Mixed Models for Longitudinal Count Data

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Hedeker, D. & Gibbons, R.D. (2006). Longitudinal Data Analysis, chapter 12. Wiley.

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Dependent variable is a count

- number of hospitalizations
- number of service uses
- number of headaches (or some kind of disease symptom)
- number of times that an event occurs

Poisson distribution is often used to model count data

$$\Pr(y \mid \mu) = \frac{\exp(-\mu)\mu^y}{y!} \quad \text{for } y = 0, 1, 2, \ldots$$

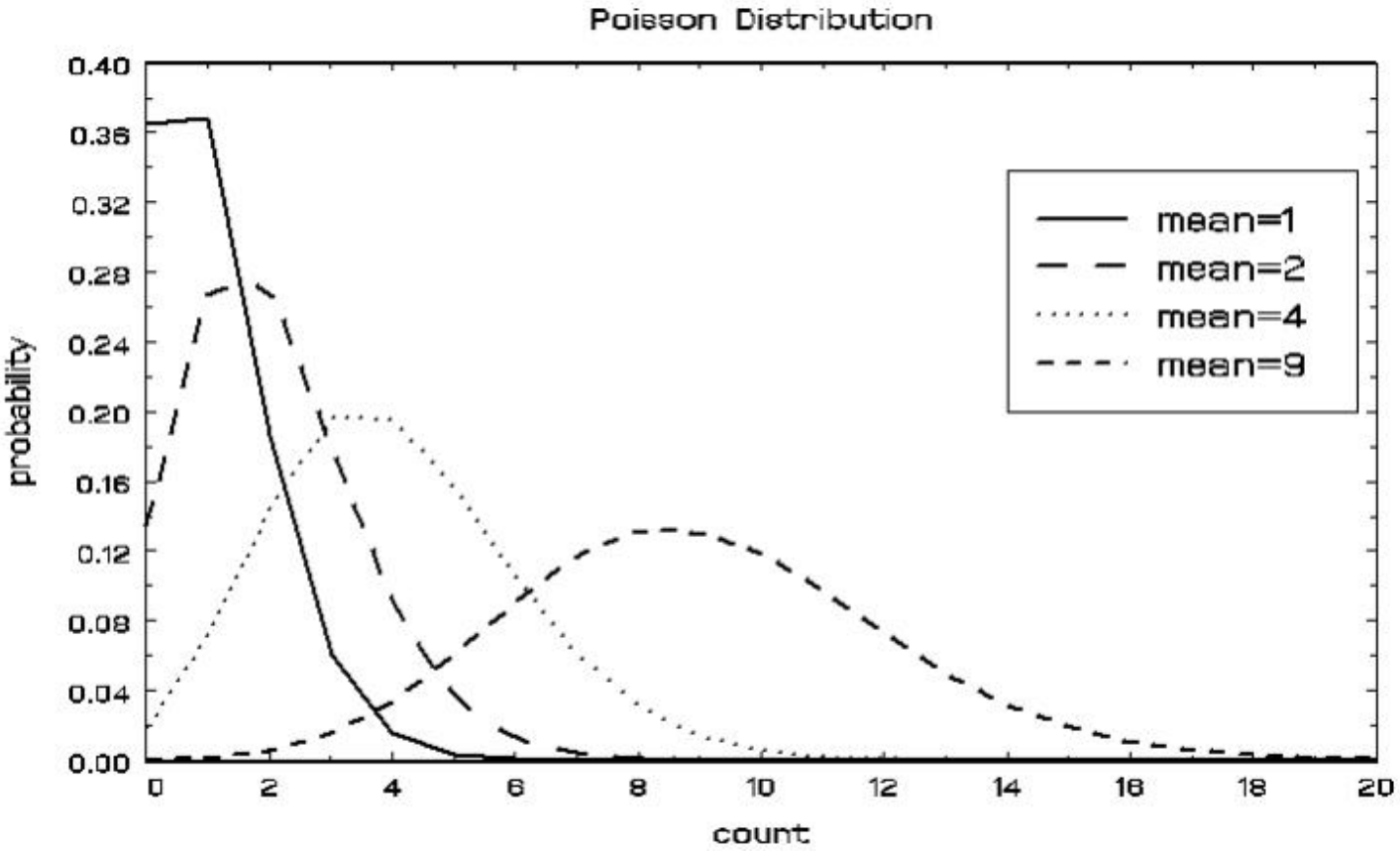
μ is the expected count (per unit of time)

Can't I just analyze as continuous normal?

- count distribution is too skewed to satisfy normality (incorrect test results)
- normal model does not necessarily prevent negative estimated counts

Can't I just dichotomize count (0 vs >0) and analyze using logistic regression?

- loss of information resulting in under-powered tests
- is 1 event really equal to 100 events?



- expected number of counts (per unit of time), strictly positive
- as mean increases, probability of 0s decreases, distribution approximates normal
- mean equals the variance (if variance is greater, then overdispersion)

Reading materials and examples

- Cameron & Trivedi (1998) *Regression analysis of count data*, Cambridge Univ Press
- Long (1997) *Regression models for categorical and limited dependent variables*, Sage
- Elhai, Calhoun, & Ford (2008) Statistical procedures for analyzing mental health services data. *Psychiatry Research, 160*, 129-136.
- Walters (2007) Using Poisson Class Regression To Analyze Count Data in Correctional and Forensic Psychology. *Criminal Justice and Behavior, 34*, 1659-1674.
- Gagnon, Doron-LaMarca, Bell, O'Farrell, & Taft (2008) Poisson regression for modeling count and frequency outcomes in trauma research. *Journal of Traumatic Stress, 21*, 448-454.

- Supermix http://www.ssicentral.com/supermix/downloads.html
  - http://www.ssicentral.com/supermix/examples/Count-offset.html
  - in Supermix (even the free student version), from Help menu, select "Contents," "Examples from SMIX primer," "Count outcomes"

Notation is our friend!

- $i = 1, \ldots, N$ level-2 units (clusters or subjects)
- $j = 1, \ldots, n_i$ level-1 units (subjects or multiple observations)
- y_{ij} is the value of the count outcome, the number of events (y_{ij} can equal $0, 1, \ldots$)
- t_{ij} is the length of time during which the events are recorded
  - can be equal ($t_{ij} = t$): all observations are based on the same period of time, and the number of events within that same time period is of interest
  - can vary (t_{ij}): observations are based on varying periods of time; this should be accounted for when modeling the number of events within the varying time periods

Right-hand side of model

$$\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i$$

- $\boldsymbol{x}_{ij}$ are covariates
  - at level-1, level-2, or cross-level interactions
  - can include polynomials, dummy variables, interactions, ...
- $\boldsymbol{\beta}$ are the regression coefficients for the covariates
- $\boldsymbol{z}_{ij}$ are the random effect variable(s)
  - usually just an intercept for clustered data
  - often an intercept and time for longitudinal data
- $\boldsymbol{\upsilon}_i$ are the random effects $\sim$ N(0, $\boldsymbol{\Sigma}_\upsilon$)
  - how cluster i influences the observations within the cluster
  - how a subject starts and progresses across time

Mixed-effects Poisson Regression Model

The mixed-effects Poisson regression model indicates the expected number of counts in t_{ij} as:

$$E(y_{ij}) = \mu_{ij} = t_{ij} \exp\left[\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i\right]$$

or

$$\log(\mu_{ij}) = \log(t_{ij}) + \left[\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i\right]$$

$$\log(\mu_{ij}) - \log(t_{ij}) = \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i$$

$$\log\left[\mu_{ij}/t_{ij}\right] = \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i$$

- link function for Poisson regression is the log link
- t_{ij} is sometimes called an offset variable
- $\exp\beta$ = incidence or event rate ratio

Simplest Poisson Regression example

(no random effects, no offset, dichotomous regressor)

Data and description: http:\\www.ats.ucla.edu\stat\sas\dae\poissonreg.htm

- School attendance data on 316 high school juniors
- Response variable is days absent (`daysabs`, range is 0 to 45)
- `male` is an indicator of student gender (0=F, 1=M)
  - `daysabs` mean for females = 6.6975
  - `daysabs` mean for males = 4.4877 (M to F ratio = .7281)
- $E(\texttt{daysabs}_i) = \mu_i = \exp(\beta_0 + \beta_1 \texttt{male}_i)$

$\exp \beta_0 =$ mean for females $= 6.6975$ $(\hat{\beta}_0 = \log 6.6975 = 1.9017)$

$\exp(\beta_0 + \beta_1) = \exp(\beta_0) \times \exp(\beta_1) =$ mean for males $= 4.4877$

$\exp(\hat{\beta}_1) = 4.4877/\exp(\hat{\beta}_0) = 4.4877/6.6975 = .7281$ (M to F ratio)

$(\hat{\beta}_1 = \log .7281 = -.3173)$

Longitudinal example - Aspartame and headaches

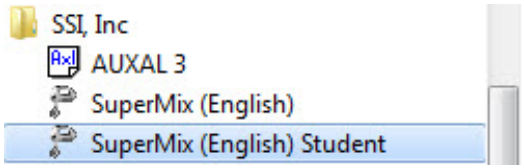
- data from McKnight and Van Den Eeden (1993) *Statistics in Medicine*, also Van Den Eeden *et al.*, (1994) *Neurology*
- number of headaches in a two treatment, multiple period crossover trial
- number of headaches per week was repeatedly measured for 27 subjects
- Following a seven-day placebo run-in period, subjects received either aspartame or placebo in four seven-day treatment periods according to a double-blind crossover treatment design
- Each treatment period was separated by a washout day

Table 4. The number of headaches, treatment days, and belief about aspartame effects by subject and treatment period

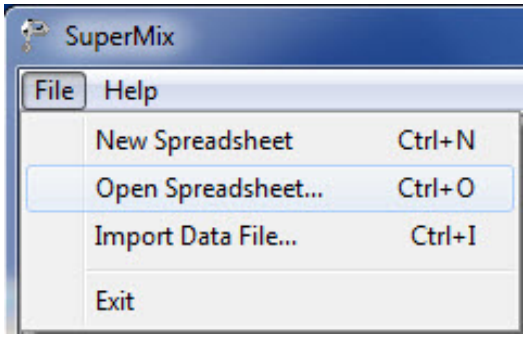
Treatment order*	ID	Run-in		Treatment period†								Belief‡
				1		2		3		4		
		HA	Days	HA	Days	HA	Days	HA	Days	HA	Days	
APAP	2	0	7	5	7	2	7	—	—	—	—	V
	5	3	7	0	7	2	7	0	7	0	7	N
	13	7	7	7	7	7	7	6	7	7	7	N
	16	1	7	3	7	1	7	—	—	—	—	V
	19	0	7	1	7	1	7	0	7	1	7	V
	23	7	7	2	7	3	7	3	7	2	7	S
	25	1	7	6	7	1	7	7	7	0	7	V
APPA	1	3	7	0	7	3	7	1	7	0	7	N
	3	2	7	2	7	3	7	2	7	2	7	V
	6	1	7	1	7	0	7	3	7	1	7	S
	9	2	7	2	7	0	7	1	5	—	—	V
	17	4	7	1	1	—	—	—	—	—	—	S
	18	0	7	1	7	1	7	1	7	0	7	V
	21	1	7	2	7	3	7	3	7	6	7	V
	22	2	7	1	7	0	7	0	7	1	7	S
PAPA	7	1	7	1	7	4	7	2	7	3	7	N
	10	0	7	0	7	0	7	0	7	0	7	S
	11	0	7	3	7	1	7	0	7	1	3	S
	14	2	7	2	7	1	7	0	7	2	7	N
	24	1	7	0	7	1	7	0	7	2	7	V
	27	3	7	3	7	3	7	0	7	2	4	S
PAAP	4	0	7	0	7	0	7	0	7	0	7	V
	8	1	7	1	7	0	7	1	7	1	2	S
	12	0	7	0	7	5	7	0	7	0	7	S
	15	0	7	3	7	2	7	1	7	1	7	S
	20	1	7	6	7	1	2	—	—	—	—	V
	26	0	7	1	7	—	—	—	—	—	—	S

* A = aspartame; P = placebo. Run-in period used placebo capsules.
† HA = number of days on which subject reported a headache; Days = number of days subject participated during that period.
‡ Belief about how strongly subject felt aspartame caused headaches was asked prior to the start of the study. V = very sure; S = somewhat sure; N = not very sure or do not know.

- Under SSI, Inc > "SuperMix (English)" or 'SuperMix (English) Student"



- Under "File" click on "Open Spreadsheet"



- Open C:\SuperMixEn Examples\Primer\Count\aspart.ss3
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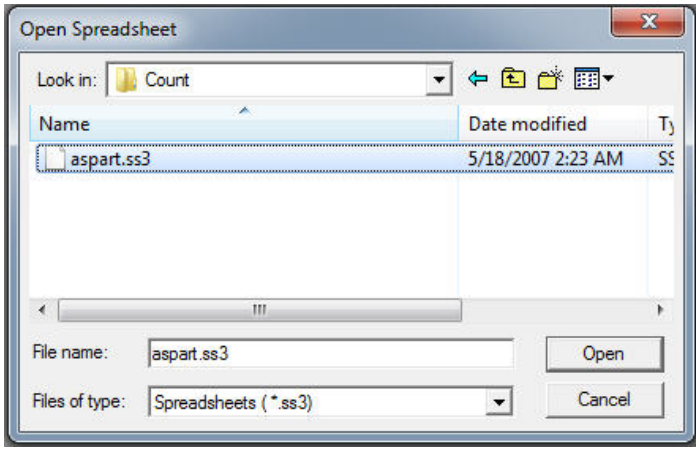

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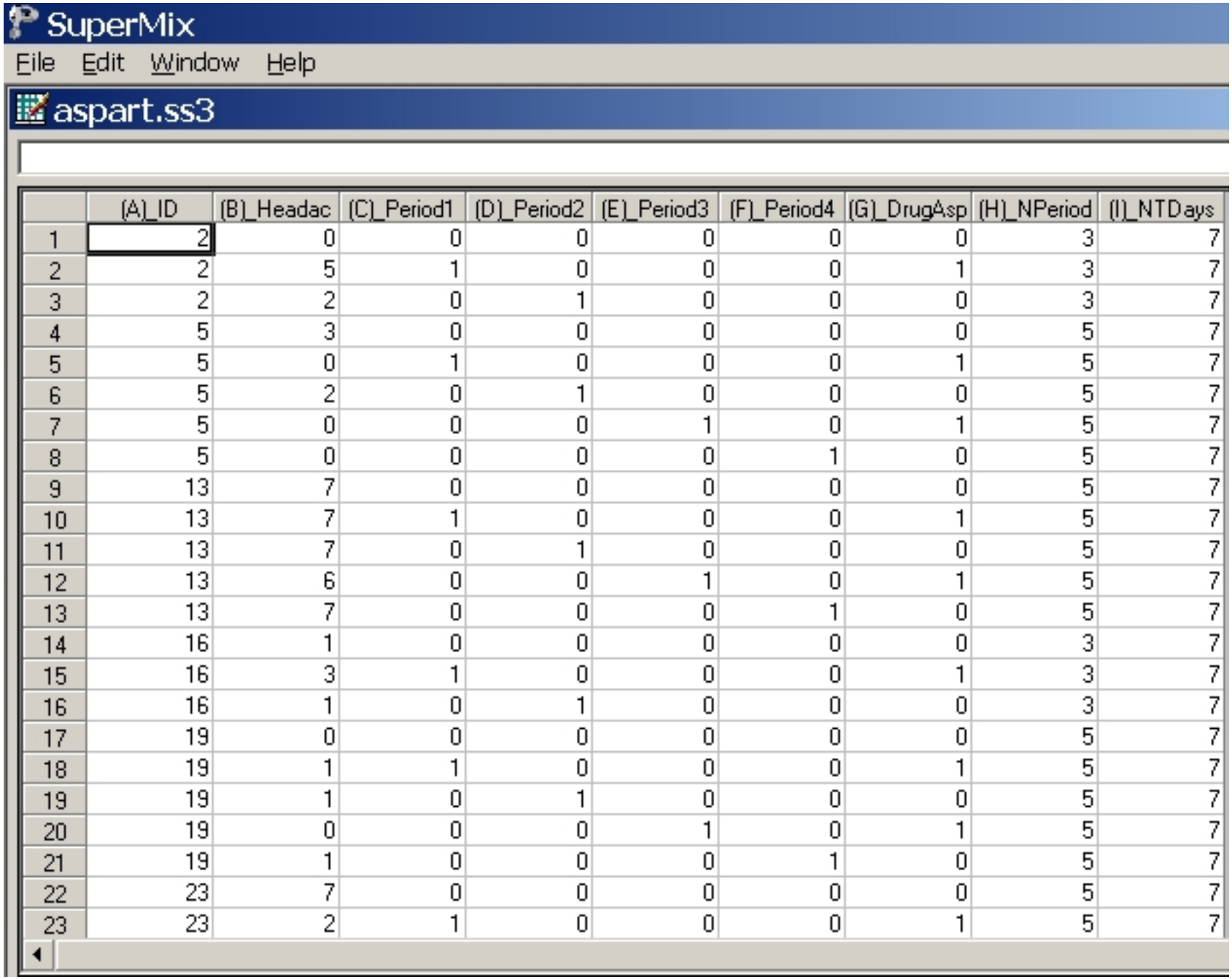
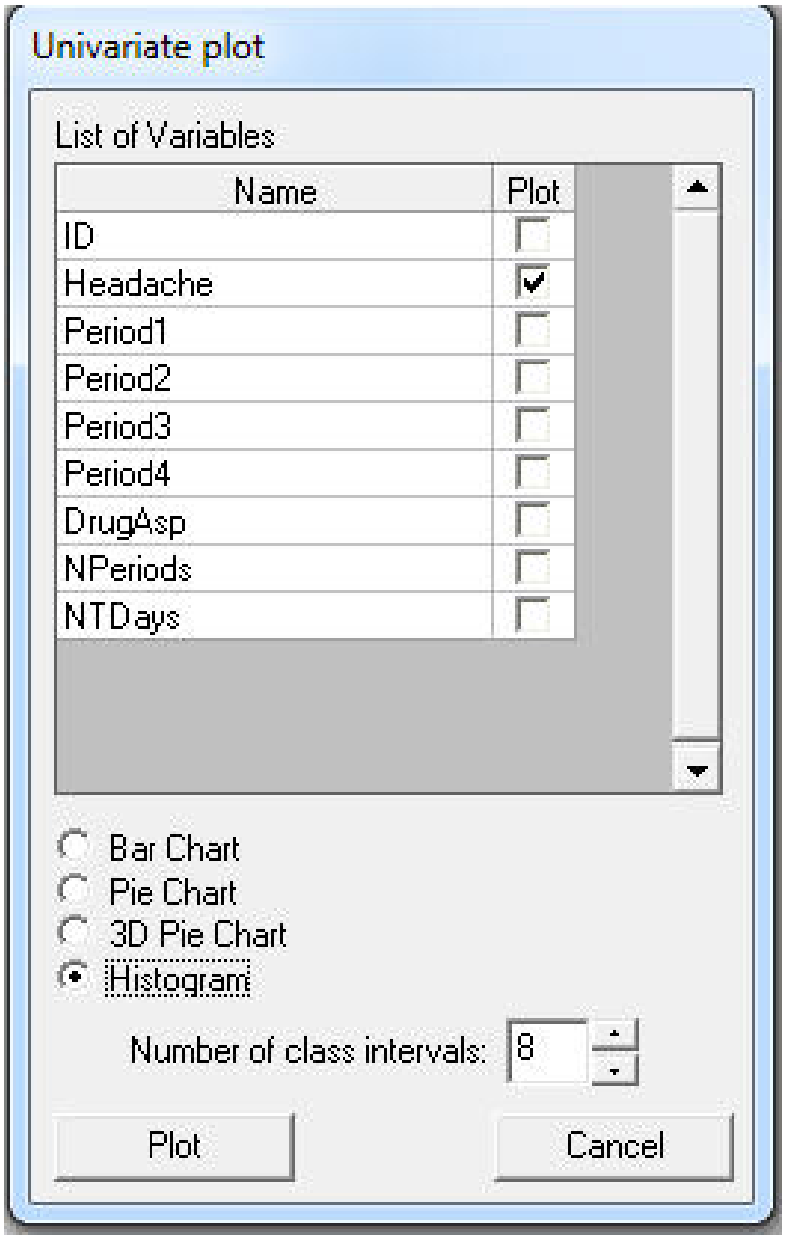
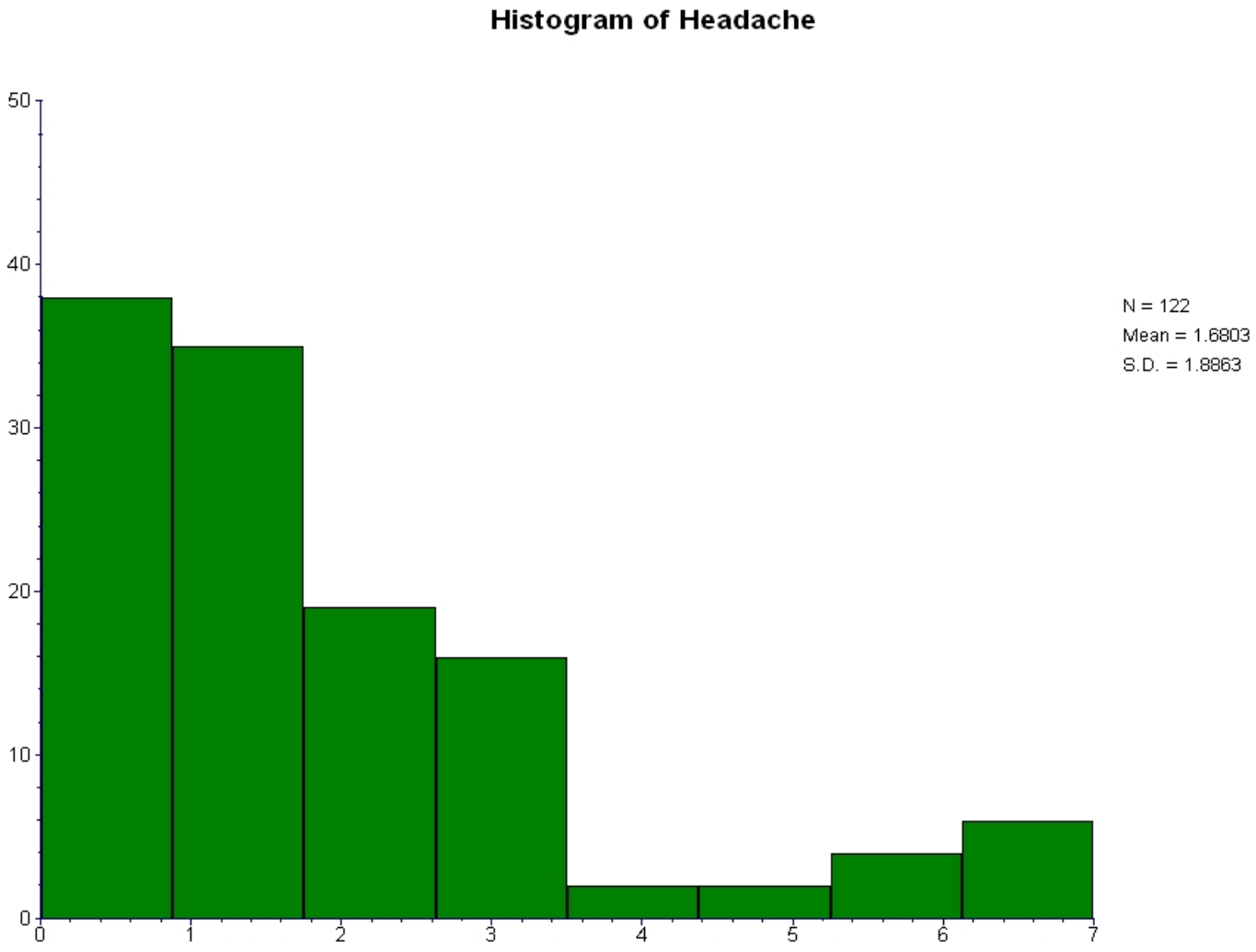


