# 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 & Löe plaque index (PI) on a four scores scale (Silness and Löe 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?

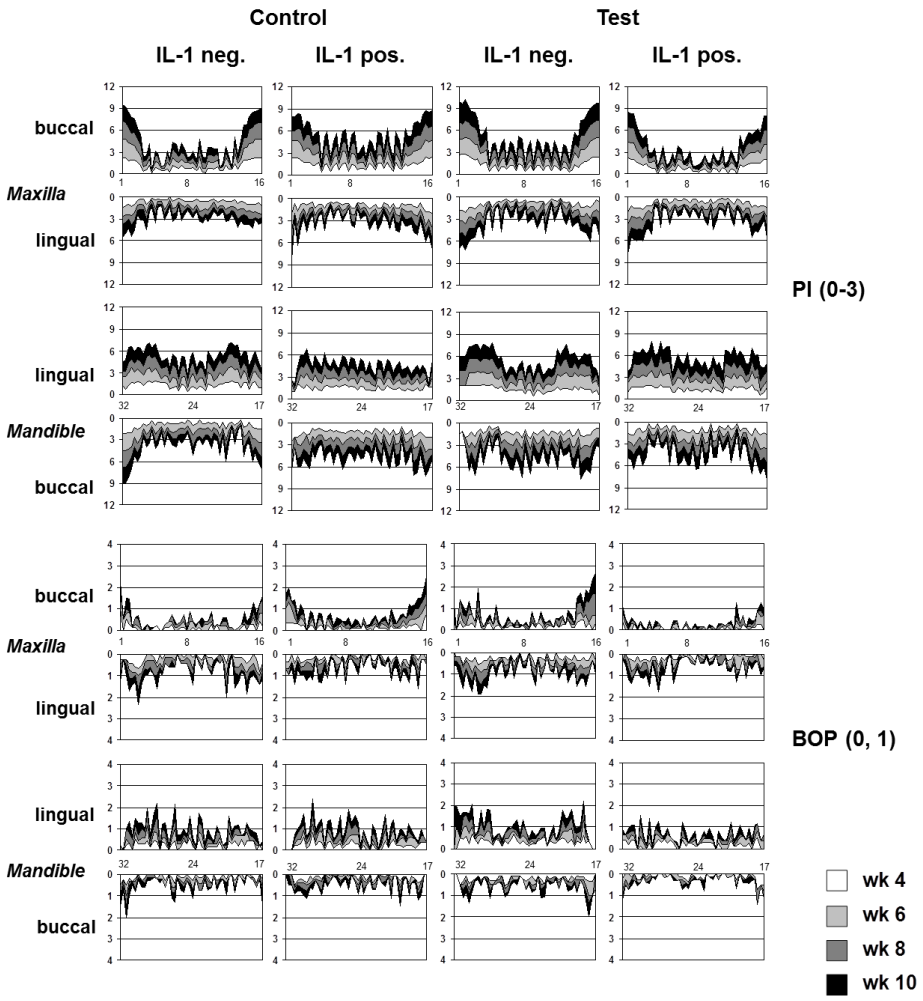



*Fig. 6.1* Topographical distribution (see, for orientation, tooth numbers 1, 8, 16 in the maxilla, and 17, 24, and 32 in the mandible; three sites were assessed on the buccal aspect, and three sites on the lingual aspect of each tooth) of the Silness & Löe plaque index (PI) and bleeding on probing in 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 (*IL1_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.

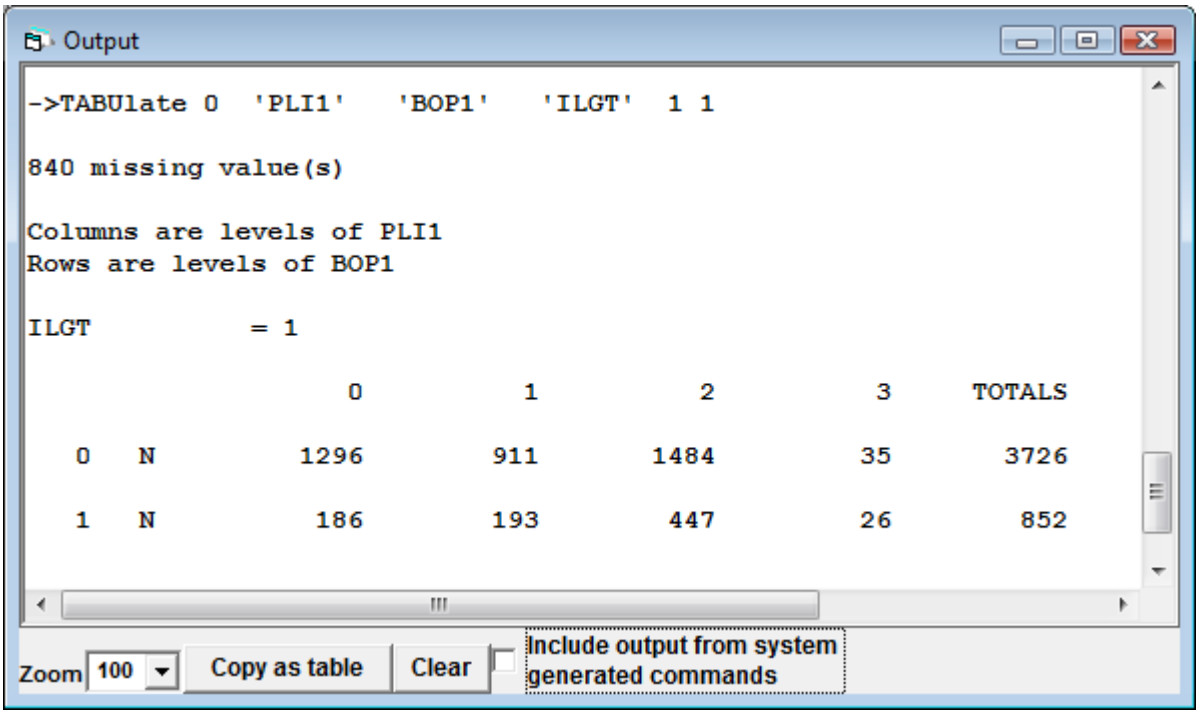
| *Variable* | *Description* |
|---|---|
| **NO** | Subject's identifier (1-50) |
| **GENDER** | (0, 1) |
| **ILGT** | Interleukin 1 genotype (0, 1) |
| **AGE** | In years |
| **TOOTH_NO** | FDI notation of teeth (11-48) |
| **TYPE** | Tooth type (1-16) |
| **SITE** | Tooth site (1-6) |
| **PPD** | Periodontal probing depth (mm) |
| **CAL** | Clinical attachment level (mm) |
| **BOP** | Bleeding on probing (0, 1) |
| **PLI** | Silness & Löe'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.

