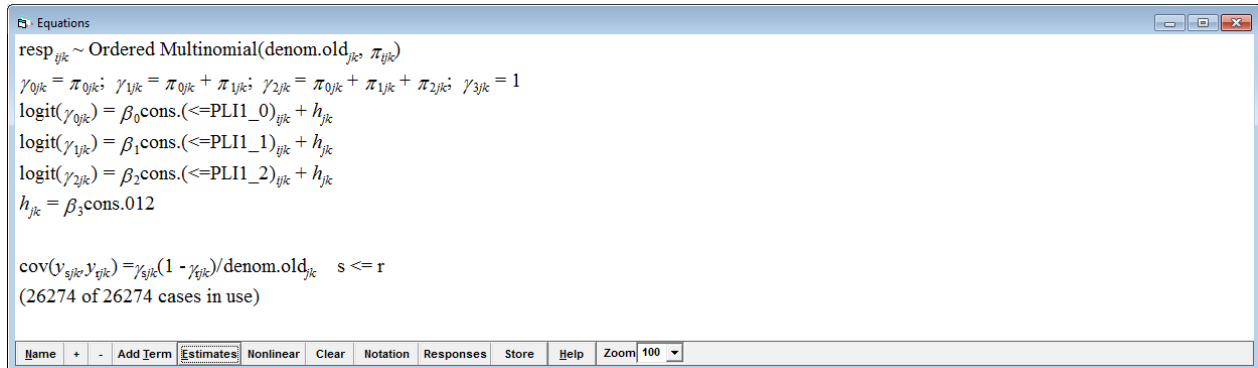
$$\pi_{ij}^{(1)} = \gamma_{ij}^{(1)}; \gamma_{ij}^{(t)} = 1$$

As we would expect, when fitting this model, *MLwiN* creates a three-level formulation. We add subject ID (**NO**) as a third (highest) level in the model we have just fitted by clicking on **resp** in the **Equations** window and selecting in the **Y variable** window **3-ijk** beside **N levels**. We select **NO** beside **level 3(k)** and click **done** (as expected, *MLwiN* has created a new column, **NO_long** to serve as actual identifier variable used during fitting; we can also see in the **Names** window the three intercept variables derived from **cons** and the full **denom** variable).

We now need to define the variation at the subject level. One possibility is to allow each plaque index category's intercept term to vary, giving us a 3 x 3 covariance matrix at level 3. To do this we would simply click on each **cons.(<=*)** term in turn and in the **X variable** window, check the **k(NO_long)** box. However, if we did this, we would essentially be fitting a simple multinomial two-level model, which also has a 3 x 3 covariance matrix. Instead, we shall fit a single variance term at the subject level by clicking on the **Add Term** button on the **Equations** window toolbar, select **cons** in the **variable** box of the **Specify term** window, but click on **add Common coefficient**. In the appearing **Specify common pattern** window we can check boxes (**<=PLI1_0**), (**<=PLI1_1**) and (**<=PLI1_2**), corresponding to the

terms entered in the model. We fit our common level 3 variance by clicking on

Include all and then **Done**.



```
Equations
respijk ~ Ordered Multinomial(denom.oldijk, πijk)
γ0jk = π0jk; γ1jk = π0jk + π1jk; γ2jk = π0jk + π1jk + π2jk; γ3jk = 1
logit(γ0jk) = β0cons.<=PLI1_0>ijk + hjk
logit(γ1jk) = β1cons.<=PLI1_1>ijk + hjk
logit(γ2jk) = β2cons.<=PLI1_2>ijk + hjk
hjk = β3cons.012

cov(ysijkytijk) = γsijk(1 - γtijk)/denom.oldijk  s <= r
(26274 of 26274 cases in use)
```

As can be seen, a term h_{jk} has been added to the equation for each response category. It represents terms common to the set of equations and defined following the equations for the response categories. In our example, it consists of the single common coefficient associated with the newly created variable **cons.012**. If we had specified a pattern that included only response categories 0 and 2, the new variable would have been named **cons.02**, and its term would have appeared only in the respective equations. Apparently, this procedure allows complete flexibility in specifying patterns of shared coefficients across response categories.