	(A)_ID	(B)_Headac	(C)_Period1	(D)_Period2	(E)_Period3	(F)_Period4	(G)_DrugAsp	(H)_NPeriod	(I)_NTDays
1	2	0	0	0	0	0	0	3	7
2	2	5	1	0	0	0	1	3	7
3	2	2	0	1	0	0	0	3	7
4	5	3	0	0	0	0	0	5	7
5	5	0	1	0	0	0	1	5	7
6	5	2	0	1	0	0	0	5	7
7	5	0	0	0	1	0	1	5	7
8	5	0	0	0	0	1	0	5	7
9	13	7	0	0	0	0	0	5	7
10	13	7	1	0	0	0	1	5	7
11	13	7	0	1	0	0	0	5	7
12	13	6	0	0	1	0	1	5	7
13	13	7	0	0	0	1	0	5	7
14	16	1	0	0	0	0	0	3	7
15	16	3	1	0	0	0	1	3	7
16	16	1	0	1	0	0	0	3	7
17	19	0	0	0	0	0	0	5	7
18	19	1	1	0	0	0	1	5	7
19	19	1	0	1	0	0	0	5	7
20	19	0	0	0	1	0	1	5	7
21	19	1	0	0	0	1	0	5	7
22	23	7	0	0	0	0	0	5	7
23	23	2	1	0	0	0	1	5	7

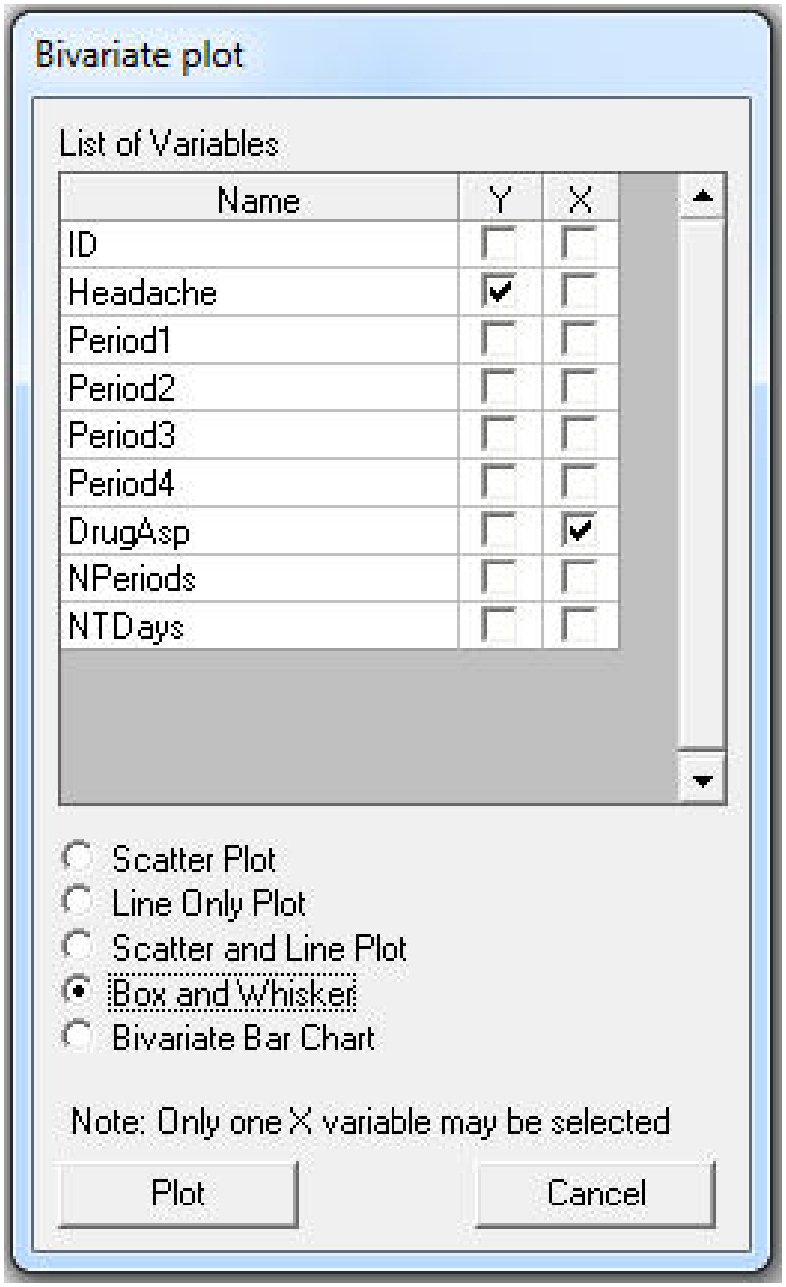
- ID = patient ID (27 patients in total)
- HeadAche = number of headaches during the week (0 to 7)
- Period1 = period 1 indicator (1 = first tx period, else 0)
- Period2 = period 2 indicator (1 = second tx period, else 0)
- Period3 = period 3 indicator (1 = third tx period, else 0)
- Period4 = period 4 indicator (1 = fourth tx period, else 0)
- DrugAsp = period-specific drug (0 = placebo, 1 = aspartame)
- Nperiods = number of periods person was observed (2 to 5)
- NTDays = number of treatment days in the period (1 to 7)

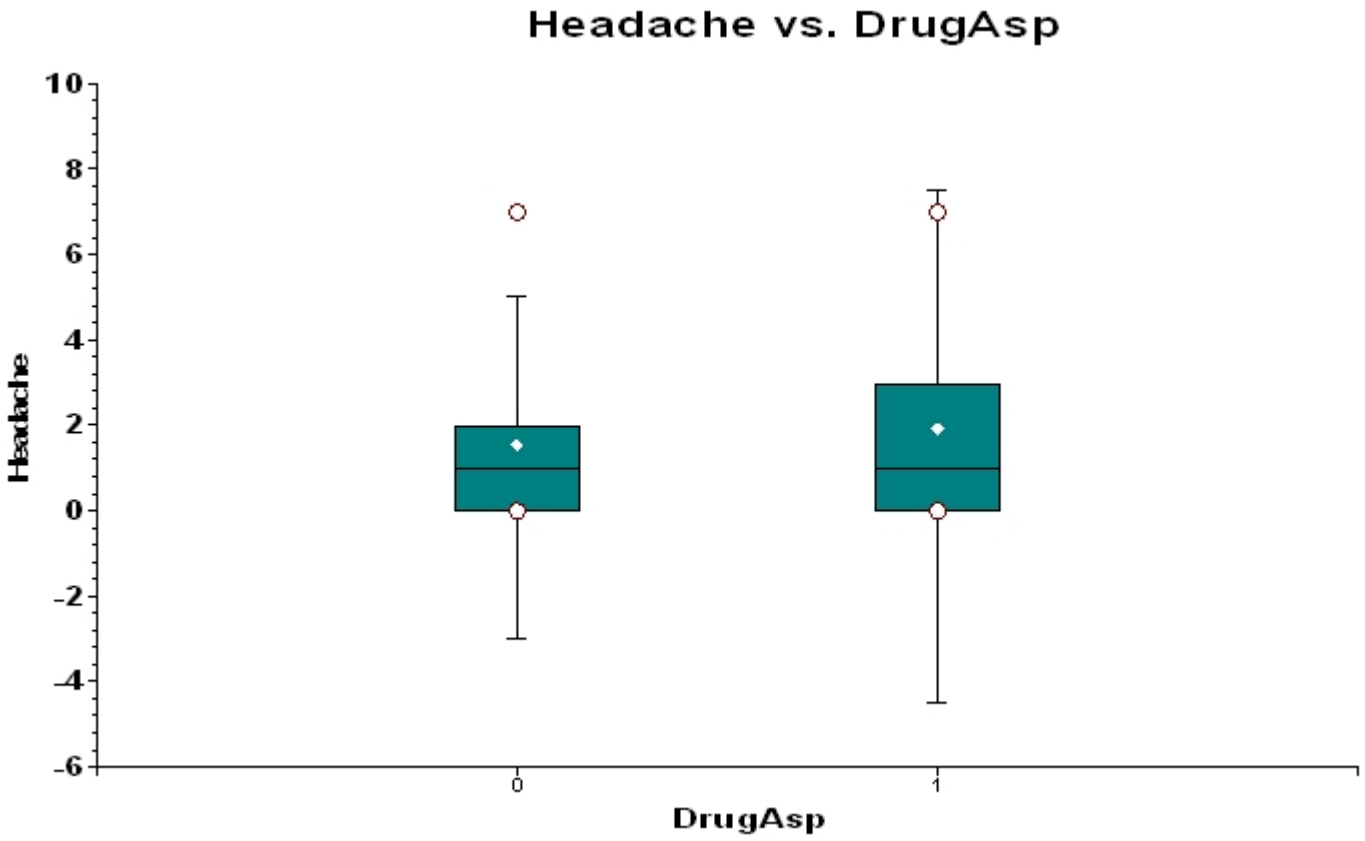
Select "File" > "Data-based Graphs" > "Univariate"




Histogram of Headache
50
40
30
20
10
0
0
1
2
3
4
5
6
7
N = 122
Mean = 1.6803
S.D. = 1.8863

Select "File" > "Data-based Graphs" > "Bivariate"

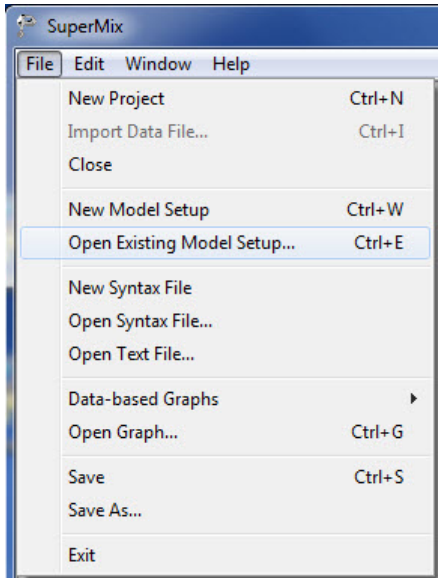




Plc mean $= 1.5333$ Asp mean $= 1.9149$

$\Rightarrow$ ratio $= 1.25$, $\log 1.25 = .223$

Under "File" click on "Open Existing Model Setup"