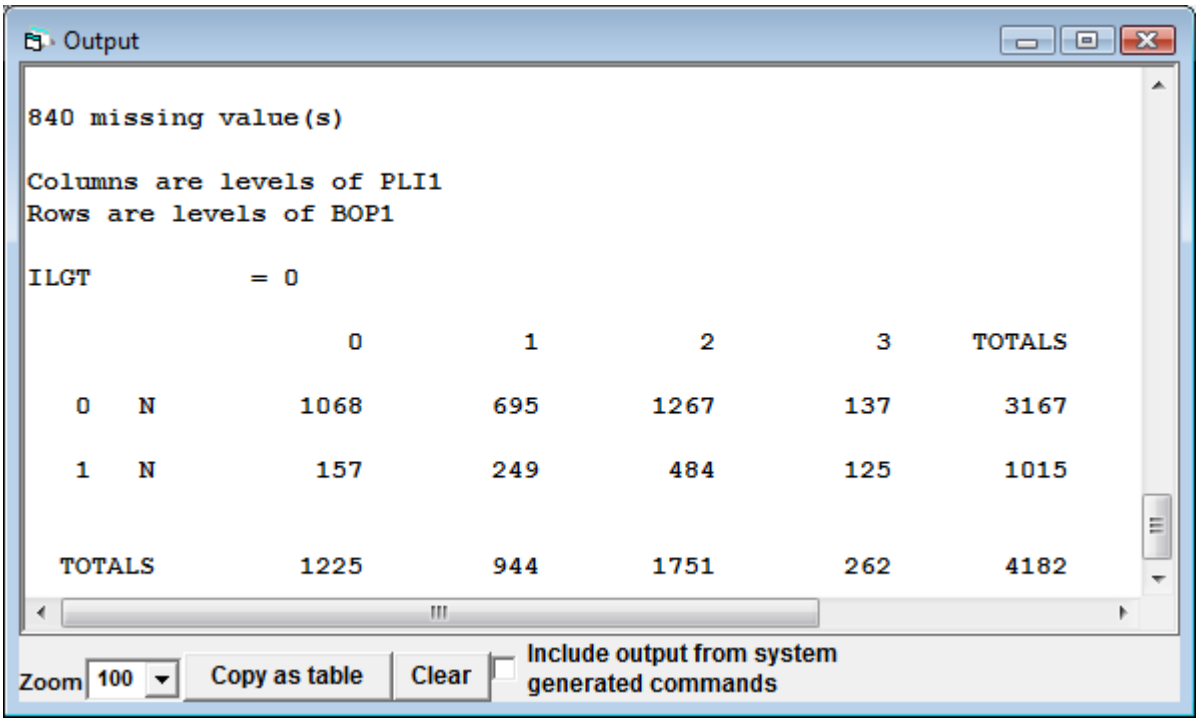
After we have opened a new worksheet in *MLwiN* by clicking on **File** in the main menu and **New worksheet**, we can import the EXCEL data by copy them to the clipboard and paste them into *MLwiN*. For that we click on **Edit** in the main menu and **Paste**. We check the box **Use first row as names**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

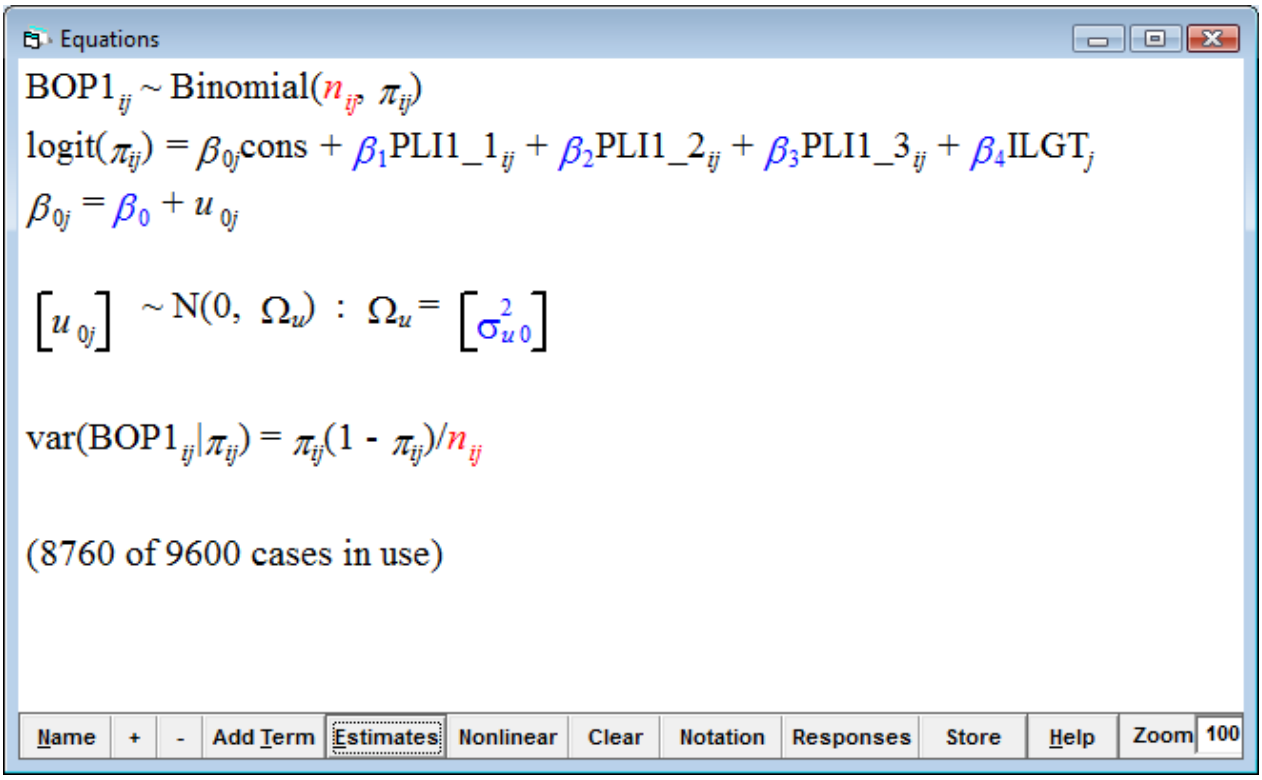



A respective table for IL-1 genotype negatives can easily be generated as well.