As to now, the model is over-parameterized with a unique coefficient for every response category and a common coefficient. We want to use the coefficient of the common variable, **cons012**, only to specify a common between-subject variability. So we do not need this variable in the fixed part of the model. To specify how the

variable is used, we click on the **cons.012 terms**, uncheck the **Fixed Parameter** check box in the **X variable** window, check the **k(NO_long)** check box and click on **Done**. We start with the default **Nonlinear** estimation procedure (1st order MQL) and run the first estimation.

```

Equations
resp_ijk ~ Ordered Multinomial(denom.old_ijk, pi_ijk)
gamma_0jk = pi_0jk; gamma_1jk = pi_0jk + pi_1jk; gamma_2jk = pi_0jk + pi_1jk + pi_2jk; gamma_3jk = 1
logit(gamma_0jk) = -0.783(0.111)cons.(<=PLI1_0)_ijk + h_jk
logit(gamma_1jk) = 0.193(0.111)cons.(<=PLI1_1)_ijk + h_jk
logit(gamma_2jk) = 3.284(0.123)cons.(<=PLI1_2)_ijk + h_jk
h_jk = v_3k cons.012

[v_3k] ~ N(0, Omega_v) : Omega_v = [0.592(0.122)]

cov(y_sjk, y_tjk) = gamma_sjk(1 - gamma_tjk)/denom.old_ijk  s <= t
(26274 of 26274 cases in use)

```

So far, the second line indicates that we have specified the cumulative category model. This is followed by three response variable equations, one for each cumulative category (PLI1 = 0, PLI1 <=1, and PLI1 <=2). The explanatory variable in each case is a constant, allowing the intercept to be different for each. The other explanatory variable, **cons.012**, is also a constant (=1) whose sole contribution to the model – via its random coefficient – is to add the same random

error term to each of the five categories' equations. A common subject-level variance is thus estimated for each category.

Next, we switch, in the **Nonlinear Estimation** menu, to the preferable method of estimation, 2nd order PQL. We rather click on **Start** again and get the following.

```

Equations
respijk ~ Ordered Multinomial(denom.oldjk, πijk)
γ0jk = π0jk; γ1jk = π0jk + π1jk; γ2jk = π0jk + π1jk + π2jk; γ3jk = 1
logit(γ0jk) = -0.919(0.129)cons.(<=PLI1_0)ijk + hjk
logit(γ1jk) = 0.218(0.129)cons.(<=PLI1_1)ijk + hjk
logit(γ2jk) = 3.661(0.141)cons.(<=PLI1_2)ijk + hjk
hjk = v3kcons.012

[ v3k ] ~ N(0, Ωv) : Ωv = [ 0.806(0.165) ]

cov(ysjk, ytjk) = γsjk(1 - γtjk)/denom.oldjk  s <= t
(26274 of 26274 cases in use)

```

Note that the previous 1st order MQL procedure has in fact largely underestimated all parameters.

We now want to add subject level covariates gender, ILGT and centered (on the **grand mean**) age using common coefficients across response categories. We click, in turn, on **Add Term** and select in the **variable** box of the **Specify term** window

respective variables GENDER, ILGT, and AGE, click on **add Common coefficient** and **Include all** in the **Specify common pattern** window, then click on **Done**.

```

Equations
respijk ~ Ordered Multinomial(denom.oldijk, πijk)
γ0jk = π0jk; γ1jk = π0jk + π1jk; γ2jk = π0jk + π1jk + π2jk; γ3jk = 1
logit(γ0jk) = -0.894(0.197)cons.(≤PLI1_0)ijk + hjk
logit(γ1jk) = 0.253(0.197)cons.(≤PLI1_1)ijk + hjk
logit(γ2jk) = 3.724(0.205)cons.(≤PLI1_2)ijk + hjk
hjk = -0.596(0.268)GENDER.012k + 0.303(0.242)ILGT.012k + -0.035(0.080)(AGE-gm).012k
      + v3kcons.012

[ v3k ] ~ N(0, Ωv) : Ωv = [ 0.707(0.146) ]

cov(ysjk, ytjk) = γsjk(1 - γtjk)/denom.oldjk  s ≤ t
(26274 of 26274 cases in use)

```

Note that the (unexplained) subject-level variance is reduced when the model is adjusted for gender, ILGT, and age.