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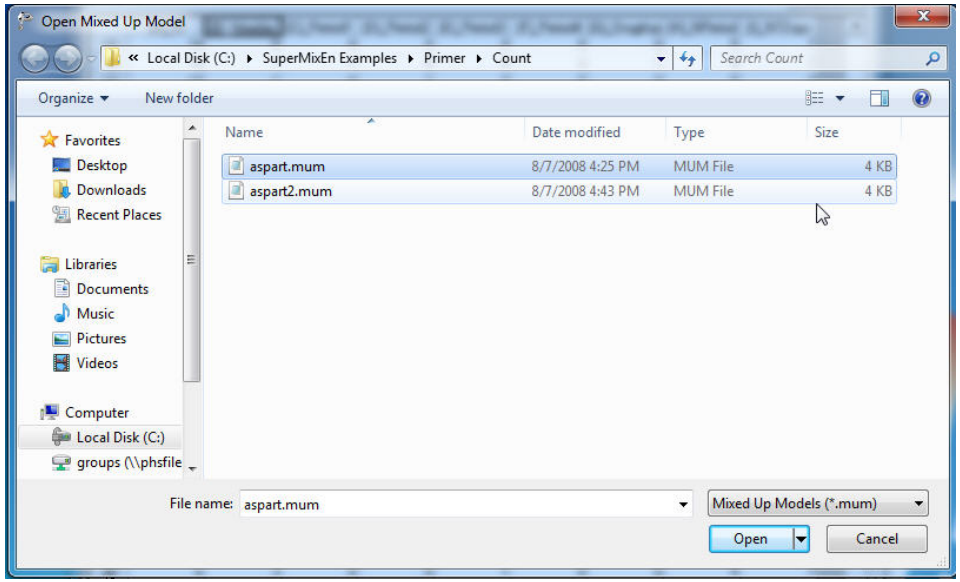
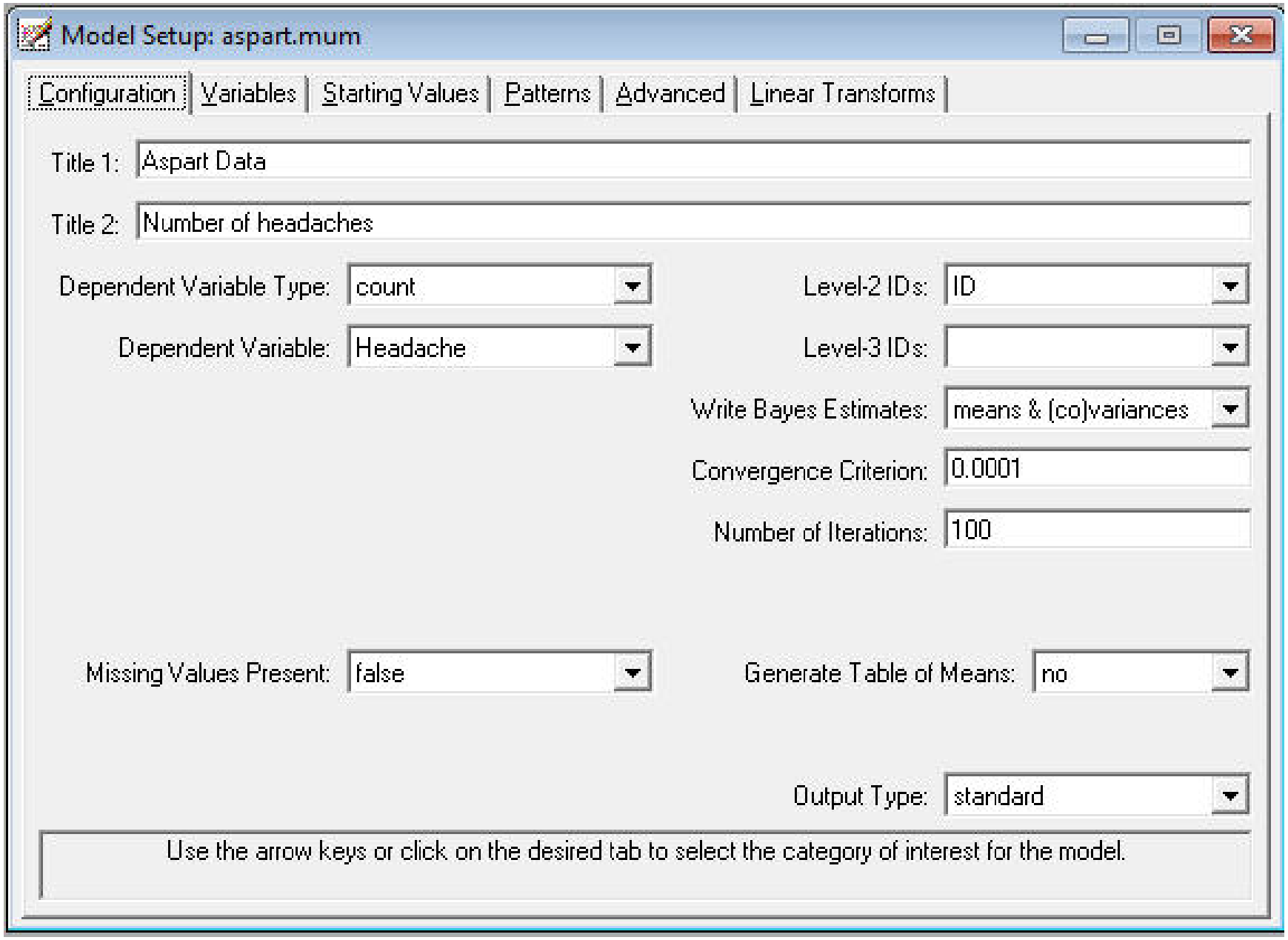
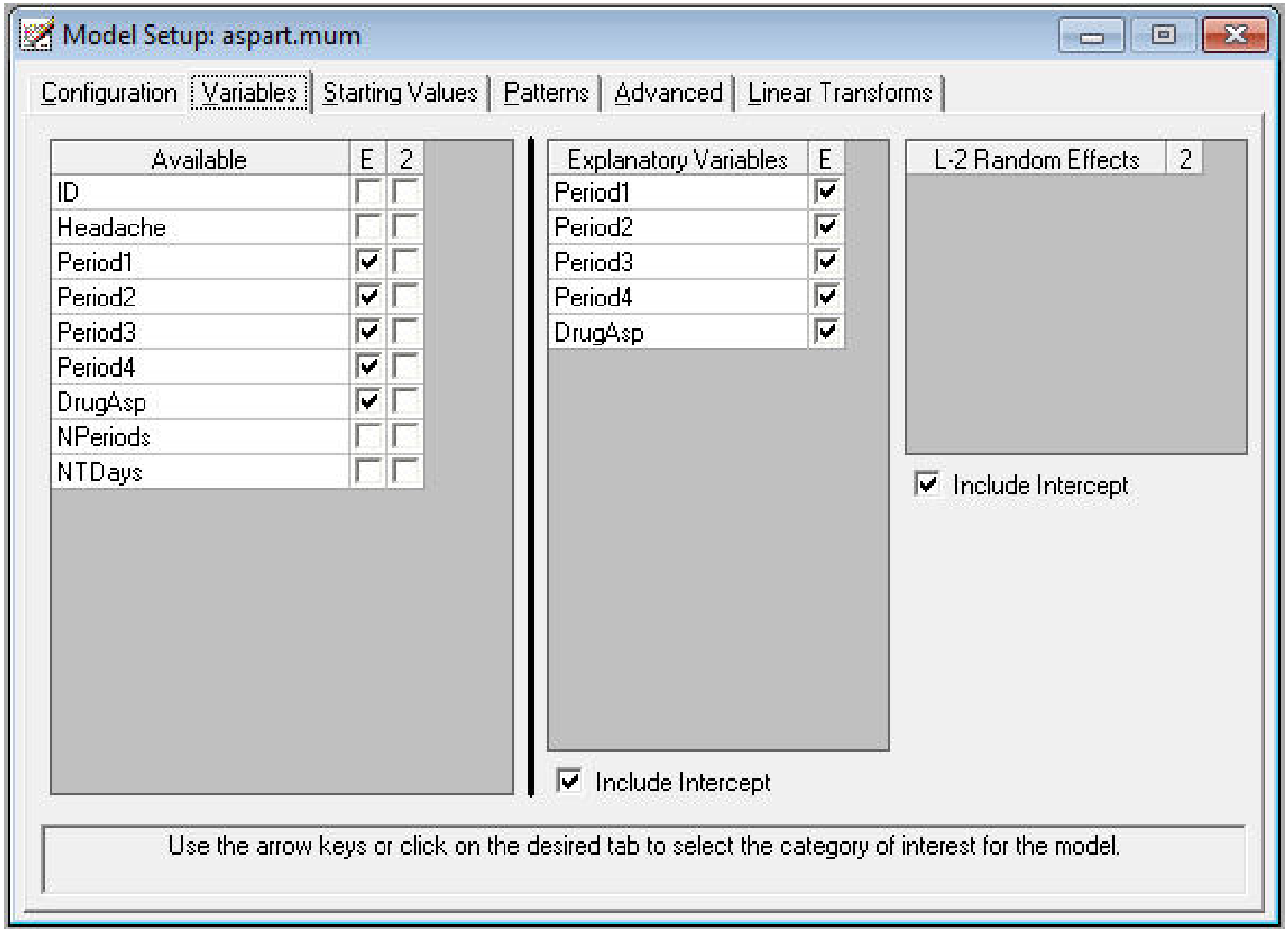
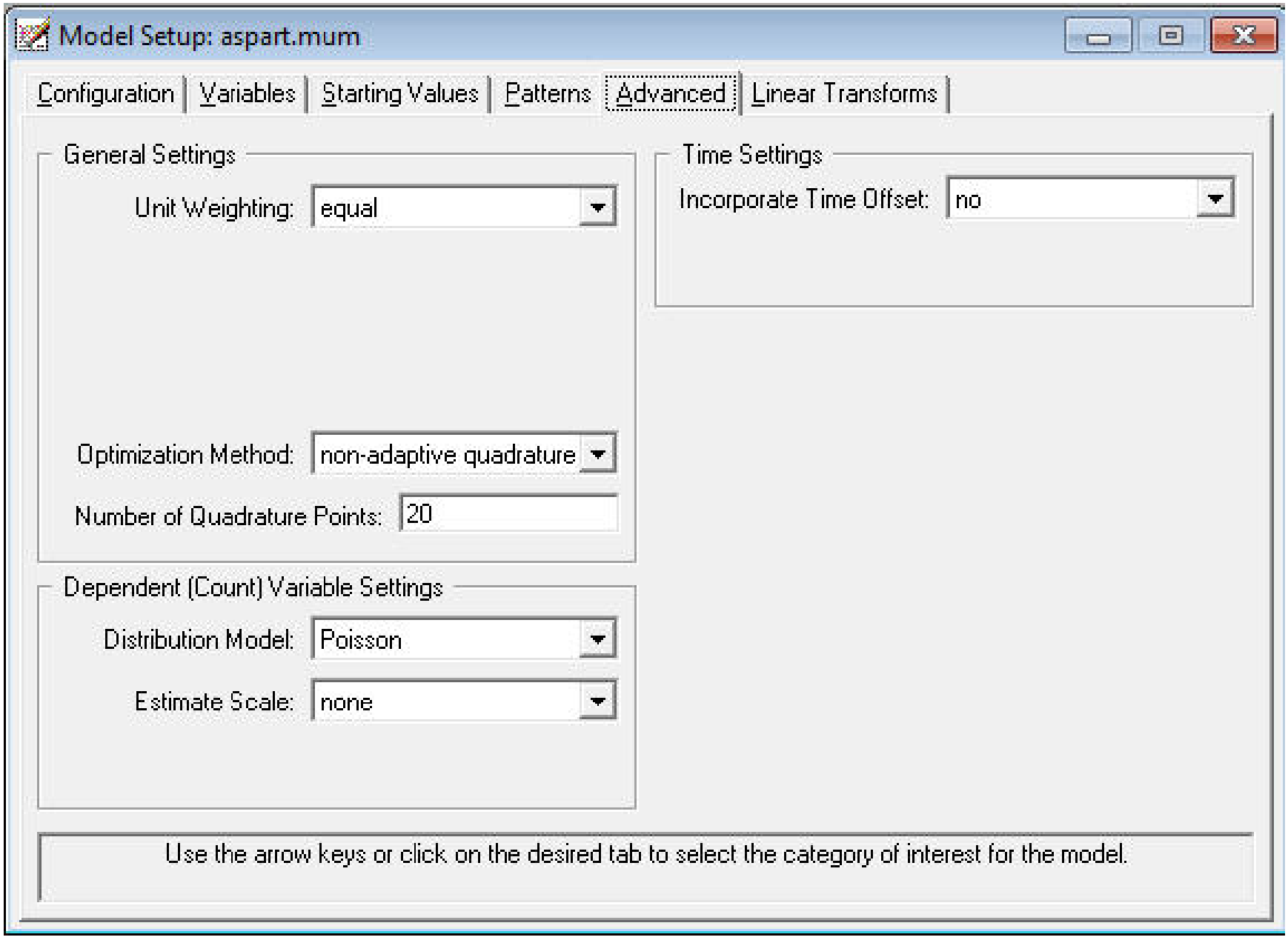
(or C:\SuperMixEn Student Examples\Primer\Count\aspart.mum)




Model Setup: aspart.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1:
Aspart Data
Title 2:
Number of headaches
Dependent Variable Type:
count
Dependent Variable:
Headache
Level-2 IDs:
ID
Level-3 IDs:
Write Bayes Estimates:
means & (co)variances
Convergence Criterion:
0.0001
Number of Iterations:
100
Missing Values Present:
false
Generate Table of Means:
no
Output Type:
standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.


Model Setup: aspart.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
Headache
Period1
Period2
Period3
Period4
DrugAsp
NPeriods
NTDays
Explanatory Variables
E
Period1
Period2
Period3
Period4
DrugAsp
Include Intercept
L-2 Random Effects
2
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


Model Setup: aspart.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
non-adaptive quadrature
Number of Quadrature Points:
20
Dependent (Count) Variable Settings
Distribution Model:
Poisson
Estimate Scale:
none
Time Settings
Incorporate Time Offset:
no
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SuperMix - [aspart.out]

File Analysis Window Help

```
o=====================o
| Aspart Data         |
| Number of headaches |
o=====================o


            Model and Data Descriptions

   Sampling Distribution                    = Poisson
   Link Function                            = Log
   Number of Level-2 Units                    27
   Number of Level-1 Units                    122
   Number of Level-1 Units per Level-2 Unit =
     3     5     5     3     5     5     5     5     5     5     4     2
     5     5     5     5     5     5     5     5     5     5     5     5
     5     3     2



    o=========================================================o
    | Descriptive statistics for all the variables in the model |
    o=========================================================o
                                                          Standard
   Variable             Minimum     Maximum        Mean   Deviation
   --------             -------     -------        ----   ---------
   Headache              0.0000      7.0000      1.6803      1.8863
   intercept             1.0000      1.0000      1.0000      0.0000
   Period1               0.0000      1.0000      0.2213      0.4168
   Period2               0.0000      1.0000      0.2049      0.4053
   Period3               0.0000      1.0000      0.1803      0.3860
   Period4               0.0000      1.0000      0.1721      0.3791
   DrugAsp               0.0000      1.0000      0.3852      0.4887



    o=================================================o
    | Results for the model without any random effects |
    o=================================================o

                     Goodness of fit statistics

   Statistic                                 Value          DF          Ratio
   ---------                                 -----          --          -----
   Likelihood Ratio Chi-square             243.8257         116         2.1019
   Pearson Chi-square                      253.8934         116         2.1887
```

Save As... Close

SuperMix - [aspart.out]

File Analysis Window Help

```
 o=============================================o
 | Optimization Method: Non-Adaptive Quadrature |
 o=============================================o

Number of quadrature points =              20
Number of free parameters =                 7
Number of iterations used =                 4

-2lnL (deviance statistic) =        406.34905
Akaike Information Criterion        420.34905
Schwarz Criterion                   439.97720
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intercept	0.2572	0.2024	1.2705	0.2039
Period1	0.0807	0.2349	0.3434	0.7313
Period2	0.0345	0.2237	0.1542	0.8775
Period3	-0.2267	0.2545	-0.8909	0.3730
Period4	-0.1592	0.2529	-0.6295	0.5290
DrugAsp	0.2151	0.1638	1.3129	0.1892

Event Rate Ratio and 95% Event Rate Confidence Intervals

Parameter	Estimate	Event Rate	Bounds Lower	Bounds Upper
intercept	0.2572	1.2933	0.8697	1.9231
Period1	0.0807	1.0840	0.6840	1.7180
Period2	0.0345	1.0351	0.6677	1.6046
Period3	-0.2267	0.7971	0.4841	1.3127
Period4	-0.1592	0.8528	0.5195	1.4000
DrugAsp	0.2151	1.2400	0.8994	1.7096

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.4290	0.1715	2.5024	0.0123

Save As... Close

Interpretation of Drug Effect

- $\hat{\beta}_{\text{DrugAsp}} = .2151$
- $\exp(\hat{\beta}_{\text{DrugAsp}}) = 1.24$
- Aspartame increases the expected number of headaches (per week) by 24%, controlling for the period and random subject effects
- However, this is NOT a significant effect (p-value = .19)
- For Poisson random-intercept model, this is also the marginal effect (except for intercept β_0, conditional β = marginal β)

  Aspartame increases the expected number of headaches by 24% controlling for the period effects

Observed means: Headaches across time by drug

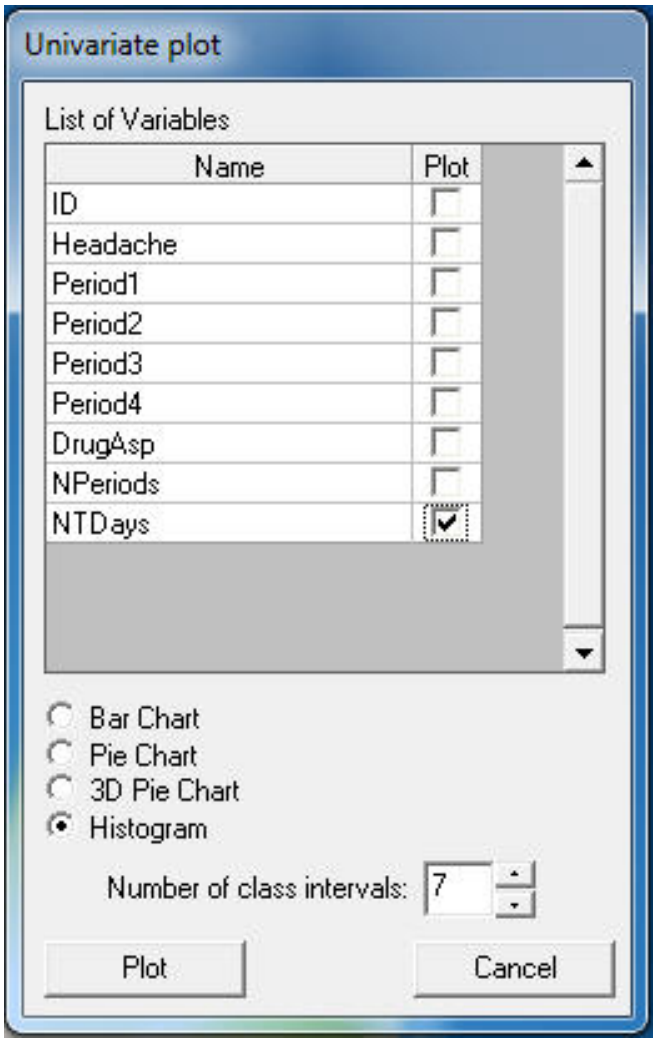
drug	baseline	period 1	period 2	period 3	period 4
placebo	1.593	1.667	1.929	1.000	1.333
	(n=27)	(n=12)	(n=14)	(n=13)	(n=9)
aspartame		2.267	1.636	2.000	1.667
		(n=15)	(n=11)	(n=9)	(n=12)
	rate ratio	1.36	0.85	2.00	1.25

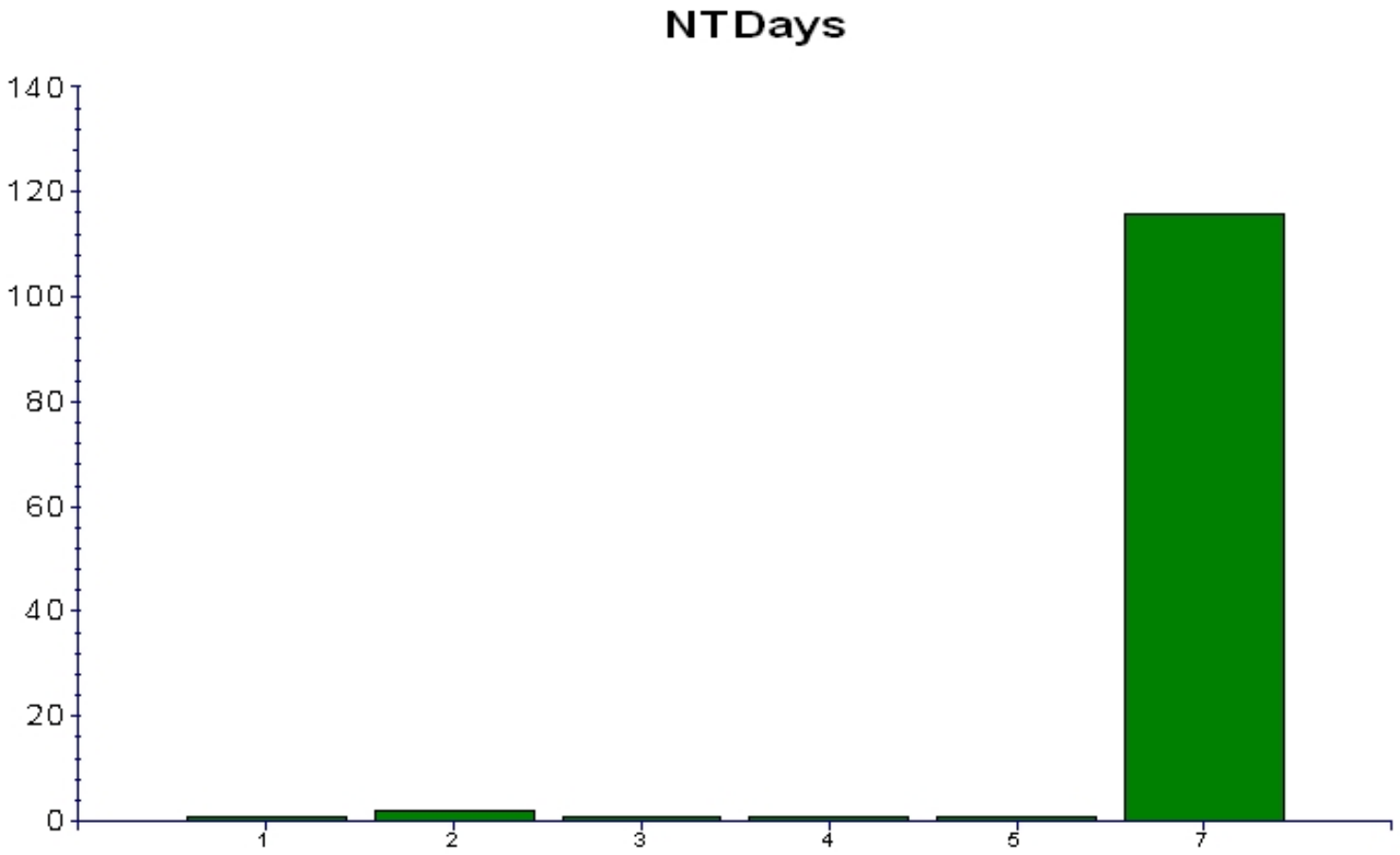
Estimated means $= \exp(\boldsymbol{x}'\hat{\boldsymbol{\beta}} + \hat{\sigma}_v^2/2)$

drug	baseline	period 1	period 2	period 3	period 4
placebo	1.603	1.737	1.659	1.278	1.367
aspartame		2.154	2.057	1.584	1.695
	rate ratio	1.24	1.24	1.24	1.24

Prior analysis assumed that all subjects were assessed for 7 days for each period. Is this true? Does it matter?

Select "File" > "Data-based Graphs" > "Univariate"




NTDays
140
120
100
80
60
40
20
0
1
2
3
4
5
7

Observations with less than 7 days in a period

Period	ID	Headaches	NTDays	DrugAsp
1	17	1	1	1
2	20	1	2	1
3	9	1	5	0
4	11	1	3	1
4	27	2	4	1
4	8	1	2	0

Question

Including this information about NTDays in the model, will the drug effect be greater or smaller? or the same?

Hint: what did the prior analysis assume about NTDays?

Mixed-effects Poisson Regression Models

The mixed-effects Poisson regression model without an offest variable:

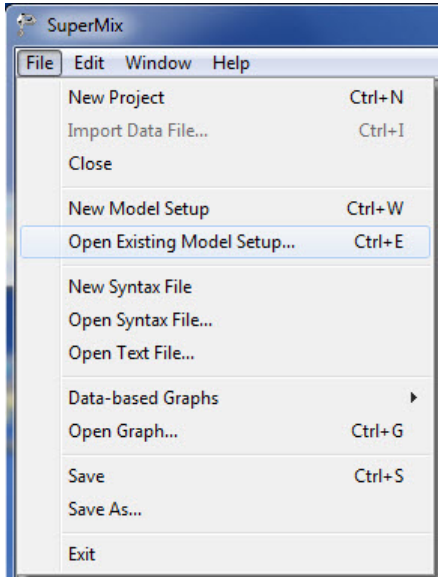
$$\log(\mu_{ij}) = \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i$$

The mixed-effects Poisson regression model WITH an offest variable t_{ij}:

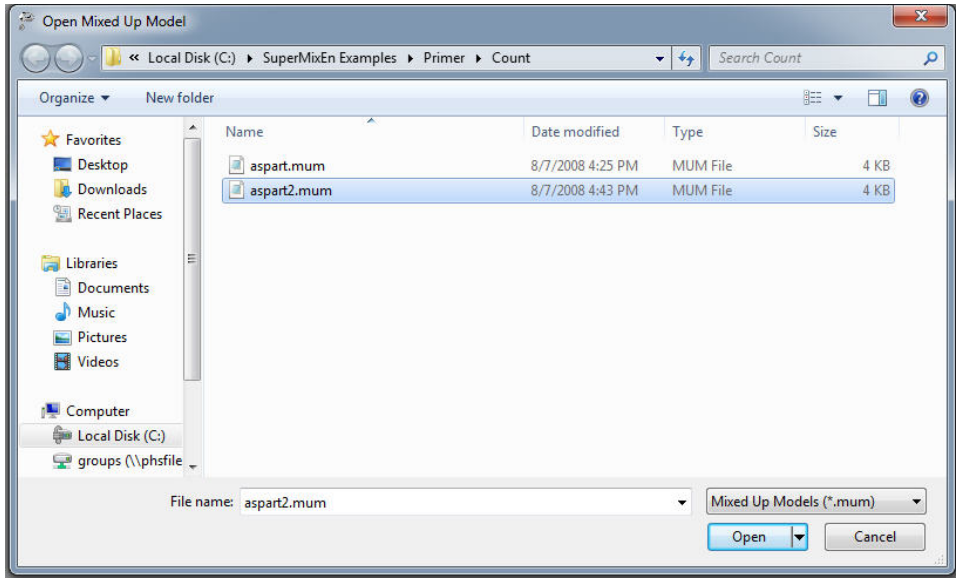
$$\log(\mu_{ij}) = \log(t_{ij}) + \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{\upsilon}_i$$

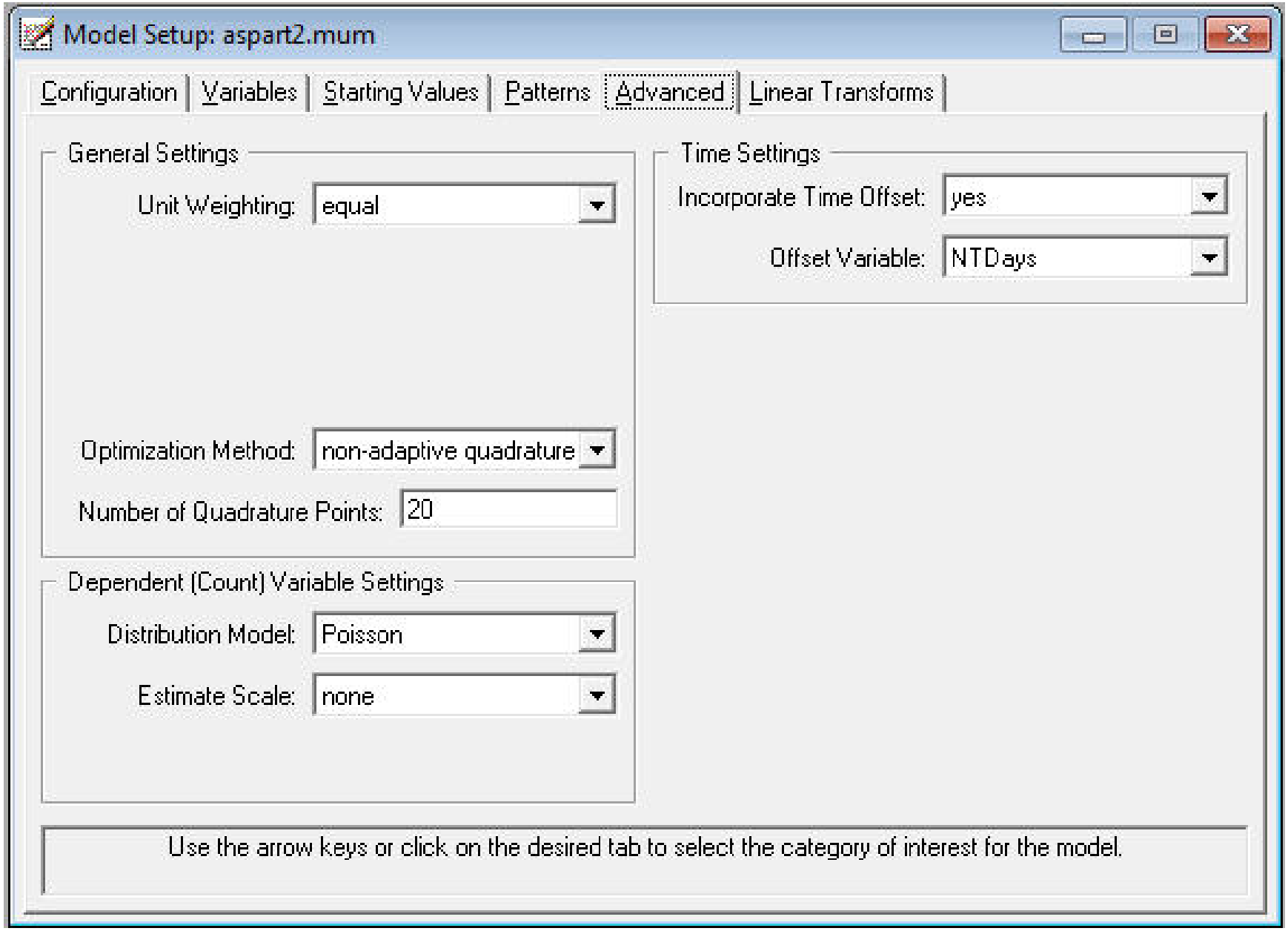
- the (log of the) offset is like a regressor with a slope=1
- for Supermix, identify t_{ij} as the offset variable (it will take the log of this variable internally)

Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Primer\Count\aspart2.mum
(or C:\SuperMixEn Student Examples\Primer\Count\aspart2.mum)




Model Setup: aspart2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
non-adaptive quadrature
Number of Quadrature Points:
20
Dependent (Count) Variable Settings
Distribution Model:
Poisson
Estimate Scale:
none
Time Settings
Incorporate Time Offset:
yes
Offset Variable:
NTDays
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SuperMix - [aspart2.out]

File Analysis Window Help