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

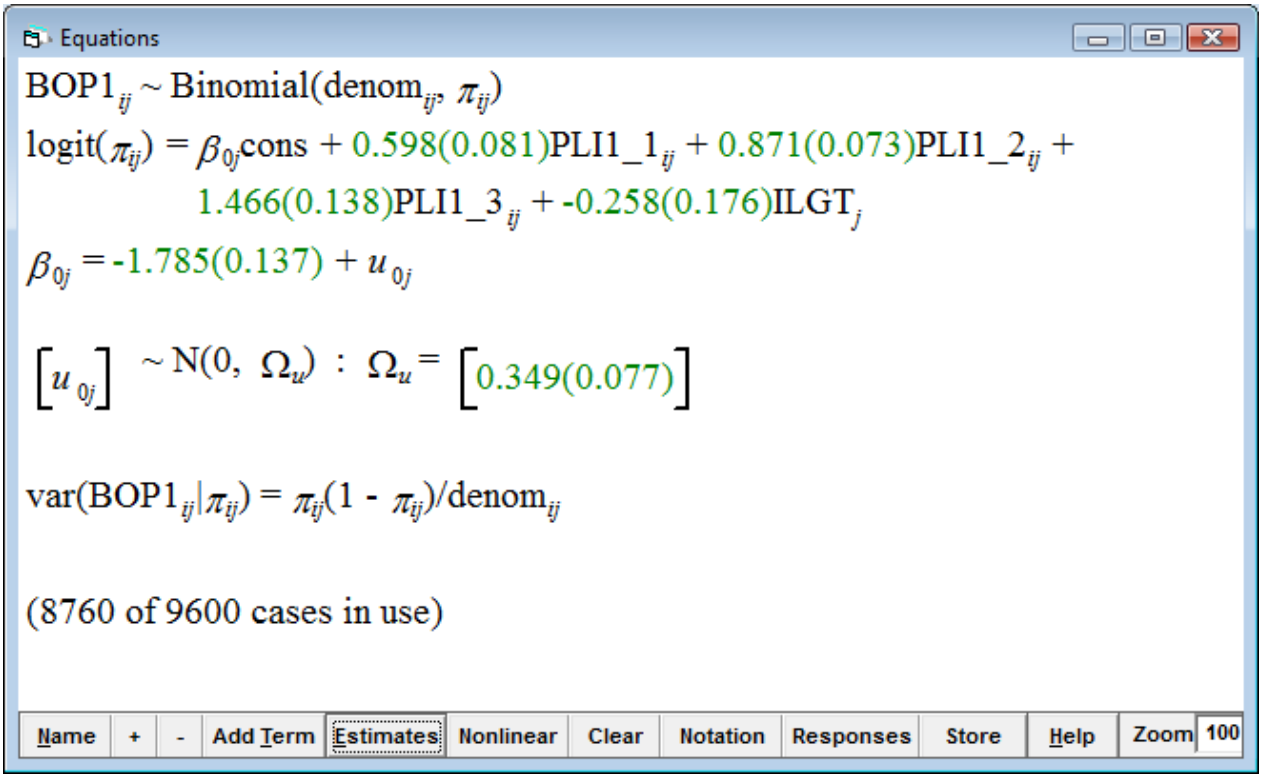
We can first assess the association in three separate two-level random intercept models where we allow for subject effects on the probability of the binary response bleeding on probing. From the **Model** menu, we select **Equations** and click on **y**. For **y**, we select from the drop-down menu of 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 $\pi_i$. 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 last line in the **Equations** window states that the variance of the binomial response is $\pi_{ij}$ (1- $\pi_{ij}$)/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 $\sigma^2_{u0}$) 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 PLI1scores 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 *IL1_02.wsz*. We may then model BOP2 and BOP3. Respective results are displayed in *Table 6.1*.

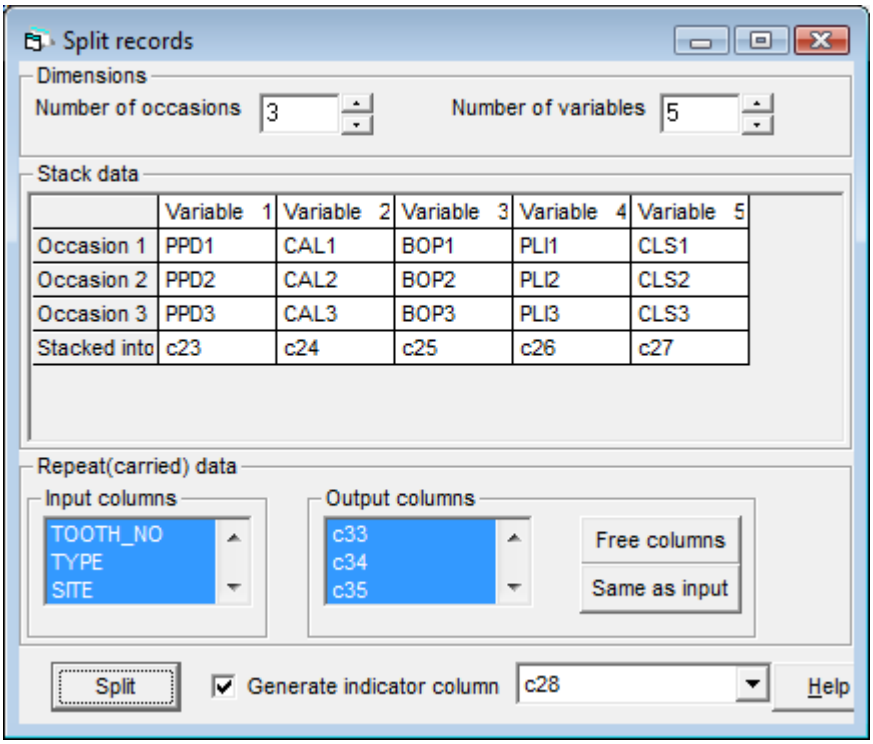
*Table 6.1* Odds ratios (95% confidence interval) of three separate two-level random intercept logistic models

| | **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) |

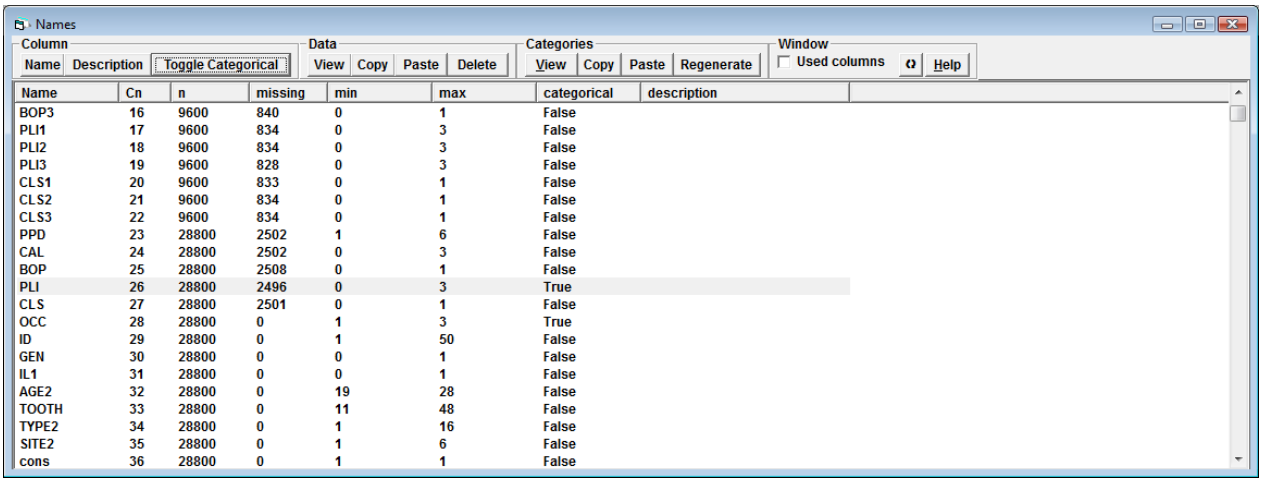
As expected, BOP was consistently associated with plaque index. The association became stronger with higher scores. The IL-1 genotype was, in general, negatively associated with BOP. However, parameter estimates do not allow us to draw any firm conclusions about the relative weight of amount of plaque (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,