We could also have chosen to use **add Separate coefficients** to allow separate coefficients for each category. Let's see the effect of allowing each response category equation to have its own coefficients for gender, ILGT, and age. To do this, we delete the common terms and add them again, this time using the **add Separate coefficients** button.

```

Equations
respijk ~ Ordered Multinomial(denom.oldijk, πijk)
γ0jk = π0jk; γ1jk = π0jk + π1jk; γ2jk = π0jk + π1jk + π2jk; γ3jk = 1
logit(γ0jk) = -0.850(0.196)cons.(≤PLI1_0)ijk + -0.531(0.268)GENDER.(≤PLI1_0)ijk + 0.187(0.241)ILGT.(≤PLI1_0)ijk +
-0.067(0.080)(AGE-gm).(≤PLI1_0)ijk + hijk
logit(γ1jk) = 0.322(0.195)cons.(≤PLI1_1)ijk + -0.683(0.267)GENDER.(≤PLI1_1)ijk + 0.240(0.240)ILGT.(≤PLI1_1)ijk +
-0.022(0.080)(AGE-gm).(≤PLI1_1)ijk + hijk
logit(γ2jk) = 3.167(0.211)cons.(≤PLI1_2)ijk + -0.285(0.294)GENDER.(≤PLI1_2)ijk + 1.584(0.281)ILGT.(≤PLI1_2)ijk +
0.050(0.094)(AGE-gm).(≤PLI1_2)ijk + hijk
hijk = v3kcons.012
[ v3k ] ~ N(0, Ωv) : Ωv = [ 0.691(0.142) ]
cov(v3k, v3k) = v3k(1 - v3k)/denom.old. s ≤ r

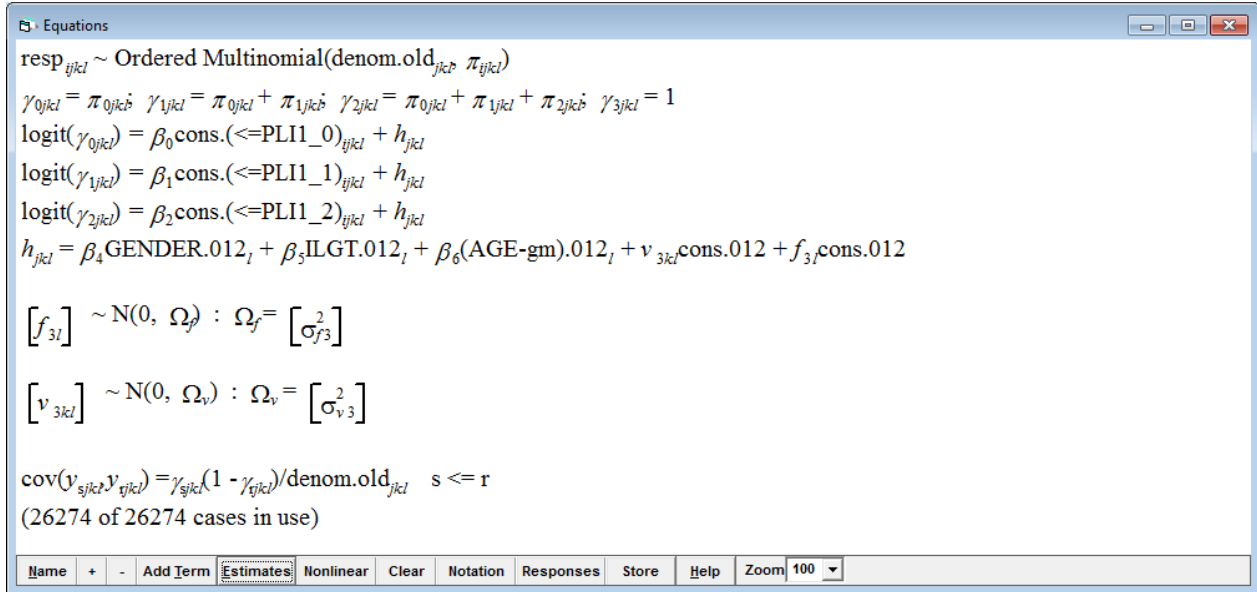
```

In general, differences among coefficients are huge which makes the model rather difficult to interpret. The important point here is that, in the previous model, we are taking advantage of the ordering in the categories to simplify the model structure.