```
 o=============================================o
 | Optimization Method: Non-Adaptive Quadrature |
 o=============================================o

Number of quadrature points =              20
Number of free parameters =                 7
Number of iterations used =                 4

-2lnL (deviance statistic) =        404.83040
Akaike Information Criterion        418.83040
Schwarz Criterion                   438.45855


                  Estimated regression weights

                                      Standard
Parameter             Estimate        Error       z Value     P Value
---------             --------        --------    -------     -------
intercept              -1.7178          0.2037    -8.4332      0.0000
Period1                 0.0999          0.2357     0.4240      0.6716
Period2                 0.0880          0.2249     0.3911      0.6958
Period3                -0.2120          0.2567    -0.8260      0.4088
Period4                -0.0789          0.2544    -0.3102      0.7564
DrugAsp                 0.2797          0.1641     1.7043      0.0883


  Event Rate Ratio and 95% Event Rate Confidence Intervals

                                                      Bounds
Parameter             Estimate        Event Rate      Lower       Upper
---------             --------        ----------      -----       -----
intercept              -1.7178            0.1795     0.1204      0.2675
Period1                 0.0999            1.1051     0.6962      1.7542
Period2                 0.0880            1.0919     0.7026      1.6970
Period3                -0.2120            0.8090     0.4892      1.3378
Period4                -0.0789            0.9241     0.5613      1.5215
DrugAsp                 0.2797            1.3227     0.9589      1.8246


              Estimated level 2 variances and covariances

                                        Standard
Parameter                   Estimate    Error       z Value   P Value
---------                   --------    --------    -------   -------
intercept/intercept           0.4805      0.1912     2.5129    0.0120
```

Save As... Close

Interpretation of Drug Effect

- $\hat{\beta}_{\text{DrugAsp}} = .2797$
- $\exp(\hat{\beta}_{\text{DrugAsp}}) = 1.32$
- Aspartame increases the expected rate of headaches (# of headaches per day) by 32%, controlling for the period and random subject effects
- 2-tailed non-significant (p-value = .09), but significant by a 1-tailed test (p-value = .09/2 = .045)
- For Poisson random-intercept model, this is also the marginal effect (except for intercept β_0, conditional β = marginal β)

  Aspartame increases the expected rate of headaches by 32% controlling for the period effects

Observed means: Headaches/Day across time by drug

drug	baseline	period 1	period 2	period 3	period 4
placebo	.228	.238	.276	.147	.230
	(n=27)	(n=12)	(n=14)	(n=13)	(n=9)
aspartame		.381	.266	.286	.272
		(n=15)	(n=11)	(n=9)	(n=12)
	rate ratio	1.60	0.96	1.95	1.18

$$\textit{Estimated means} = \exp(\boldsymbol{x}'\hat{\boldsymbol{\beta}} + \hat{\sigma}_v^2/2)$$

drug	baseline	period 1	period 2	period 3	period 4
placebo	.228	.252	.249	.185	.211
aspartame		.334	.330	.244	.279
	rate ratio	1.32	1.32	1.32	1.32

Empirical Bayes estimates of random effects

$$\log(\mu_{ij}) = \log(t_{ij}) + \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \upsilon_i \qquad \text{where } \upsilon_i \sim N(0, \sigma^2_\upsilon)$$

- Random effects υ_i are also estimated
- can be of interest to indicate how particular subjects are doing
- can be used to rank or compare subjects, or indicate unusual subjects
- For a list: "Analysis" > "View level-2 Bayes results"
  (also saved as a file with .ba2 extension)
- or to graph them:
  "File" > "Model-based Graphs" > "Confidence Intervals"

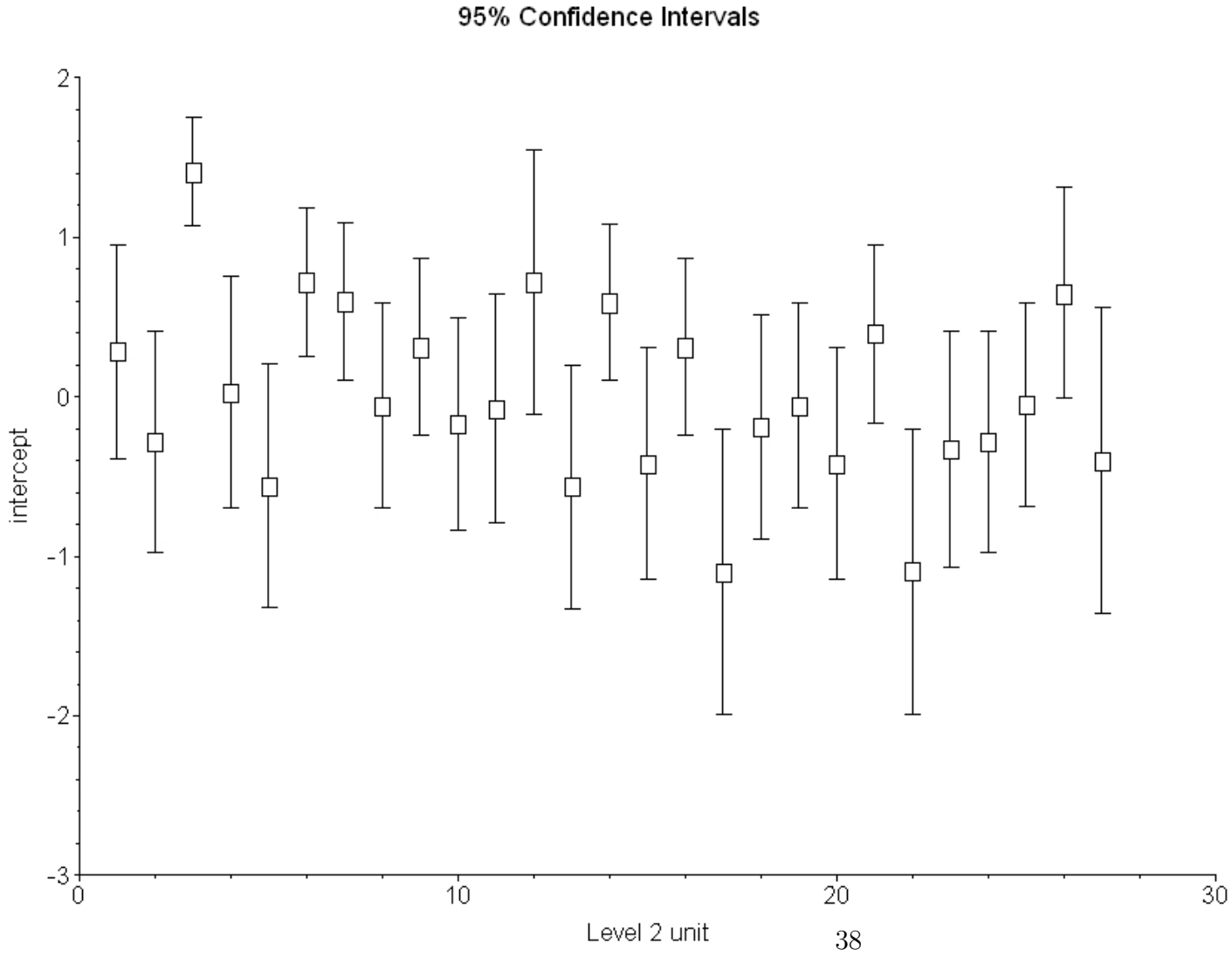
SuperMix - [aspart2.ba2]

File Analysis Window Help

2.00	1	0.2820055	0.1157325	intercept
5.00	1	-0.2815830	0.1261306	intercept
13.00	1	1.4144061	0.0302535	intercept
16.00	1	0.0288379	0.1385211	intercept
19.00	1	-0.5588343	0.1523994	intercept
23.00	1	0.7194387	0.0566844	intercept
25.00	1	0.6001086	0.0628373	intercept
1.00	1	-0.0549907	0.1062628	intercept
3.00	1	0.3121607	0.0795425	intercept
6.00	1	-0.1657291	0.1154253	intercept
9.00	1	-0.0747851	0.1341228	intercept
17.00	1	0.7199570	0.1773089	intercept
18.00	1	-0.5631501	0.1521707	intercept
21.00	1	0.5944396	0.0627877	intercept
22.00	1	-0.4181832	0.1381145	intercept
7.00	1	0.3128923	0.0795531	intercept
10.00	1	-1.0979646	0.2085982	intercept
11.00	1	-0.1911466	0.1295054	intercept
14.00	1	-0.0543137	0.1062803	intercept
24.00	1	-0.4175713	0.1381413	intercept
27.00	1	0.3932671	0.0807324	intercept
4.00	1	-1.0945001	0.2089433	intercept
8.00	1	-0.3269765	0.1422071	intercept
12.00	1	-0.2809423	0.1261539	intercept
15.00	1	-0.0492987	0.1064099	intercept
20.00	1	0.6505165	0.1136551	intercept
26.00	1	-0.3980607	0.2384099	intercept

ID, random effect number, random effect estimate (standardized $\theta_i = \upsilon_i/\sigma_\upsilon$), (posterior) variance, random effect label

$$\hat{\theta}_i \pm 1.96\sqrt{\text{subject's posterior variance}}$$



Large empirical Bayes estimates of random effects

- ID 13 (third subject) has large positive value (1.414) and has observed data: 7, 7, 7, 6, 7 headaches

  note, also that this subject has the smallest posterior variance (.0303) due to number and consistency of responses

  95% C.I. $= 1.414 \pm 1.96\sqrt{.0303} = (1.073, 1.755)$

- IDs 4 and 10 (17th and 22nd subjects) have large negative values ($<$ -1) and have observed headaches of 0 for all periods

Random drug effect?

- In many studies, drug or treatment is a subject-level variable and doesn't vary across time
- In a crossover study, however, drug is a time-varying variable and DOES vary across time
- A time-varying variable can be considered as random at the subject level
  - Does the drug effect vary across subjects?
  - Is there subject heterogeneity in the number of headaches for aspartame relative to placebo?

Model in multilevel representation

$i = 1, \ldots, 27$ subjects $\qquad$ $j = 1, \ldots, n_i$ periods (max = 5)

Level-1 model (within-subjects)

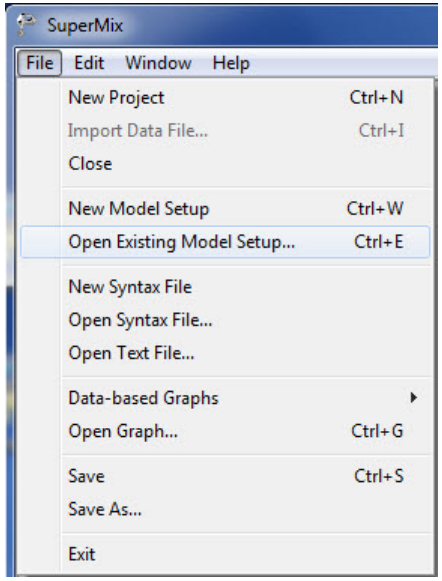
$$\log(\mu_{ij}) = \log(t_{ij}) + b_{0i} + b_{1i}P1_j + b_{2i}P2_j + b_{3i}P3_j + b_{4i}P4_j + b_{5i}Drug_{ij}$$

Level-2 model (between-subjects)

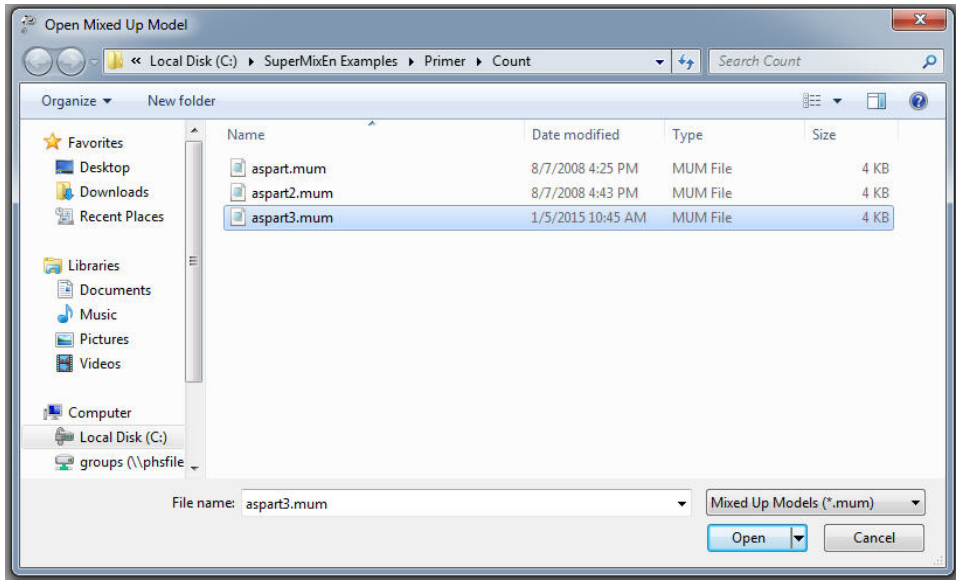
$$\begin{aligned} b_{0i} &= \beta_0 + \upsilon_{0i} \\ b_{1i} &= \beta_1 \\ b_{2i} &= \beta_2 \\ b_{3i} &= \beta_3 \\ b_{4i} &= \beta_4 \\ b_{5i} &= \beta_5 + \upsilon_{5i} \end{aligned}$$

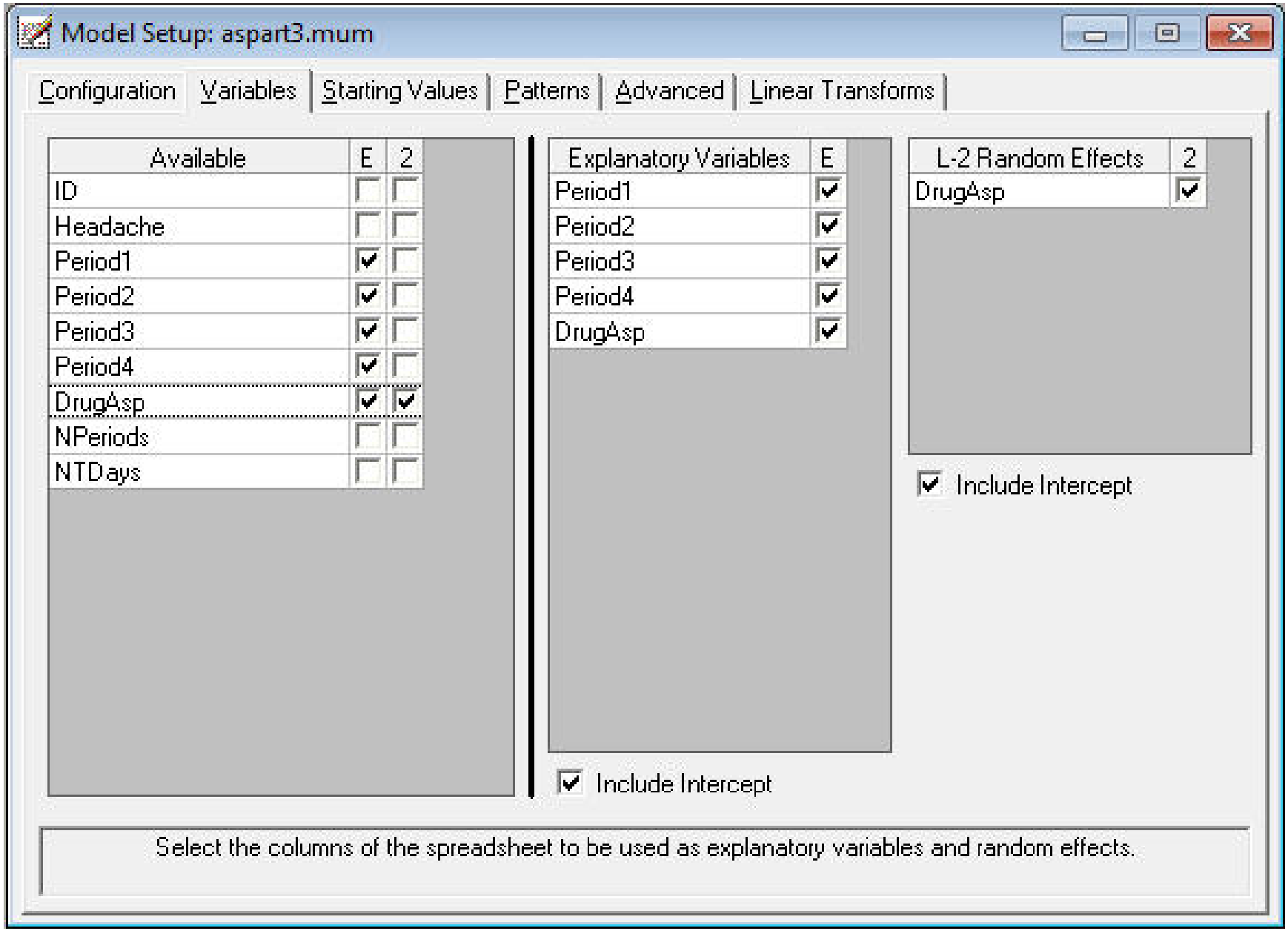
Does the effect of aspartame on headaches vary across subjects? (is υ_{5i} necessary?)

Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Primer\Count\aspart3.mum
(or C:\SuperMixEn Student Examples\Primer\Count\aspart3.mum)




Model Setup: aspart3.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
Headache
Period1
Period2
Period3
Period4
DrugAsp
NPeriods
NTDays
Explanatory Variables
E
Period1
Period2
Period3
Period4
DrugAsp
Include Intercept
L-2 Random Effects
2
DrugAsp
Include Intercept
Select the columns of the spreadsheet to be used as explanatory variables and random effects.

SuperMix - [aspart3.out]

File Analysis Window Help