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

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, $\pi_{tij}$ as follows,

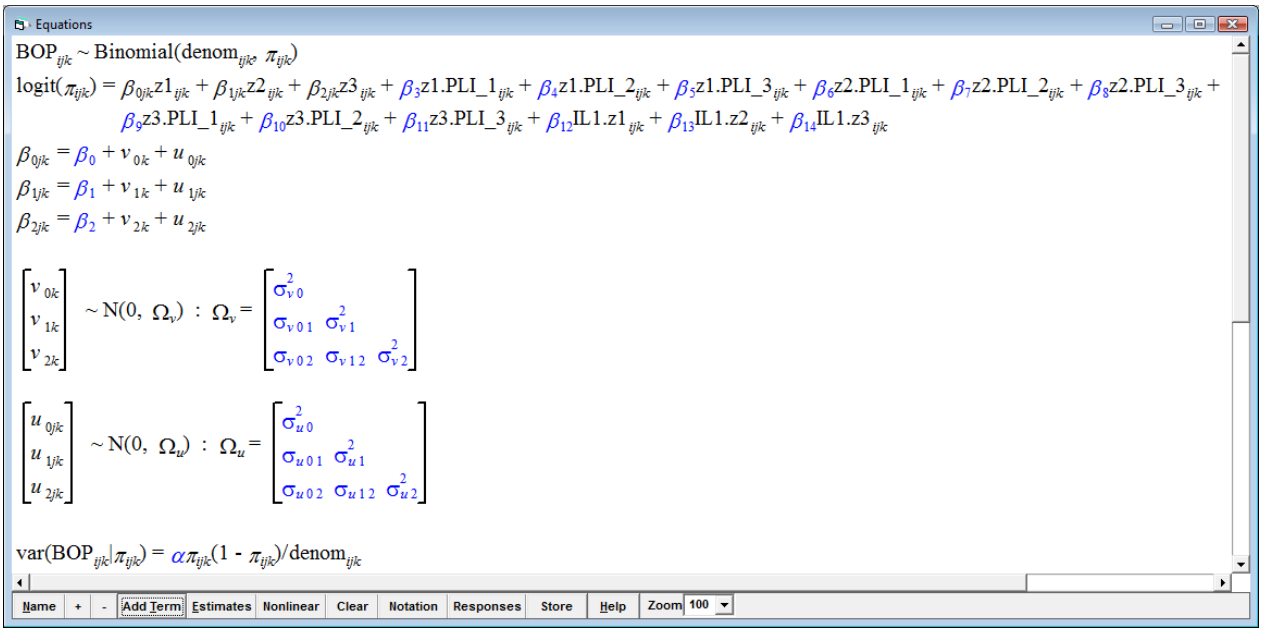
$$\text{logit}(\pi_{tij}) = \sum_{t=1}^{3} \beta_{0,t}\, z_{tij} + \sum_{t=1}^{3}\sum_{h=1}^{4} \beta_{h,t}\, z_{tij} x_{h,tij} \sum_{t=1}^{3} v_{tj} z_{tij} + u_{tij} z_{tij}$$

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

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

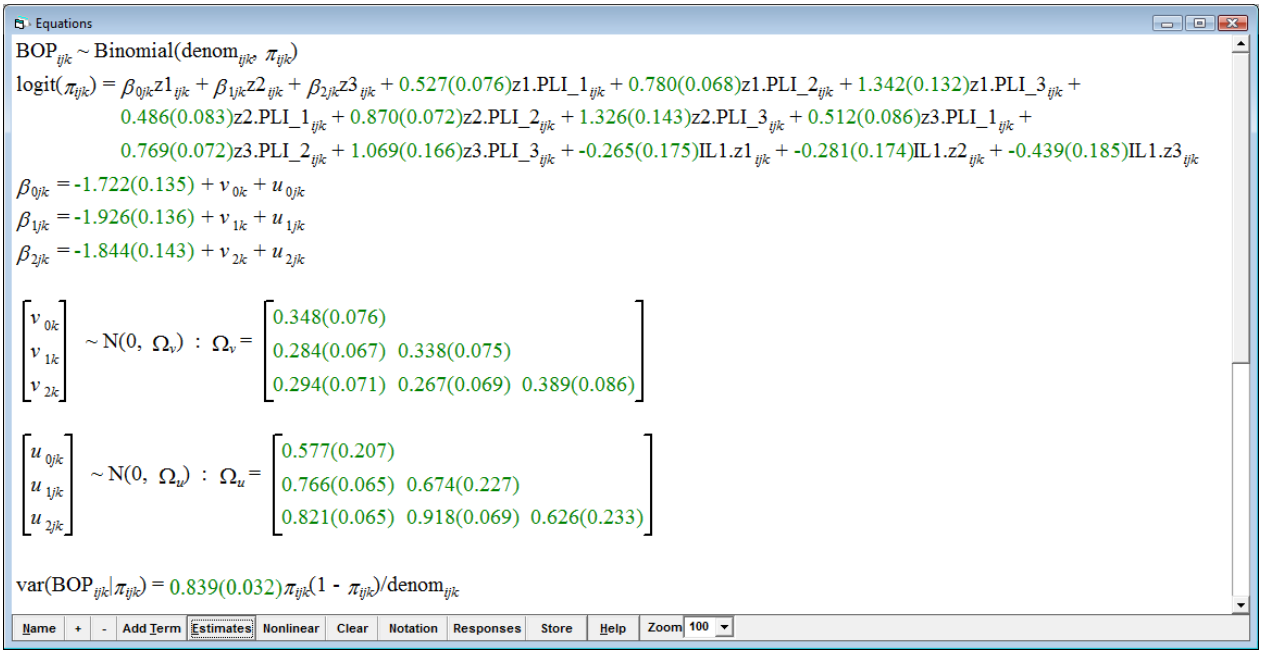
(6.1)

Where $v_{tj}$ 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.