7.5 A Three-level Model

So far, one important level is missing in our model of plaque index scores, the tooth. We may consider the tooth level by clicking on the response variable in the **Equations** window and change **N levels** to **4-ijk**. We then select **NO_long** for **4-l**, **TOOTH_NO2** for **3-k**, **SITE_long** for **2-j** and click **done**. We then click on **v_{3kl}.cons012** in the **Equations** window and check the box **l(NO_long)**. We note that we have introduced two random error terms, tooth-level v_{3kl} and subject level f_{3l} , to each of the three categories equations. We make sure, in **Nonlinear**, that the

default estimation is selected first (1st order MQL), click on **Done** and then click on **Start**.



We now want to add tooth type and site into the model. We first both toggle **TYPE** and **SITE**, in the **Names** window, categorical, then click successively on **Add Term** and on **add Common coefficients** (with TYPE_1, i.e. the central incisor in the maxilla, and SITE_1, i.e. mesiobuccal as references). We click on the **More** button and run the model. We can check, in **Nonlinear**, 2nd order MQL (2nd order PQL won't converge) and get the result below. When comparing the below results with those obtained in section 7.2, we see that we would make similar inferences about the common effect of gender, ILGT, age, tooth type and site.

```

Equations
respijkl ~ Ordered Multinomial(denom.oldijkl, πijkl)
γ0ijkl = π0ijk, γ1ijkl = π0ikl + π1ijk, γ2ijkl = π0ikl + π1jkl + π2ijk, γ3ijkl = 1
logit(γ0ijkl) = -0.258(0.222)cons.(≤=PLI1_0)ijkl + hijkl
logit(γ1ijkl) = 1.032(0.224)cons.(≤=PLI1_1)ijkl + hijkl
logit(γ2ijkl) = 4.770(0.253)cons.(≤=PLI1_2)ijkl + hijkl
hijkl = -0.632(0.269)GENDER.012l + 0.319(0.243)ILGT.012l + -0.029(0.080)(AGE-gm).012l + -0.107(0.131)TYPE_2.012kl + -0.202(0.131)TYPE_3.012kl +
0.041(0.137)TYPE_4.012kl + -0.275(0.131)TYPE_5.012kl + -0.978(0.134)TYPE_6.012kl + -1.760(0.142)TYPE_7.012kl +
-2.412(0.178)TYPE_8.012kl + -0.928(0.133)TYPE_9.012kl + -0.916(0.133)TYPE_10.012kl + -1.099(0.134)TYPE_11.012kl +
-1.503(0.143)TYPE_12.012kl + -1.472(0.139)TYPE_13.012kl + -1.679(0.142)TYPE_14.012kl + -2.019(0.146)TYPE_15.012kl +
-2.020(0.183)TYPE_16.012kl + 0.859(0.075)SITE_2.012jkil + -0.324(0.072)SITE_3.012jkil + 0.190(0.071)SITE_4.012jkil + 0.675(0.073)SITE_5.012jkil +
0.002(0.071)SITE_6.012jkil + v3iklcons.012 + f3lcons.012

[f3l] ~ N(0, Ωf) : Ωf = [0.701(0.147)]
[v3ikl] ~ N(0, Ωv) : Ωv = [0.250(0.033)]

cov(vs1ikl, vs2ikl) = γs1ikl(1 - γs2ikl) / denom.oldijkl s <= r

```

However, albeit the above model provides a more detailed description of the probabilities of each plaque index score, this applies only to one (the first) examination. *MLwiN* does not provide the possibility to examine, in one model, repeated measures of multinomial responses.

8 References

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