```
Number of quadrature points =              20
Number of free parameters =                 9
Number of iterations used =                 4

-2lnL (deviance statistic) =        400.16027
Akaike Information Criterion        418.16027
Schwarz Criterion                   443.39646
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intercept	-1.7405	0.2192	-7.9404	0.0000
Period1	0.1231	0.2478	0.4967	0.6194
Period2	0.0572	0.2318	0.2466	0.8052
Period3	-0.2131	0.2654	-0.8029	0.4220
Period4	-0.0656	0.2620	-0.2505	0.8022
DrugAsp	0.2454	0.2352	1.0434	0.2968

Event Rate Ratio and 95% Event Rate Confidence Intervals

Parameter	Estimate	Event Rate	Bounds Lower	Bounds Upper
intercept	-1.7405	0.1754	0.1142	0.2696
Period1	0.1231	1.1310	0.6959	1.8381
Period2	0.0572	1.0588	0.6723	1.6676
Period3	-0.2131	0.8081	0.4803	1.3595
Period4	-0.0656	0.9365	0.5603	1.5650
DrugAsp	0.2454	1.2781	0.8061	2.0265

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.5257	0.2349	2.2375	0.0253
DrugAsp/intercept	-0.1431	0.2060	-0.6947	0.4873
DrugAsp/DrugAsp	0.3928	0.2876	1.3655	0.1721

Save As... Close

Likelihood ratio test

compare deviances (-2 log L) from two models, where one is nested within the other. Smaller deviance values are better, and the difference can be compared to a χ^2 distribution with q df (q = # of additional parameters in larger model)

Deviance equals 404.83 from model without random drug effect, and 400.16 from model with random drug

$\chi^2_2 = 404.83 - 400.16 = 4.67$

- 2 df for drug variance and drug, intercept covariance
- critical values are 4.605 ($p = .10$) and 5.991 ($p = .05$)
- suggestion of halved p-values for testing variance and covariance parameters (Berkhof & Snijders, JEBS, 2001)

Observed means: Headaches/Day across time by drug

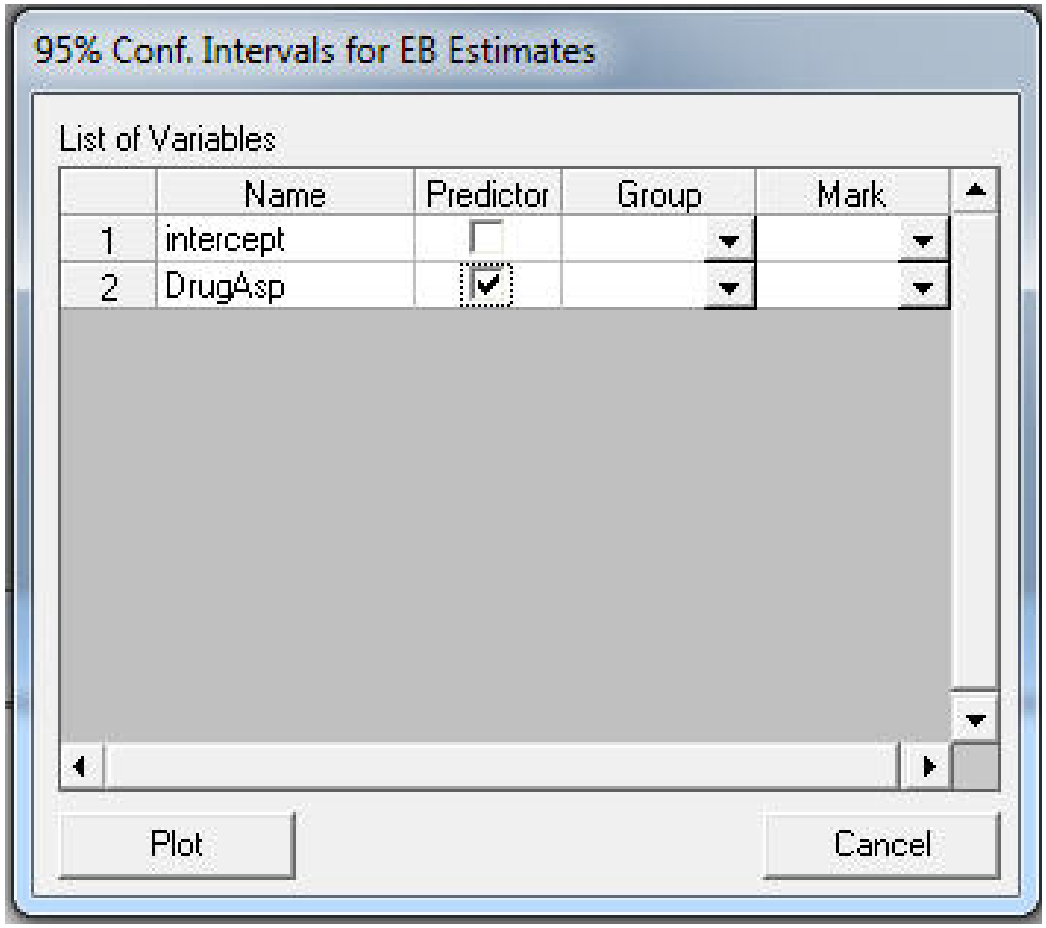
drug	baseline	period 1	period 2	period 3	period 4
placebo	.228	.238	.276	.147	.230
	(n=27)	(n=12)	(n=14)	(n=13)	(n=9)
aspartame		.381	.266	.286	.272
		(n=15)	(n=11)	(n=9)	(n=12)
	rate ratio	1.60	0.96	1.95	1.18

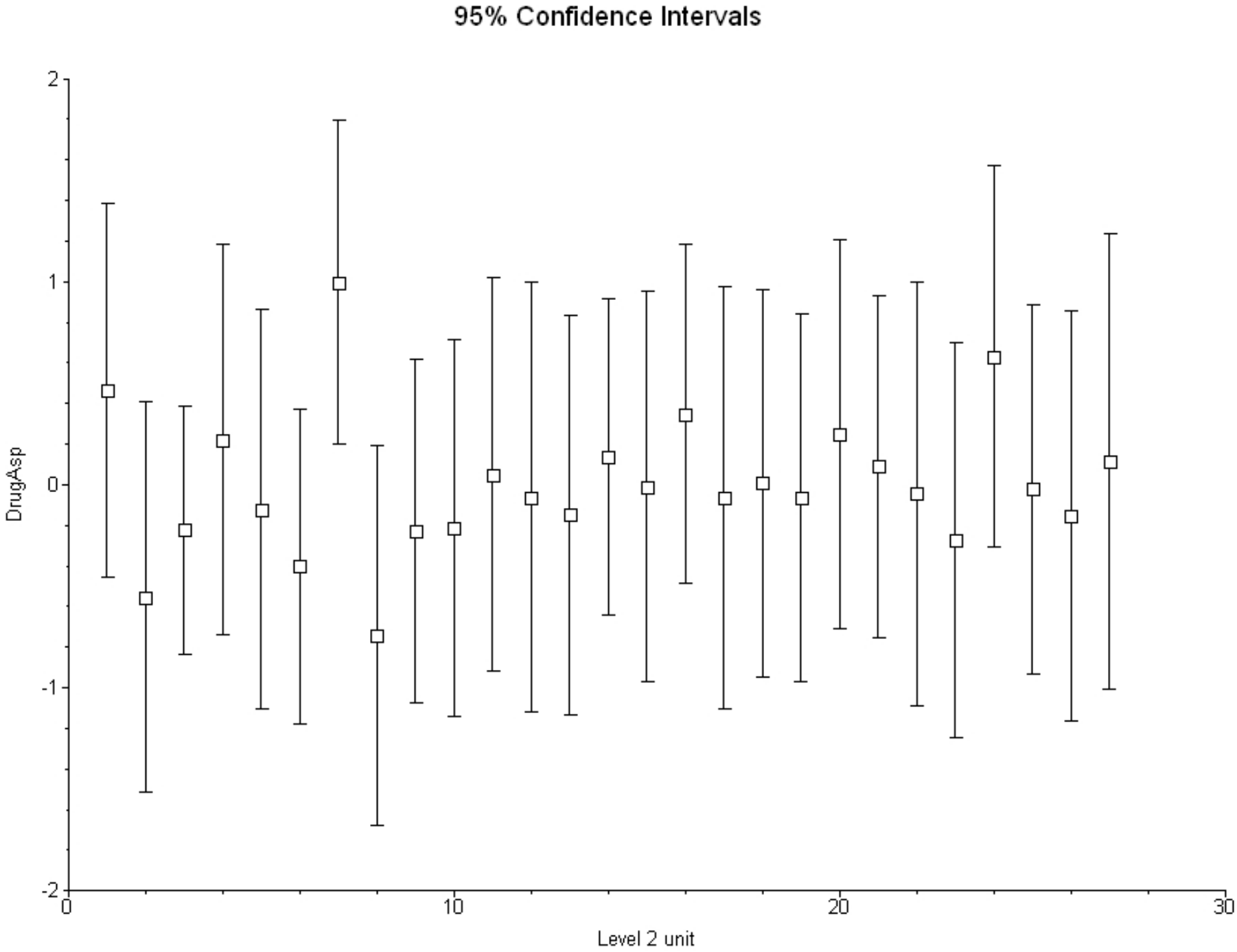
Estimated means $= \exp(\boldsymbol{x}'\hat{\boldsymbol{\beta}} + \hat{\sigma}^2_{v_0}/2)$ *for placebo*
$= \exp(\boldsymbol{x}'\hat{\boldsymbol{\beta}} + 1/2(\hat{\sigma}^2_{v_0} + \hat{\sigma}^2_{v_1} + 2\hat{\sigma}_{v_0 v_1}))$ *for aspartame*

drug	baseline	period 1	period 2	period 3	period 4
placebo	.228	.258	.242	.184	.217
aspartame		.348	.326	.249	.288
	rate ratio	1.35	1.35	1.35	1.35

Graph of Random Drug Effects

"File" > "Model-based Graphs" > "Confidence Intervals"




95% Confidence Intervals
DrugAsp
2
1
0
-1
-2
0
10
20
30
Level 2 unit

Very interesting subject

Empirical Bayes estimate of drug effect is very large (≈ 1) for ID=25 (7th subject)

observed number of headaches:
1 (placebo), 6 (drug), 1 (placebo), 7 (drug), 0 (placebo)

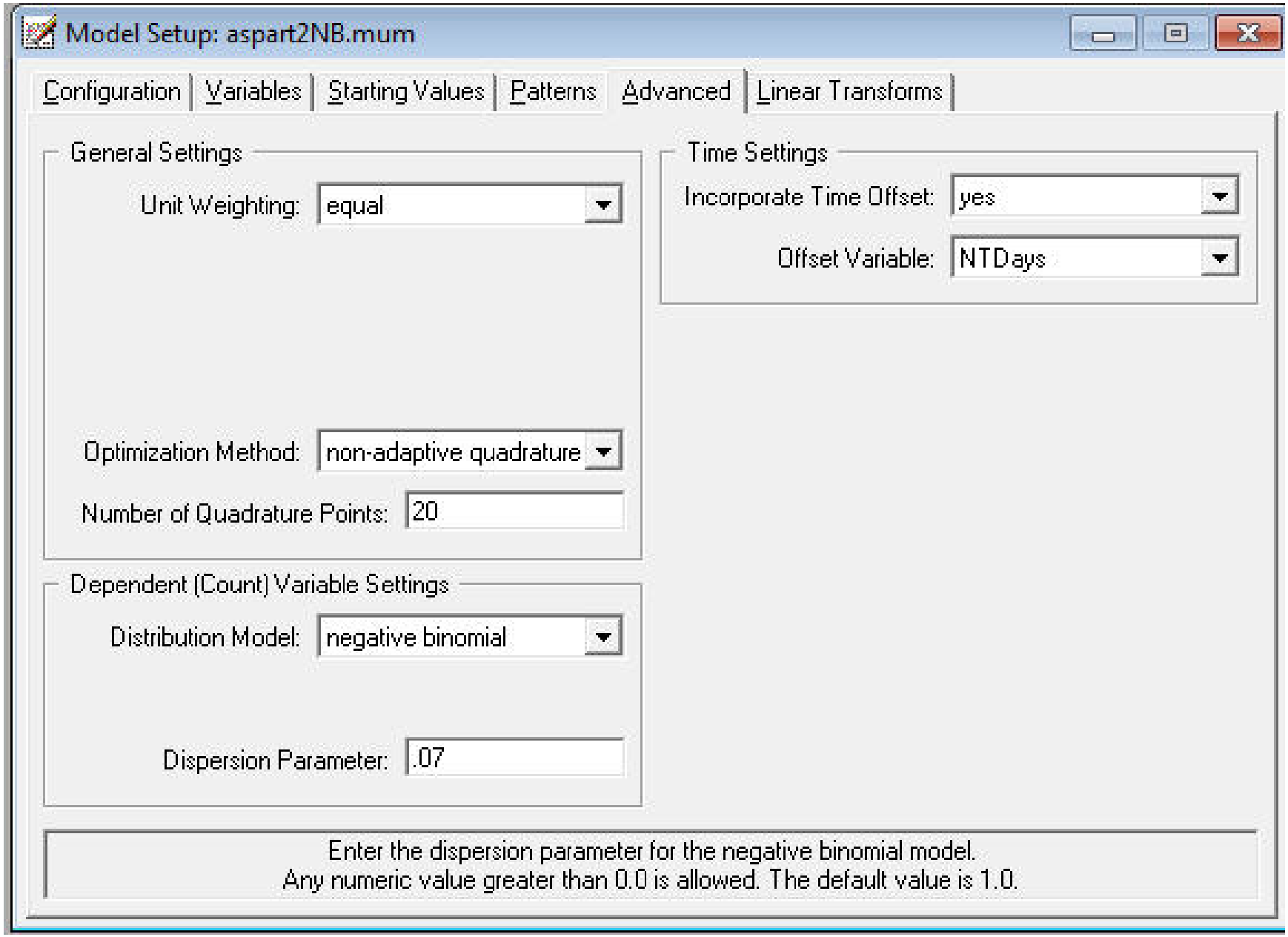
Drug Effect Estimates

	model	estimate	std error	p-value
with ID=25	rand int	0.2797	0.1641	0.0883
	rand drug	0.2454	0.2352	0.2968
without ID=25	rand int	0.1384	0.1698	0.4149
	rand drug	0.1462	0.1955	0.4545

also, from random drug models, estimate of drug variance goes from 0.3928 (se = 0.2876) to 0.0030 (se = 0.0330)

Overdispersion

- Poisson model assumes that the mean equals the variance
- overdispersion occurs when the variance exceeds the mean
  - often present in real data, can change model estimates
  - inclusion of random effects, by accounting for individual differences, may decrease possibility of overdispersion
- Negative Binomial model relaxes this assumption by including an overdispersion parameter
  - Poisson model is a special case of Negative Binomial when this overdispersion parameter equals 0
- SuperMix can estimate Negative Binomial models, however the overdispersion parameter must be set (not estimated, yet)


Model Setup: aspart2NB.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
non-adaptive quadrature
Number of Quadrature Points:
20
Dependent (Count) Variable Settings
Distribution Model:
negative binomial
Dispersion Parameter:
.07
Time Settings
Incorporate Time Offset:
yes
Offset Variable:
NTDays
Enter the dispersion parameter for the negative binomial model.
Any numeric value greater than 0.0 is allowed. The default value is 1.0.