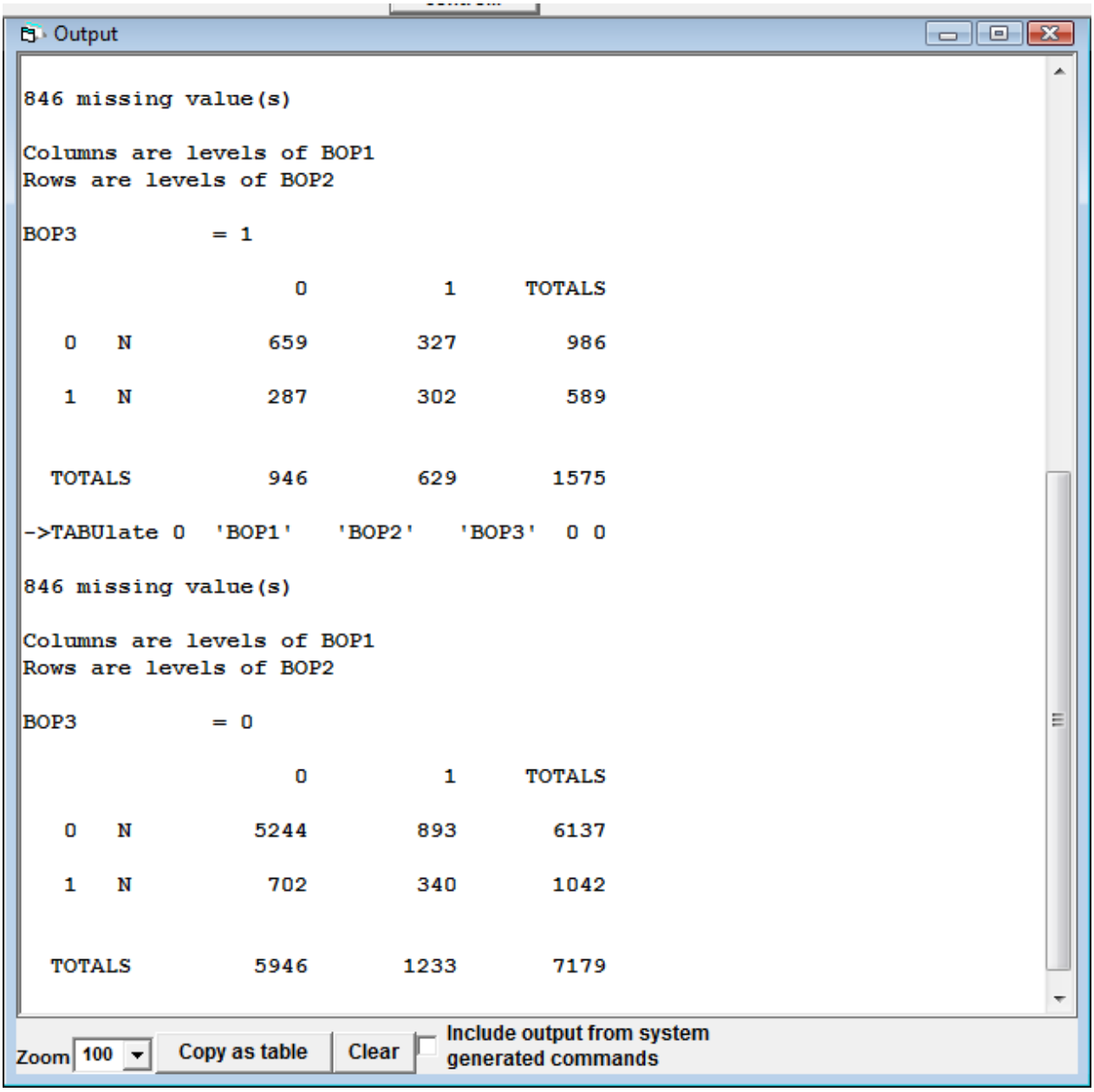

The last line in the **Equations** window states that the variance of the binomial response is $\pi_i$ (1- $\pi_i$)/denom$_i$, which, in case of binary data, simplifies to $\pi_i$ (1- $\pi_i$). Note the extrabinomial, so-called scale factor $\alpha$, which can be estimated as well. If $\alpha$ is significantly 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 $\alpha$ 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. $\alpha$ 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.




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,

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

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

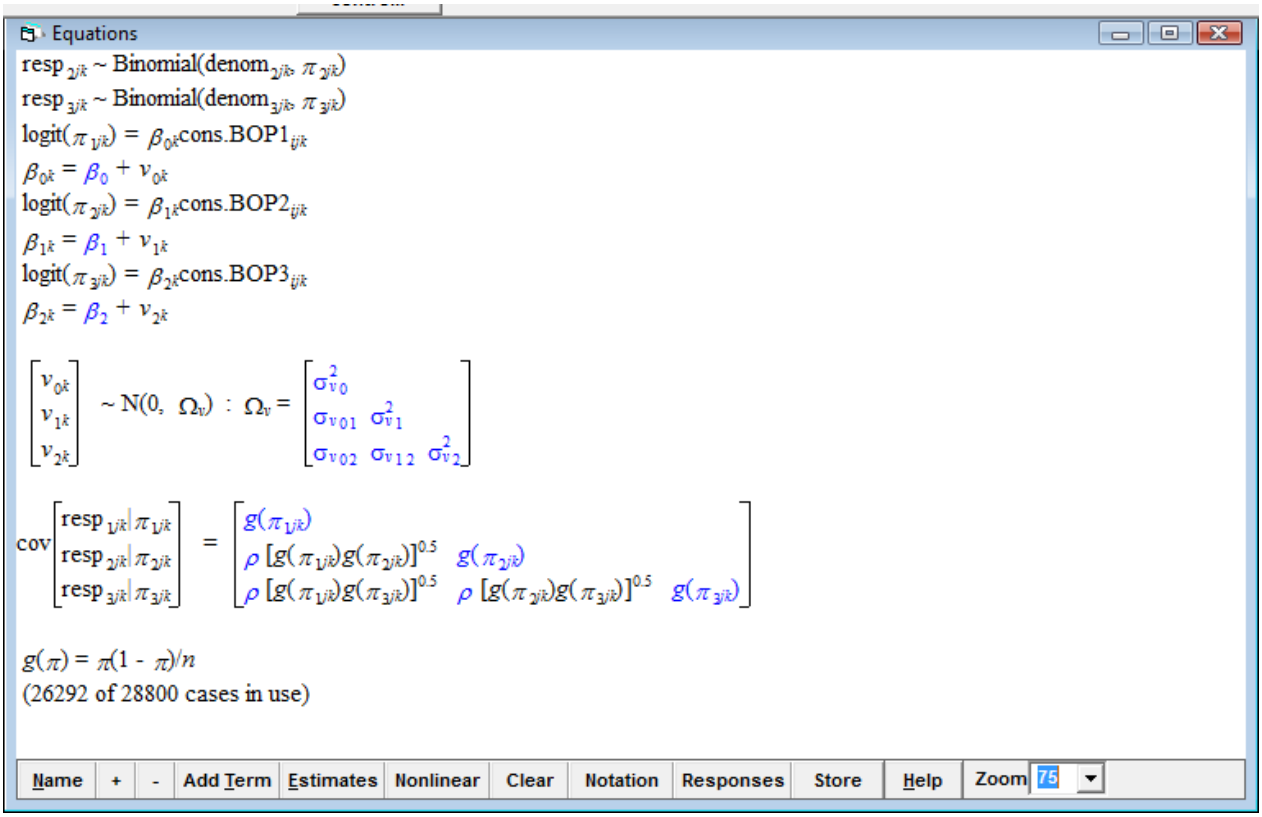
$$u_{tj} \sim N(0, \Omega_u)$$

(6.2)

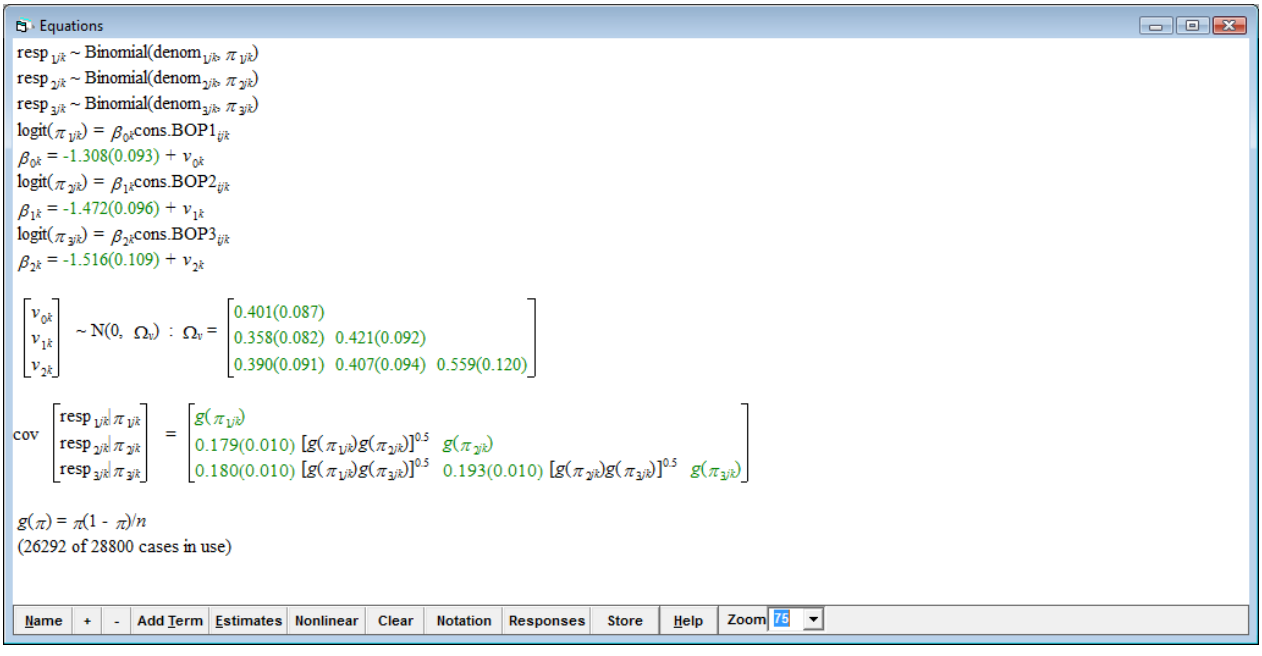
where *m* occasions and *n* covariates were considered. We make the same assumption as for the repeated measures model. Residual terms at the subject level associated with the intercept for each examination are designated $u_{tk}$. There is no level 1 (occasion) variation, because at level 2 (site), 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*