Overdispersion? considering random intercept models

Dispersion parameter	Distribution	Deviance (-2 logL)
0	Poisson	404.83040
.01	Negative Binomial	404.65575
.02	Negative Binomial	404.51392
.05	Negative Binomial	404.25692
.07	Negative Binomial	404.20301
.10	Negative Binomial	404.26229

- dispersion of .07 is (approximately) best, with a difference in deviance of about .63
- χ^2_1 critical value is 2.706 for a one-sided .05 test
- no real evidence of overdispersion for these data

SuperMix - [aspart2NB.out]

File Analysis Window Help

```
 o=============================================o
 | Optimization Method: Non-Adaptive Quadrature |
 o=============================================o

Number of quadrature points =              20
Number of free parameters =                 7
Number of iterations used =                 4

-2lnL (deviance statistic) =        404.20301
Akaike Information Criterion        418.20301
Schwarz Criterion                   437.83115
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intercept	-1.7081	0.2164	-7.8918	0.0000
Period1	0.1113	0.2534	0.4391	0.6606
Period2	0.0870	0.2433	0.3575	0.7207
Period3	-0.2255	0.2748	-0.8205	0.4119
Period4	-0.0929	0.2754	-0.3374	0.7358
DrugAsp	0.2858	0.1768	1.6164	0.1060

Event Rate Ratio and 95% Event Rate Confidence Intervals

Parameter	Estimate	Event Rate	Bounds Lower	Bounds Upper
intercept	-1.7081	0.1812	0.1186	0.2770
Period1	0.1113	1.1177	0.6802	1.8365
Period2	0.0870	1.0909	0.6771	1.7575
Period3	-0.2255	0.7981	0.4658	1.3676
Period4	-0.0929	0.9113	0.5312	1.5634
DrugAsp	0.2858	1.3309	0.9410	1.8822

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.4629	0.1920	2.4103	0.0159

Save As... Close

Conclusions

- Van Den Eeden *et al.*, (1994), Aspartame ingestion and headaches: A randomized crossover trial, *Neurology, 44*, 1787-1793.

  "the proportion of days subjects reported having a headache was higher during aspartame treatment compared with placebo treatment (aspartame = .33, placebo = .24, $p = .04$)"

- Levy, Hedeker, & Sanders (1995) To the editor: Aspartame and headache, *Neurology, 45(8)*:1631-2; author reply 1632-3.

  Increase of headaches by aspartame only for 1-tailed test in random intercept model; random drug model and model without subject 25 (very influential subject) shows no drug effect.

- Butchkoa & Stargelb (2001), Aspartame: Scientific evaluation in the postmarketing period, *Regulatory Toxicology and Pharmacology, 34*, 221-233.

  "Evaluation of the anecdotal reports of adverse health effects, the first such system for a food additive, revealed that the reported effects were generally mild and also common in the general population and that there was no consistent or unique pattern of symptoms that could be causally linked to consumption of aspartame. Finally, the results of the extensive scientific research done to evaluate these allegations did not show a causal relationship between aspartame and adverse effects. Thus, the weight of scientific evidence confirms that, even in amounts many times what people typically consume, aspartame is safe for its intended uses as a sweetener and flavor enhancer."

Seizure Counts for 59 Epileptics

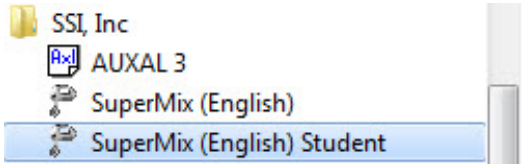
Thall & Vail (1990). Some covariance models for longitudinal count data with overdispersion. *Biometrics, 46*, 657-671.

data and description:
http:\\biosun1.harvard.edu\~fitzmaur\ala\epilepsy.txt

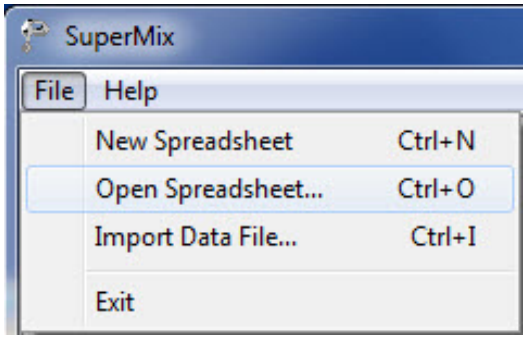
> "The data are from a placebo-controlled clinical trial of 59 epileptics. Patients with partial seizures were enrolled in a randomized clinical trial of the anti-epileptic drug, progabide. Participants in the study were randomized to either progabide or a placebo, as an adjuvant to the standard anti-epileptic chemotherapy. Progabide is an anti-epileptic drug whose primary mechanism of action is to enhance gamma-aminobutyric acid (GABA) content; GABA is the primary inhibitory neurotransmitter in the brain. Prior to receiving treatment, baseline data on the number of epileptic seizures during the preceding 8-week interval were recorded. Counts of epileptic seizures during 2-week intervals before each of four successive post-randomization clinic visits were recorded."

Variable List: Patient ID, Treatment (0=Placebo, 1=Progabide), Age, Baseline 8-week seizure count, First 2-week seizure count, Second 2-week seizure count, Third 2-week seizure count, Fourth 2-week seizure count.

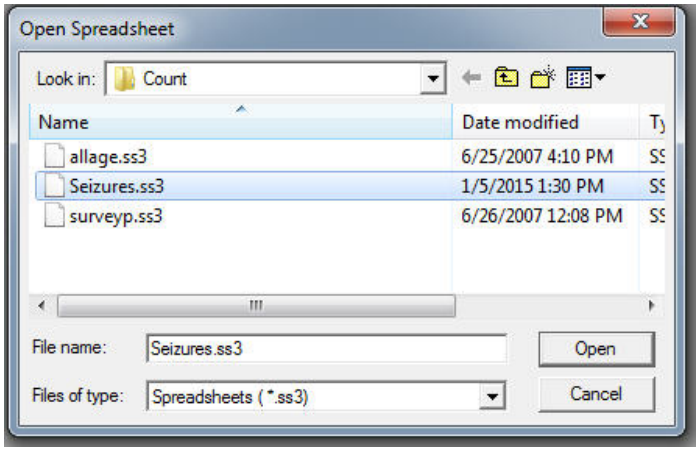
- Under SSI, Inc > "SuperMix (English)" or 'SuperMix (English) Student"

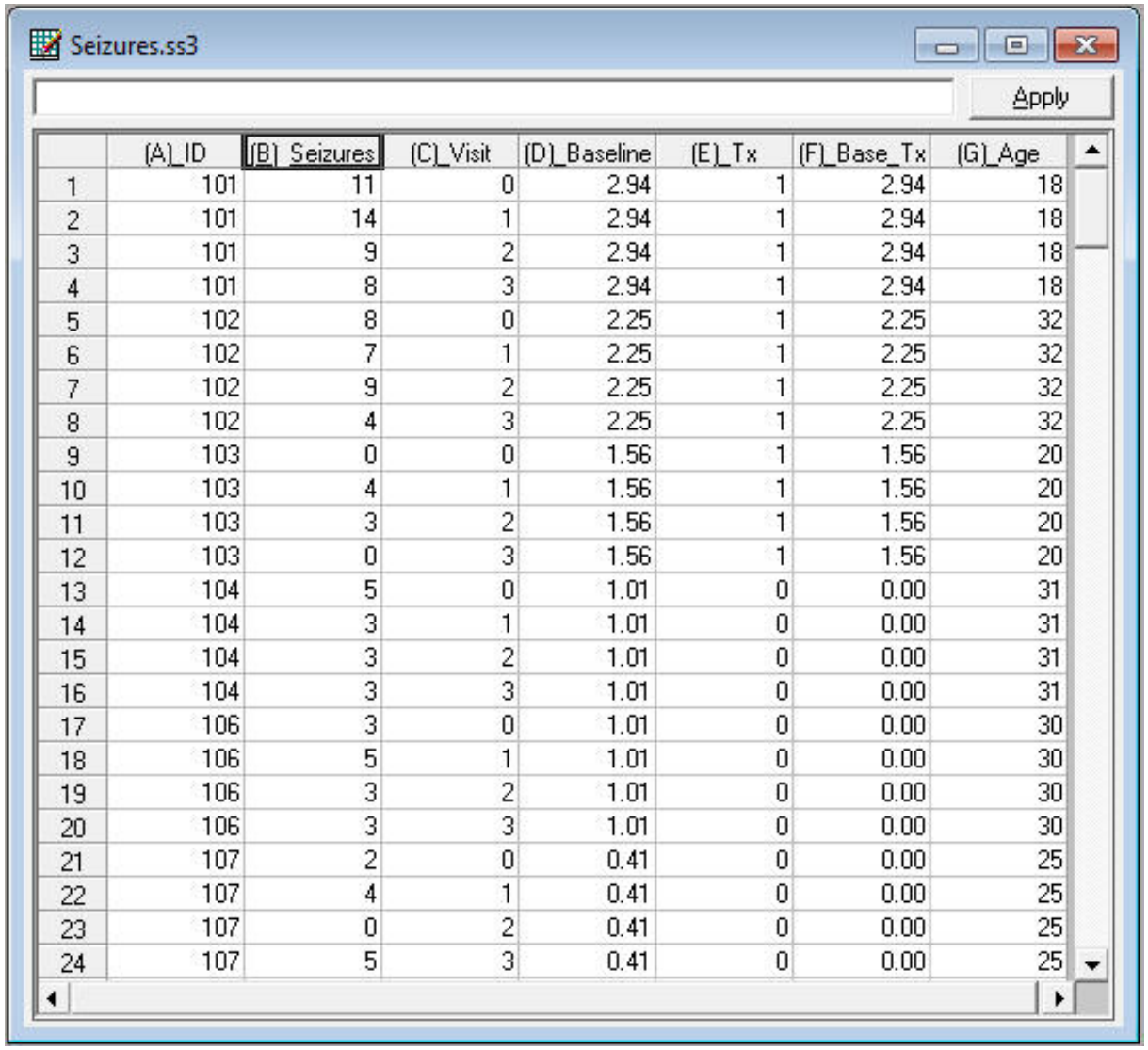


- Under "File" click on "Open Spreadsheet"



- Open C:\SuperMixEn Examples\Workshop\Count\Seizures.ss3
(or C:\SuperMixEn Student Examples\Workshop\Count\Seizures.ss3)

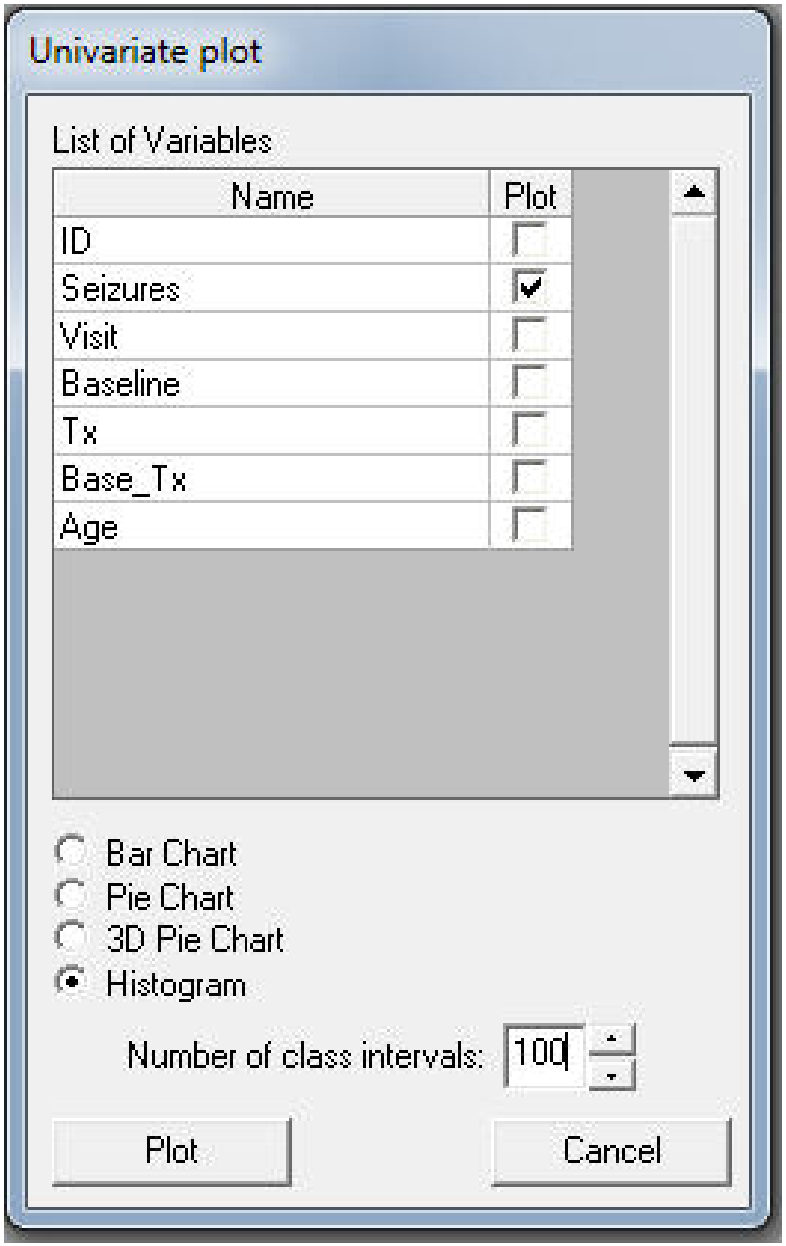


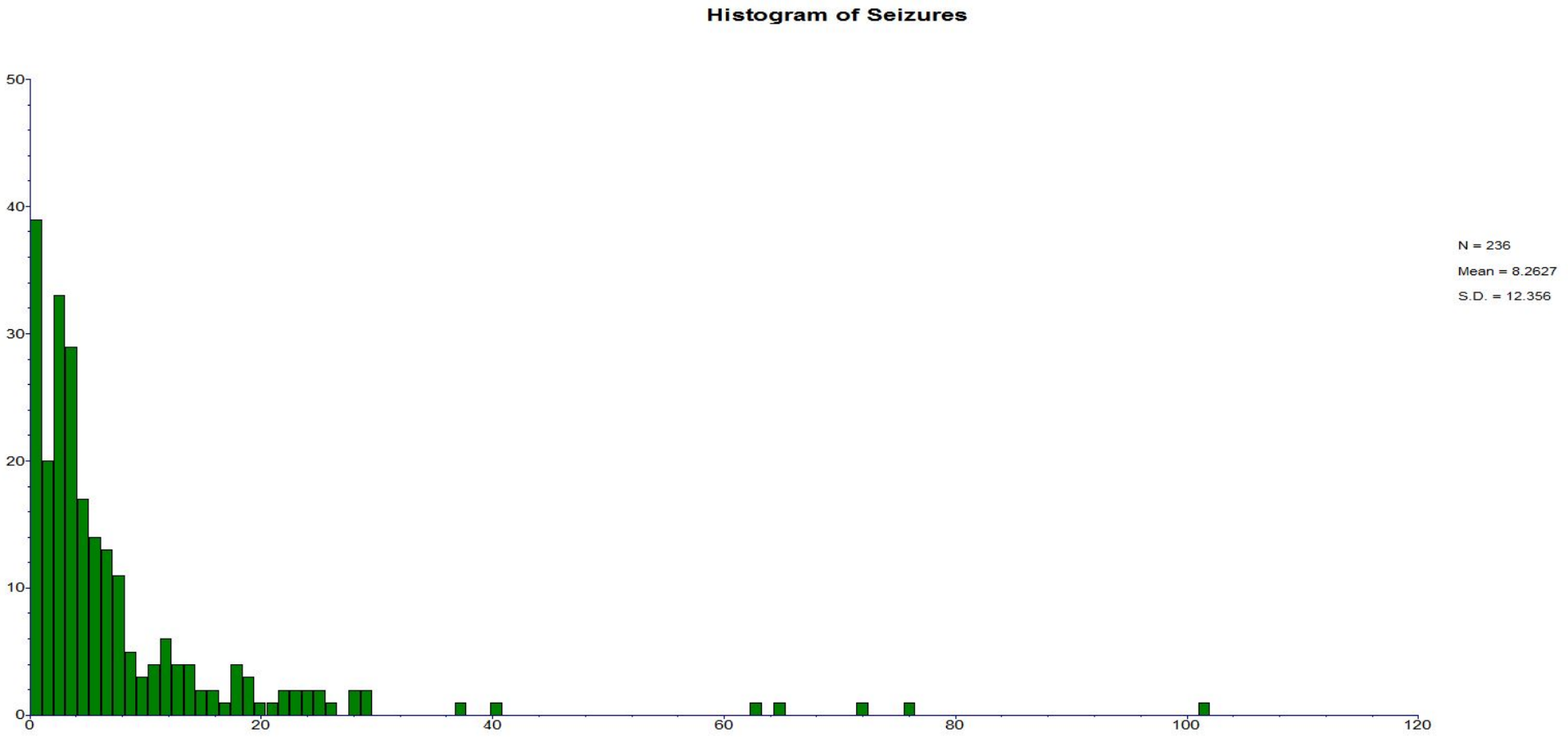


	(A)_ID	(B)_Seizures	(C)_Visit	(D)_Baseline	(E)_Tx	(F)_Base_Tx	(G)_Age
1	101	11	0	2.94	1	2.94	18
2	101	14	1	2.94	1	2.94	18
3	101	9	2	2.94	1	2.94	18
4	101	8	3	2.94	1	2.94	18
5	102	8	0	2.25	1	2.25	32
6	102	7	1	2.25	1	2.25	32
7	102	9	2	2.25	1	2.25	32
8	102	4	3	2.25	1	2.25	32
9	103	0	0	1.56	1	1.56	20
10	103	4	1	1.56	1	1.56	20
11	103	3	2	1.56	1	1.56	20
12	103	0	3	1.56	1	1.56	20
13	104	5	0	1.01	0	0.00	31
14	104	3	1	1.01	0	0.00	31
15	104	3	2	1.01	0	0.00	31
16	104	3	3	1.01	0	0.00	31
17	106	3	0	1.01	0	0.00	30
18	106	5	1	1.01	0	0.00	30
19	106	3	2	1.01	0	0.00	30
20	106	3	3	1.01	0	0.00	30
21	107	2	0	0.41	0	0.00	25
22	107	4	1	0.41	0	0.00	25
23	107	0	2	0.41	0	0.00	25
24	107	5	3	0.41	0	0.00	25

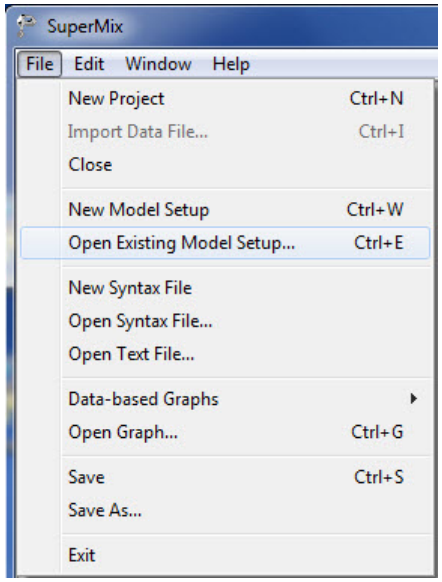
ID, (2-week) seizure counts, visit (0 to 3), log baseline seizures [log (8-week seizure count divided by four)], tx (0=placebo, 1=progabide), baseline by tx interaction, age

Select “File” > “Data-based Graphs” > “Univariate”

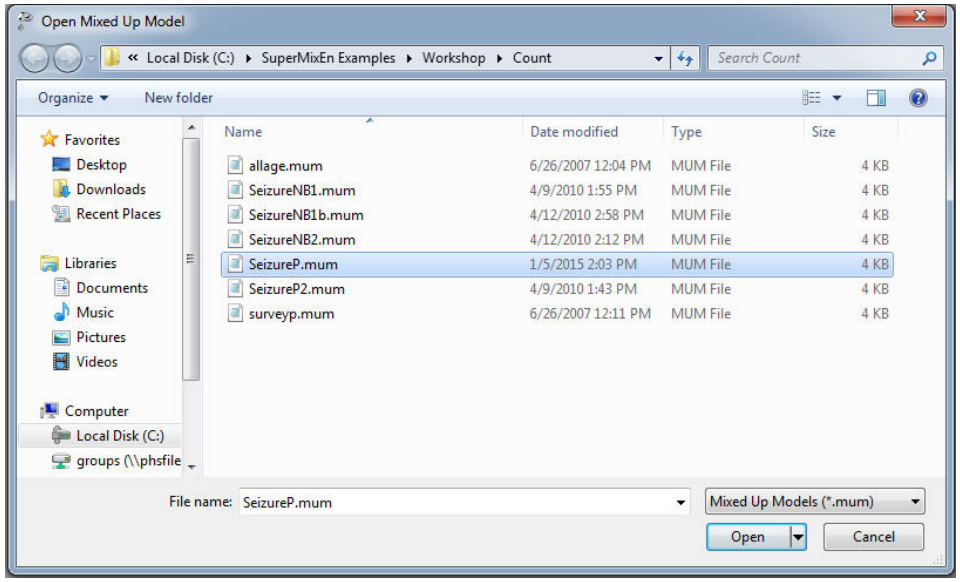


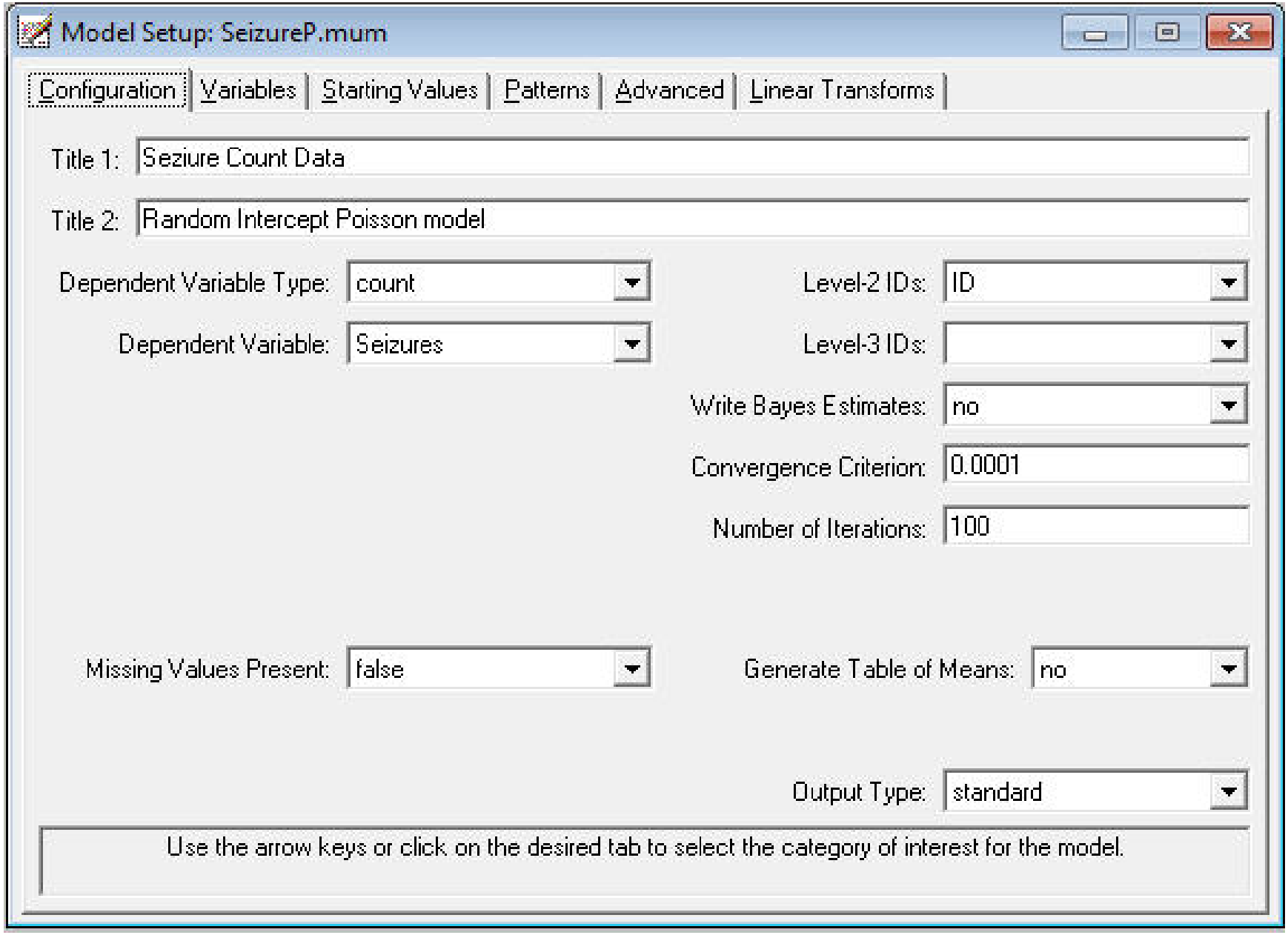

Histogram of Seizures
50
40
30
20
10
0
0
20
40
60
80
100
120
N = 236
Mean = 8.2627
S.D. = 12.356

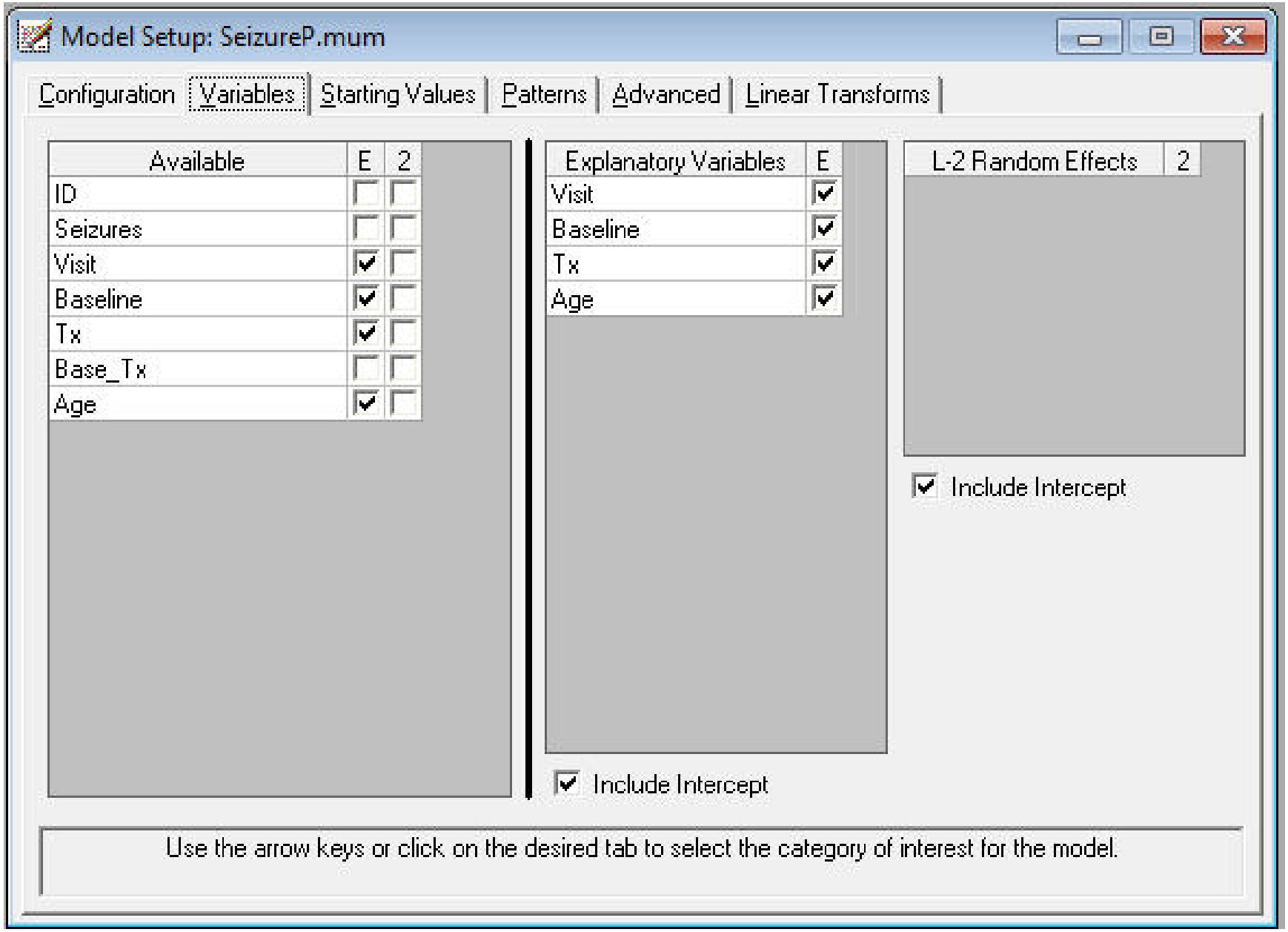
Under "File" click on "Open Existing Model Setup"

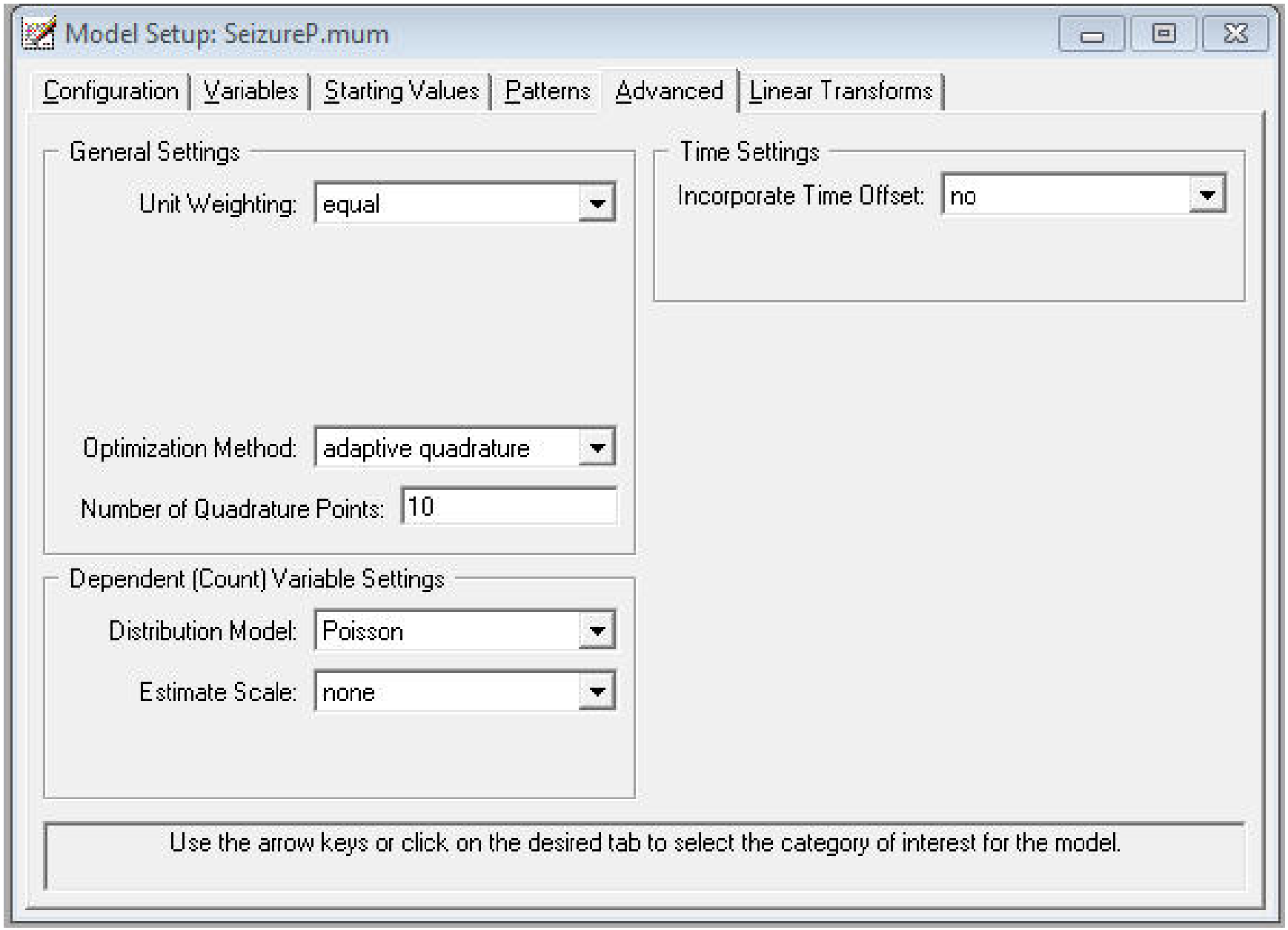


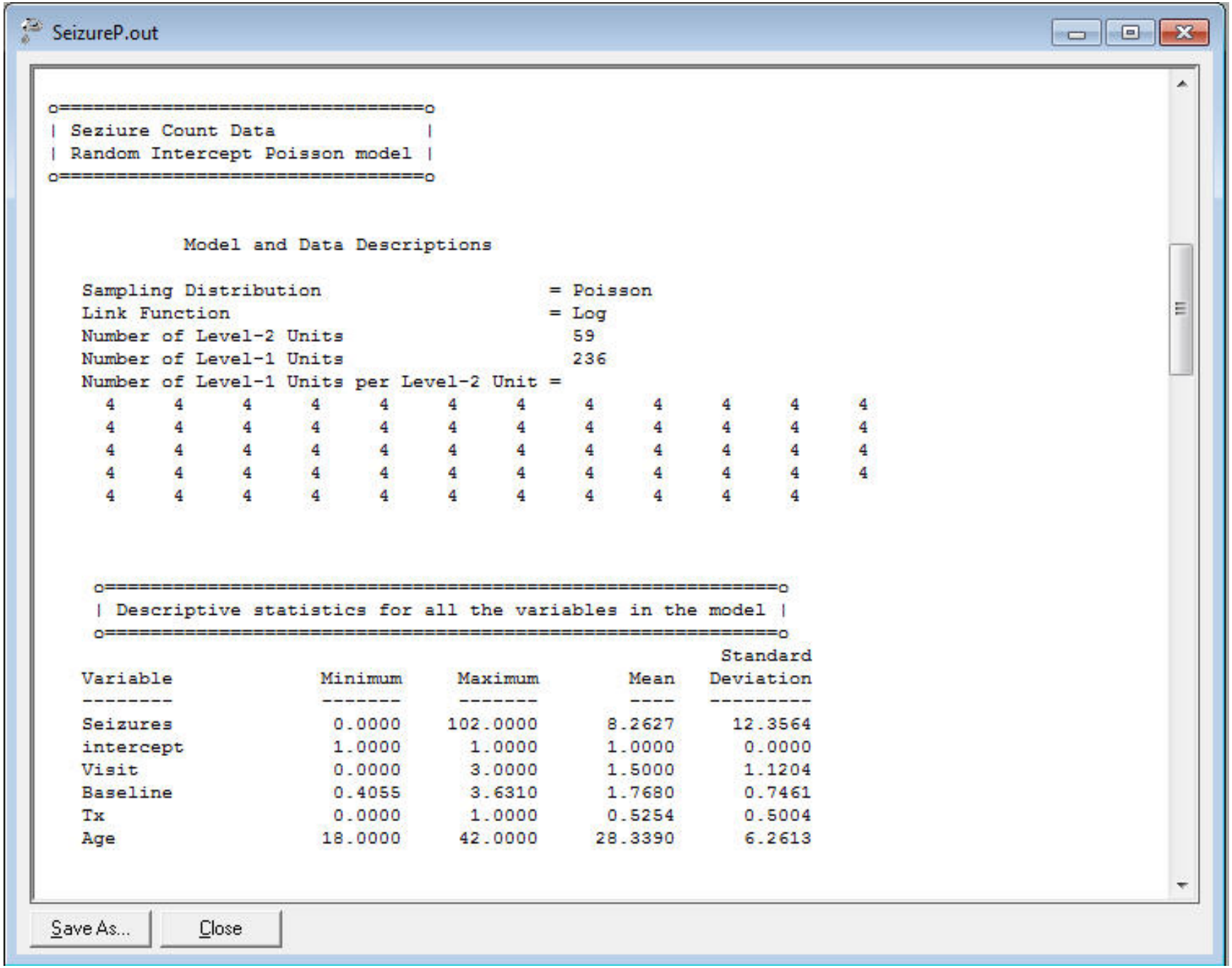
Open C:\SuperMixEn Examples\Workshop\Count\SeizureP.mum
(or C:\SuperMixEn Student Examples\Primer\Count\SeizureP.mum)

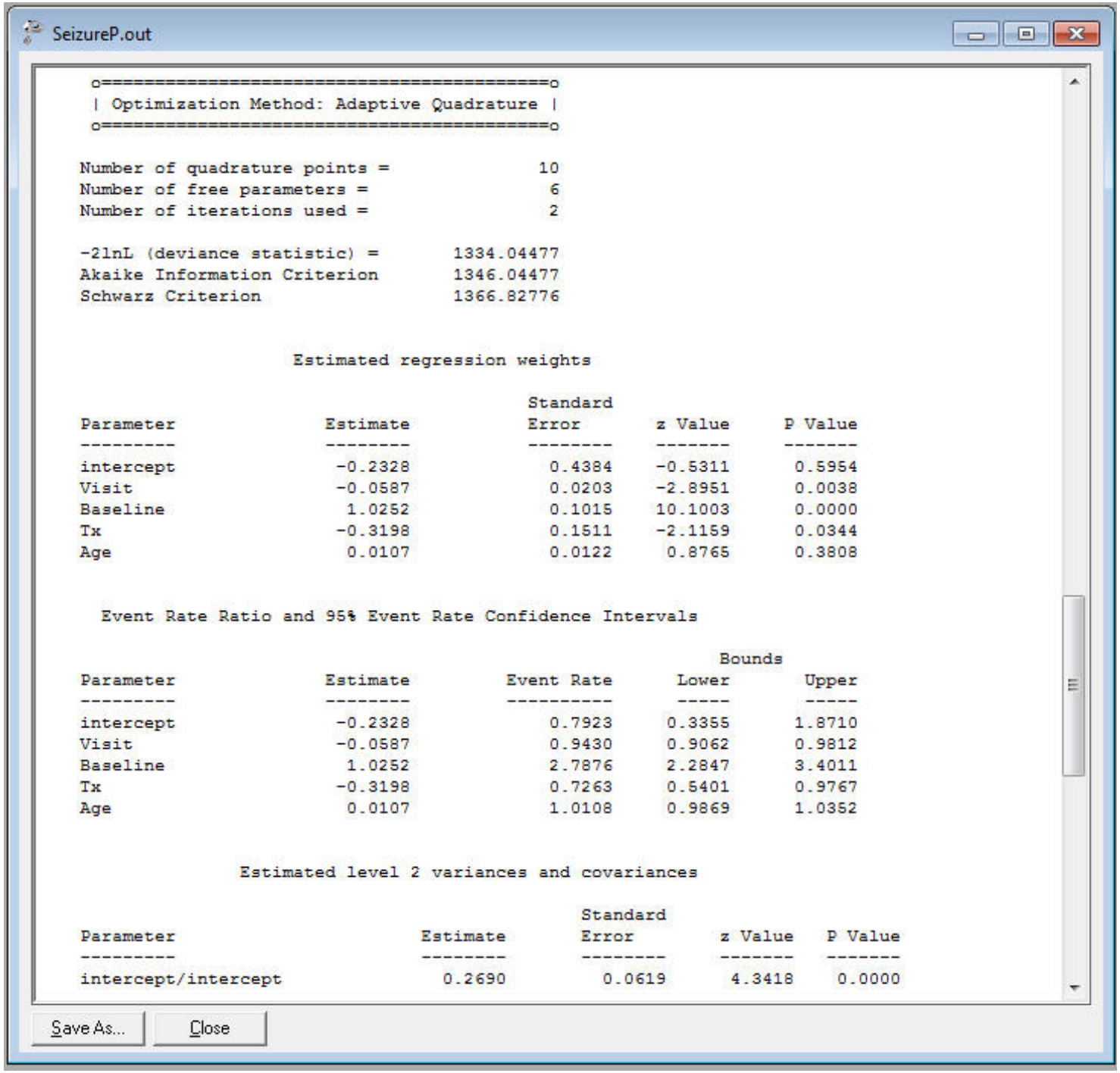



Model Setup: SeizureP.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1:
Seziure Count Data
Title 2:
Random Intercept Poisson model
Dependent Variable Type:
count
Dependent Variable:
Seizures
Level-2 IDs:
ID
Level-3 IDs:
Write Bayes Estimates:
no
Convergence Criterion:
0.0001
Number of Iterations:
100
Missing Values Present:
false
Generate Table of Means:
no
Output Type:
standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.

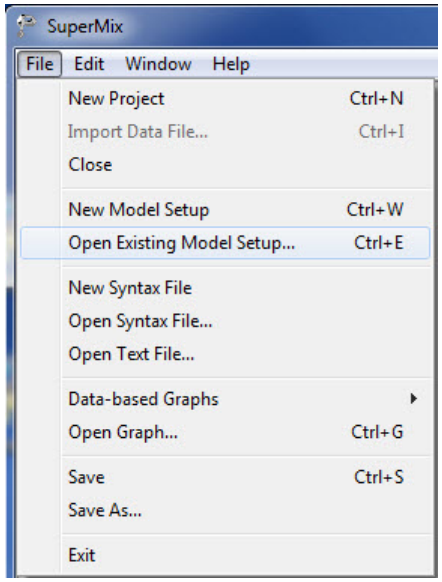

Model Setup: SeizureP.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
Seizures
Visit
Baseline
Tx
Base_Tx
Age
Explanatory Variables
E
Visit
Baseline
Tx
Age
Include Intercept
L-2 Random Effects
2
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


Model Setup: SeizureP.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
adaptive quadrature
Number of Quadrature Points:
10
Dependent (Count) Variable Settings
Distribution Model:
Poisson
Estimate Scale:
none
Time Settings
Incorporate Time Offset:
no
Use the arrow keys or click on the desired tab to select the category of interest for the model.

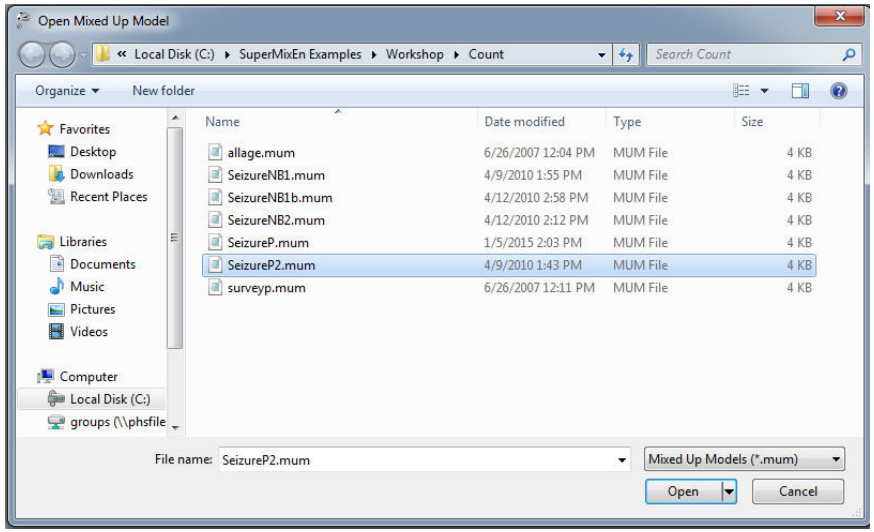

SeizureP.out
o==================================o
| Seziure Count Data |
| Random Intercept Poisson model |
o==================================o
Model and Data Descriptions
Sampling Distribution = Poisson
Link Function = Log
Number of Level-2 Units 59
Number of Level-1 Units 236
Number of Level-1 Units per Level-2 Unit =
4 4 4 4 4 4 4 4 4 4 4
4 4 4 4 4 4 4 4 4 4 4
4 4 4 4 4 4 4 4 4 4 4
4 4 4 4 4 4 4 4 4 4 4
4 4 4 4 4 4 4 4 4 4
o==========o
| Descriptive statistics for all the variables in the model |
o==========o
Variable Minimum Maximum Mean Standard Deviation
Seizures 0.0000 102.0000 8.2627 12.3564
intercept 1.0000 1.0000 1.0000 0.0000
Visit 0.0000 3.0000 1.5000 1.1204
Baseline 0.4055 3.6310 1.7680 0.7461
Tx 0.0000 1.0000 0.5254 0.5004
Age 18.0000 42.0000 28.3390 6.2613
Save As...
Close

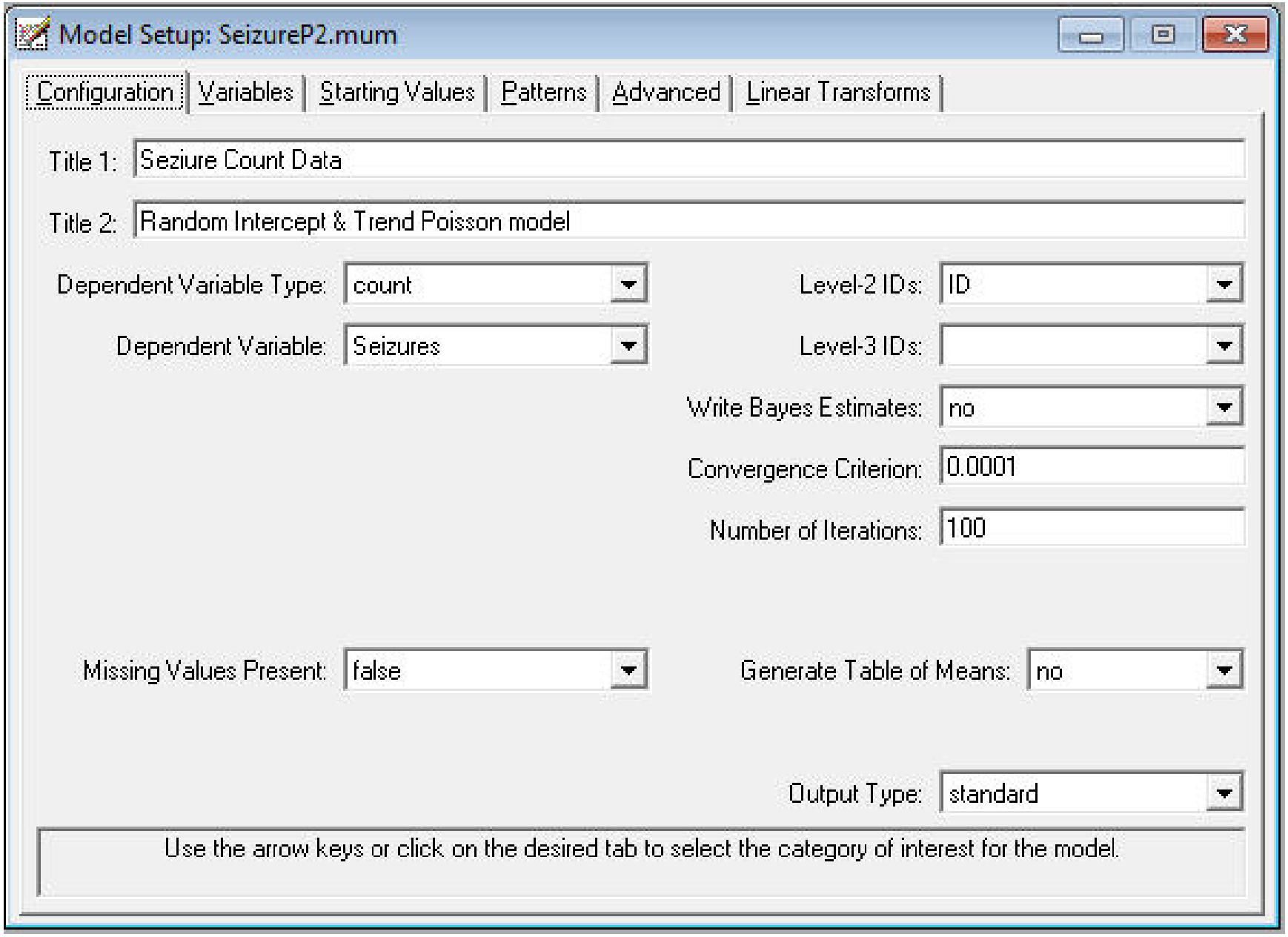

SeizureP.out
o===o
| Optimization Method: Adaptive Quadrature |
o===o
Number of quadrature points = 10
Number of free parameters = 6
Number of iterations used = 2
-2lnL (deviance statistic) = 1334.04477
Akaike Information Criterion 1346.04477
Schwarz Criterion 1366.82776
Estimated regression weights
Parameter Estimate Standard Error z Value P Value
intercept -0.2328 0.4384 -0.5311 0.5954
Visit -0.0587 0.0203 -2.8951 0.0038
Baseline 1.0252 0.1015 10.1003 0.0000
Tx -0.3198 0.1511 -2.1159 0.0344
Age 0.0107 0.0122 0.8765 0.3808
Event Rate Ratio and 95% Event Rate Confidence Intervals
Parameter Estimate Event Rate Bounds Lower Upper
intercept -0.2328 0.7923 0.3355 1.8710
Visit -0.0587 0.9430 0.9062 0.9812
Baseline 1.0252 2.7876 2.2847 3.4011
Tx -0.3198 0.7263 0.5401 0.9767
Age 0.0107 1.0108 0.9869 1.0352
Estimated level 2 variances and covariances
Parameter Estimate Standard Error z Value P Value
intercept/intercept 0.2690 0.0619 4.3418 0.0000
Save As...
Close

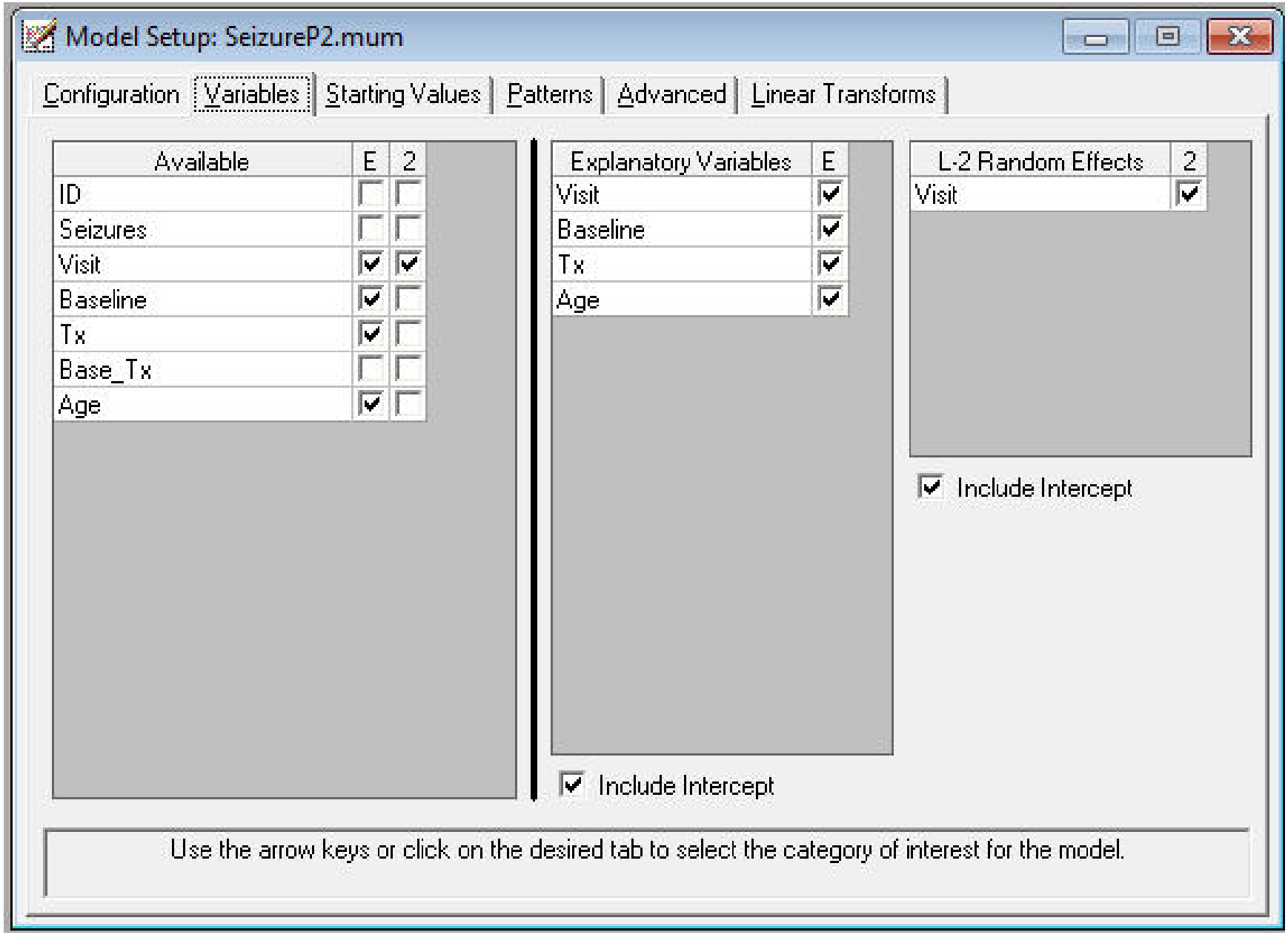
Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Workshop\Count\SeizureP2.mum
(or C:\SuperMixEn Student Examples\Primer\Count\SeizureP2.mum)




Model Setup: SeizureP2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1:
Seziure Count Data
Title 2:
Random Intercept & Trend Poisson model
Dependent Variable Type:
count
Dependent Variable:
Seizures
Level-2 IDs:
ID
Level-3 IDs:
Write Bayes Estimates:
no
Convergence Criterion:
0.0001
Number of Iterations:
100
Missing Values Present:
false
Generate Table of Means:
no
Output Type:
standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.


Model Setup: SeizureP2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
Seizures
Visit
Baseline
Tx
Base_Tx
Age
Explanatory Variables
E
Visit
Baseline
Tx
Age
Include Intercept
L-2 Random Effects
2
Visit
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SeizureP2.out

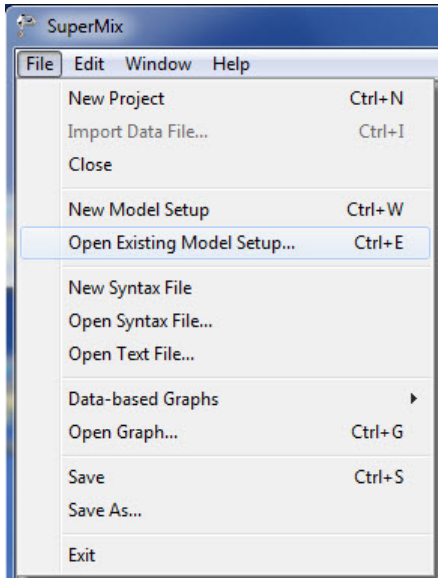
```
 o=========================================o
 | Optimization Method: Adaptive Quadrature |
 o=========================================o