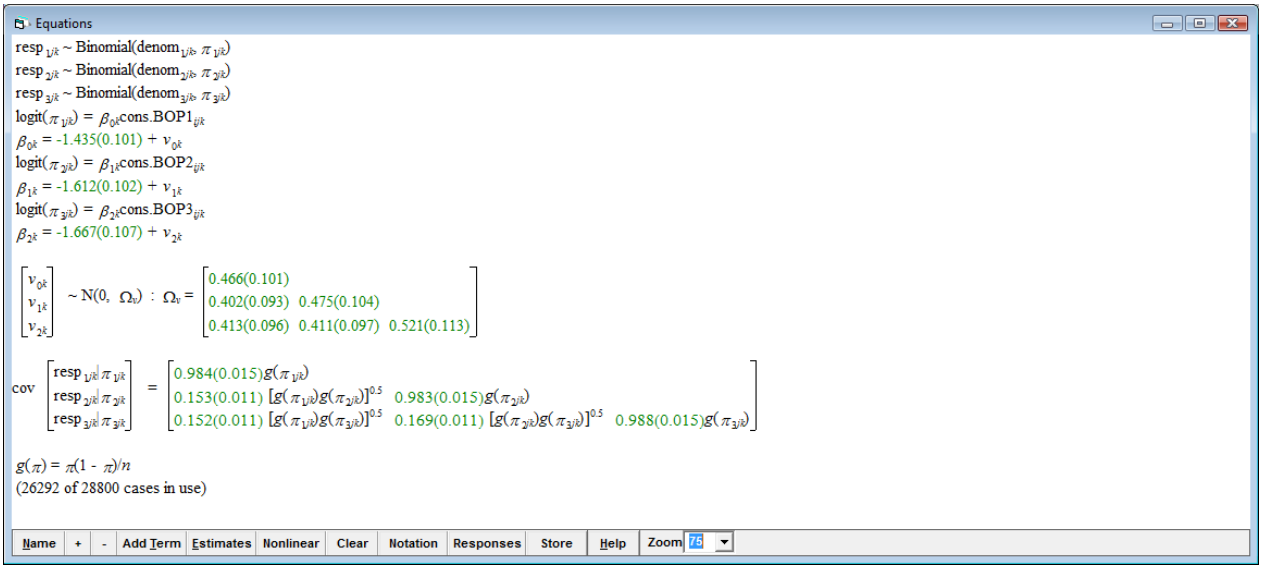
In order to set up the above model, we want to start with a variance components model without covariates. We open the worksheet saved in *IL1_02.wsz*, open the **Equations** window and click on **Clear**. In the **Responses** drop-down list, we select BOP1, BOP2, and BOP3. As before, we click on **N** 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 *IL1_05.wsz*.




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:



The predicted proportions of BOP, ALOGit ($\beta_k$) 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 $\alpha$. 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 e few iterations.

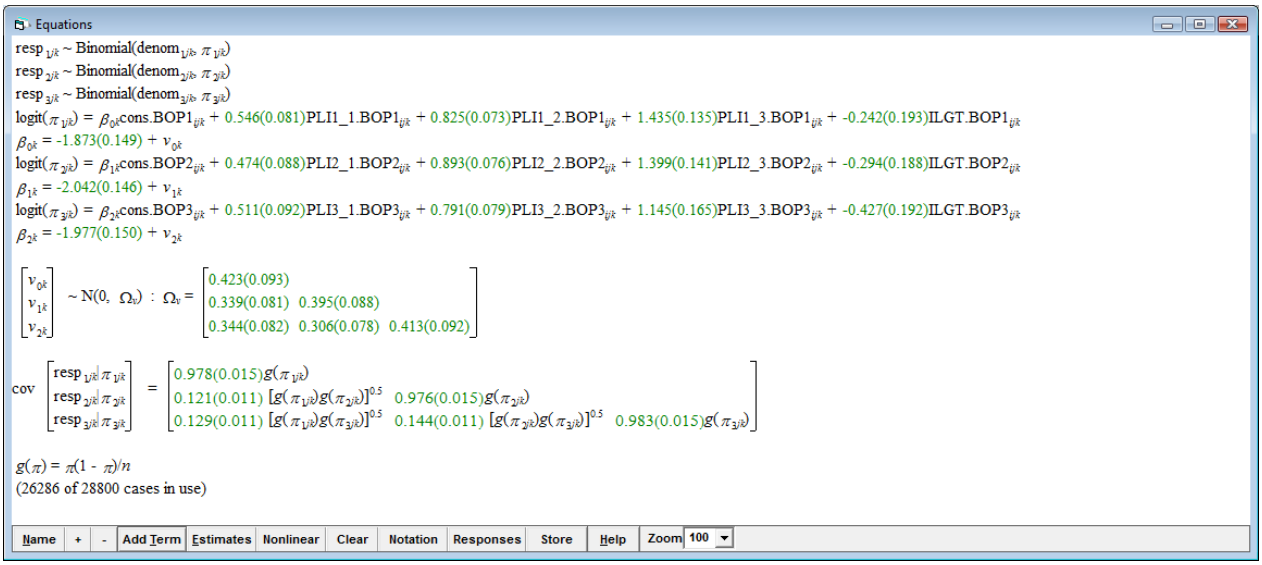



At the site level, extrabinomial parameters are all close to 1, indicating that the assumption of binomial error distribution for each examination occasion is adequate. The three biserial covariances between examination occasions are 0.153 (OCC1:OCC2), 0.152 (OCC1:OCC3), and 0.169 (OCC2:OCC3). As before (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.



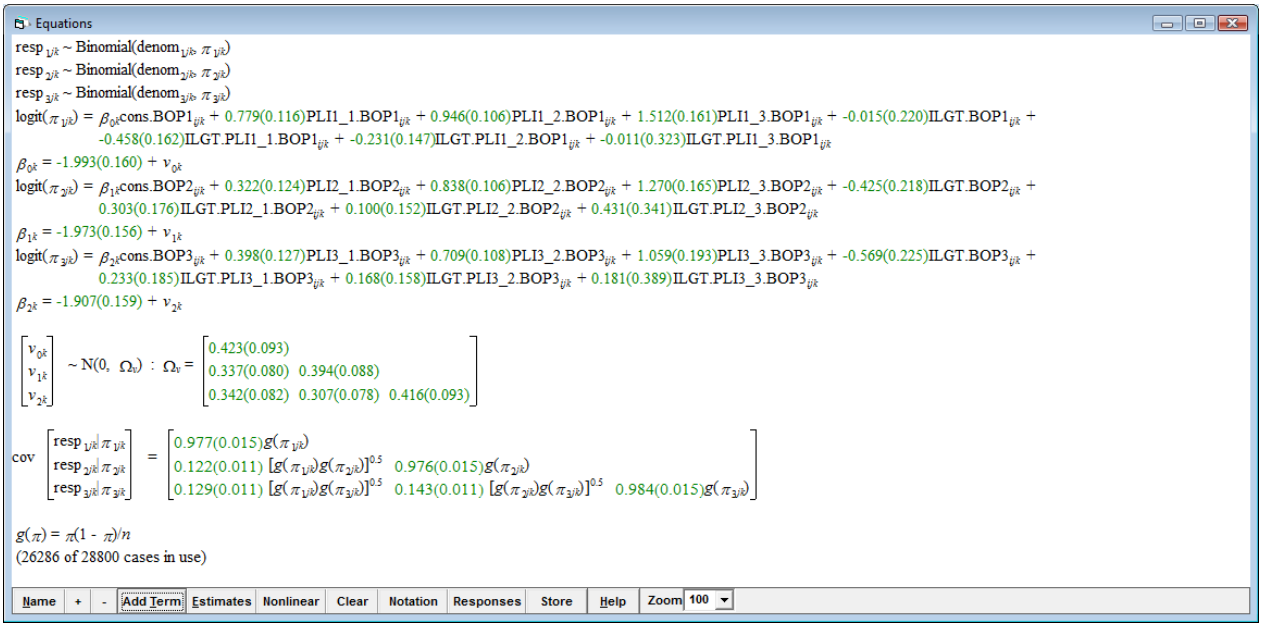

Estimates of all parameters are rather similar for each examination occasion. We may anyway want to carry out a joint approximate Wald test to compare, for instance, the estimate of PLI score 3 at occasion 1 (1.435, SE 0.135) with that at occasion 3 (1.145, SE 0.165). In the **Model** menu, we select **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*

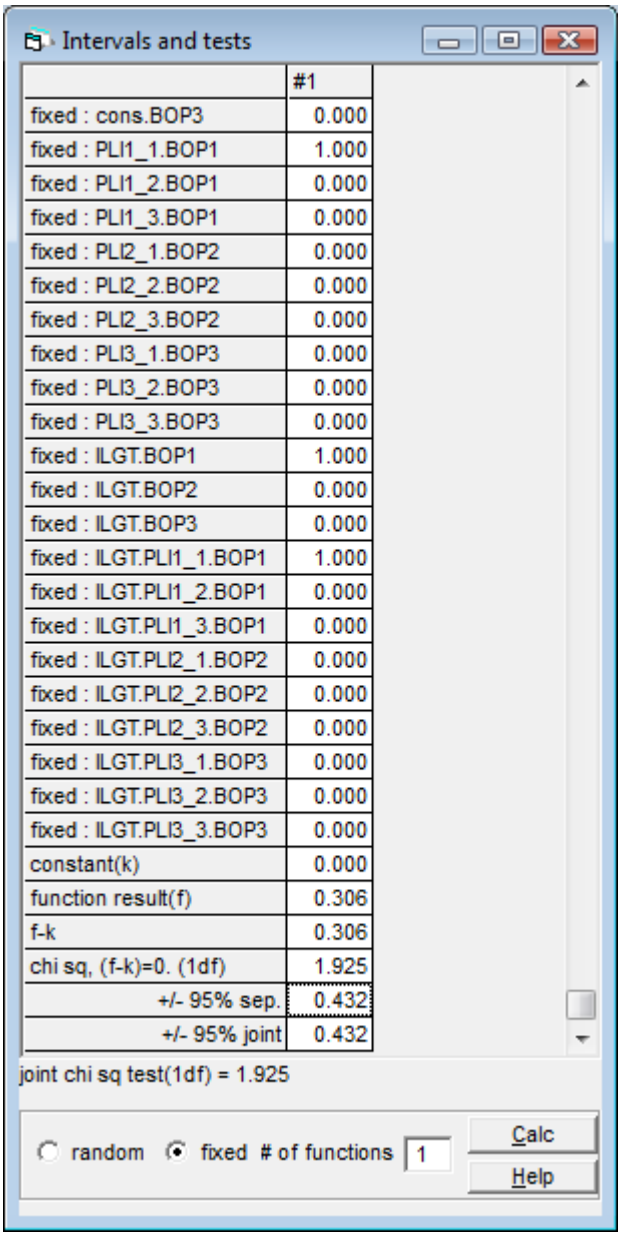
In the above model we noticed that the ILGT had a consistently negative impact on our response variable, BOP. In order to address, for instance, the important question, How does the ILGT influence the bleeding response of gingiva to different amounts of supragingival plaque?, we need to modify our model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



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 PLI 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).

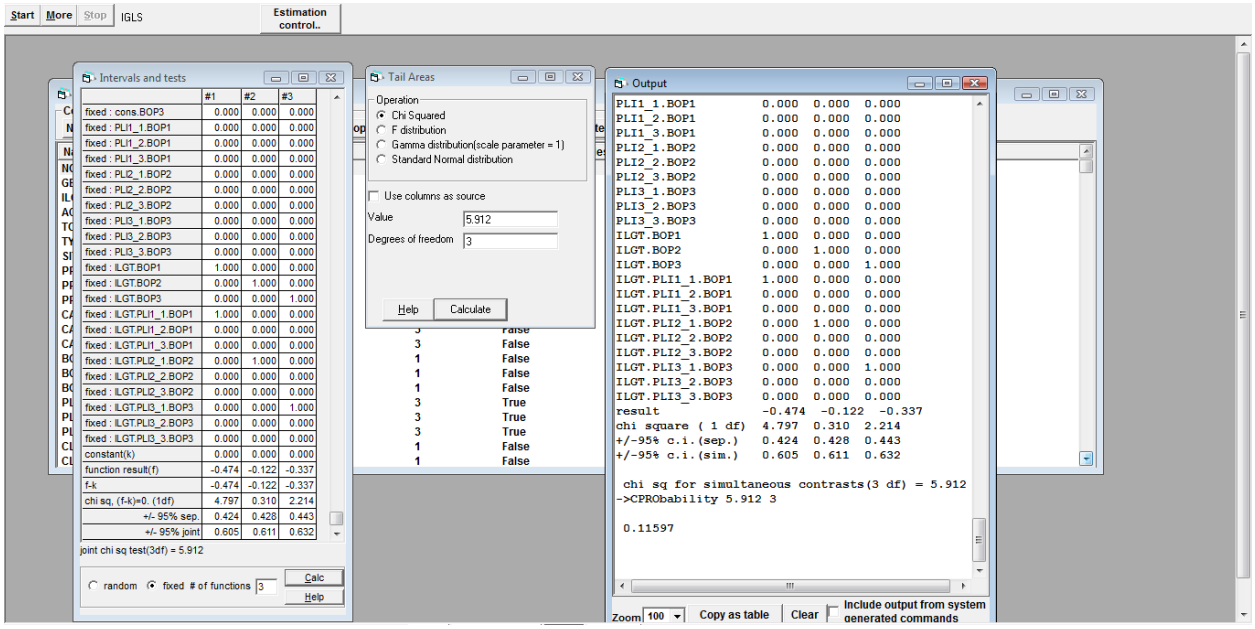



We may want to calculate respective odds ratios for examination occasion 2 and 3 as well. They are tabulated in *Table 6.2*.

| *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 joined 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

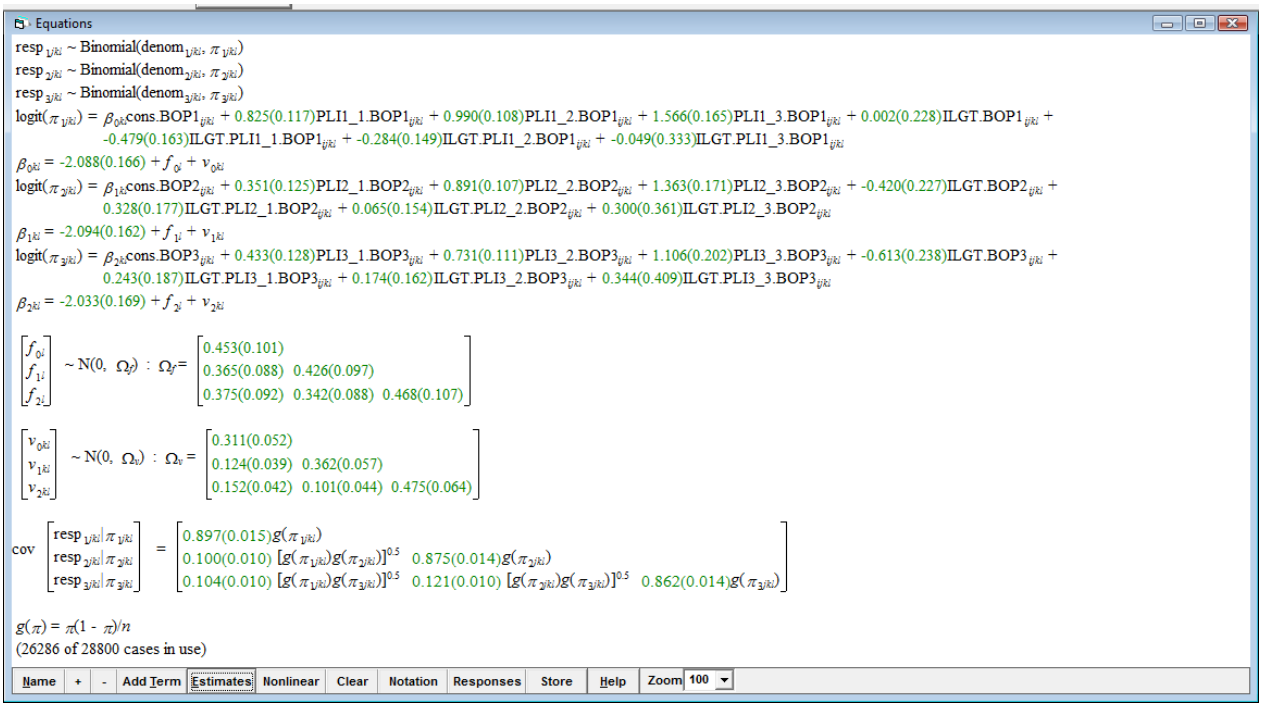
| | Chi squared (3df) | *p* |
|---|---|---|
| PLI_0 | 11.781 | 0.00817 |
| PLI_1 | 5.912 | 0.11597 |
| PLI_2 | 4.474 | 0.21462 |
| PLI_3 | 0.956 | 0.81190 |

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).

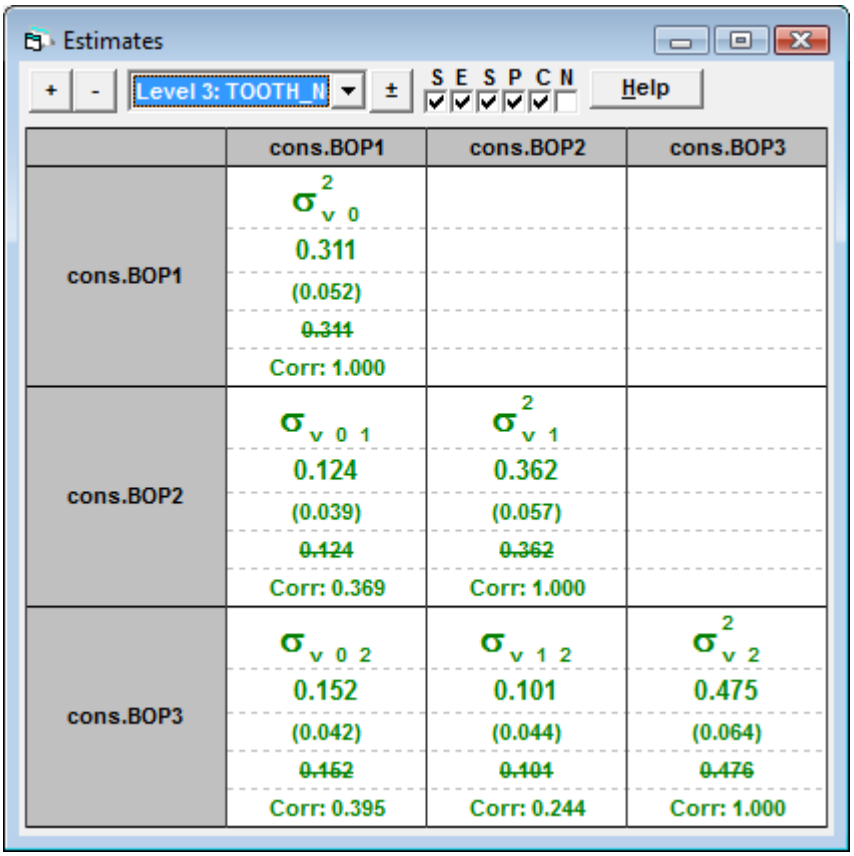
*6.4.4A four-level repeated measures multivariate logistic model*

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 **l(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**.




As can easily been 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 | $\sigma^2_{v\ 0}$ | | |
| | 0.311 | | |
| | (0.052) | | |
| | ~~0.311~~ | | |
| | Corr: 1.000 | | |
| cons.BOP2 | $\sigma_{v\ 0\ 1}$ | $\sigma^2_{v\ 1}$ | |
| | 0.124 | 0.362 | |
| | (0.039) | (0.057) | |
| | ~~0.124~~ | ~~0.362~~ | |
| | Corr: 0.369 | Corr: 1.000 | |
| cons.BOP3 | $\sigma_{v\ 0\ 2}$ | $\sigma_{v\ 1\ 2}$ | $\sigma^2_{v\ 2}$ |
| | 0.152 | 0.101 | 0.475 |
| | (0.042) | (0.044) | (0.064) |
| | ~~0.152~~ | ~~0.101~~ | ~~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.