Number of quadrature points =              10
Number of free parameters =                 8
Number of iterations used =                 2

-2lnL (deviance statistic) =       1314.21288
Akaike Information Criterion       1330.21288
Schwarz Criterion                  1357.92354


                  Estimated regression weights

                                        Standard
Parameter              Estimate         Error       z Value     P Value
---------              --------         --------    -------     -------
intercept               -0.2372           0.4423    -0.5363      0.5918
Visit                   -0.0513           0.0329    -1.5603      0.1187
Baseline                 1.0250           0.1013    10.1217      0.0000
Tx                      -0.3165           0.1508    -2.0986      0.0359
Age                      0.0100           0.0124     0.8061      0.4202


  Event Rate Ratio and 95% Event Rate Confidence Intervals

                                                      Bounds
Parameter              Estimate         Event Rate      Lower       Upper
---------              --------         ----------      -----       -----
intercept               -0.2372             0.7888     0.3315      1.8770
Visit                   -0.0513             0.9500     0.8906      1.0132
Baseline                 1.0250             2.7872     2.2854      3.3992
Tx                      -0.3165             0.7287     0.5422      0.9793
Age                      0.0100             1.0100     0.9858      1.0348


            Estimated level 2 variances and covariances

                                      Standard
Parameter                Estimate     Error       z Value   P Value
---------                --------     --------    -------   -------
intercept/intercept        0.3237       0.0857     3.7770    0.0002
Visit/intercept           -0.0349       0.0231    -1.5104    0.1309
Visit/Visit                0.0213       0.0092     2.3205    0.0203
```

Save As... Close

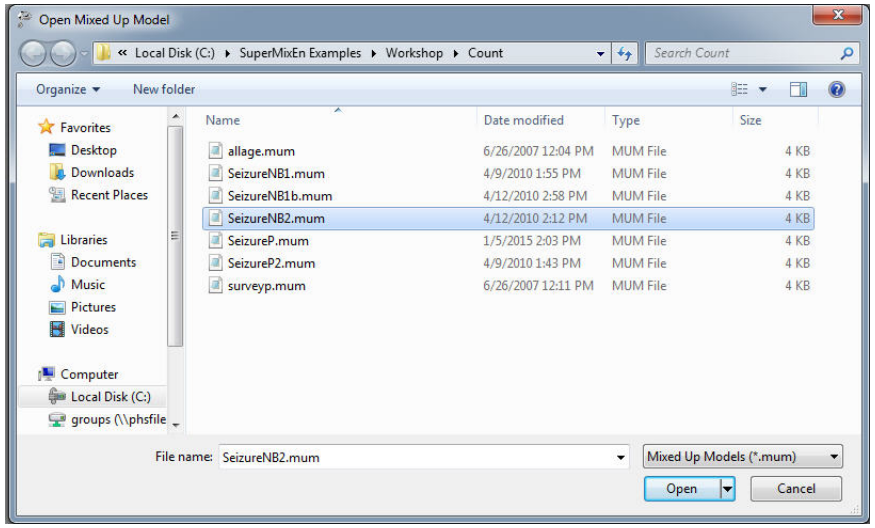
Evidence of random subject trends across time

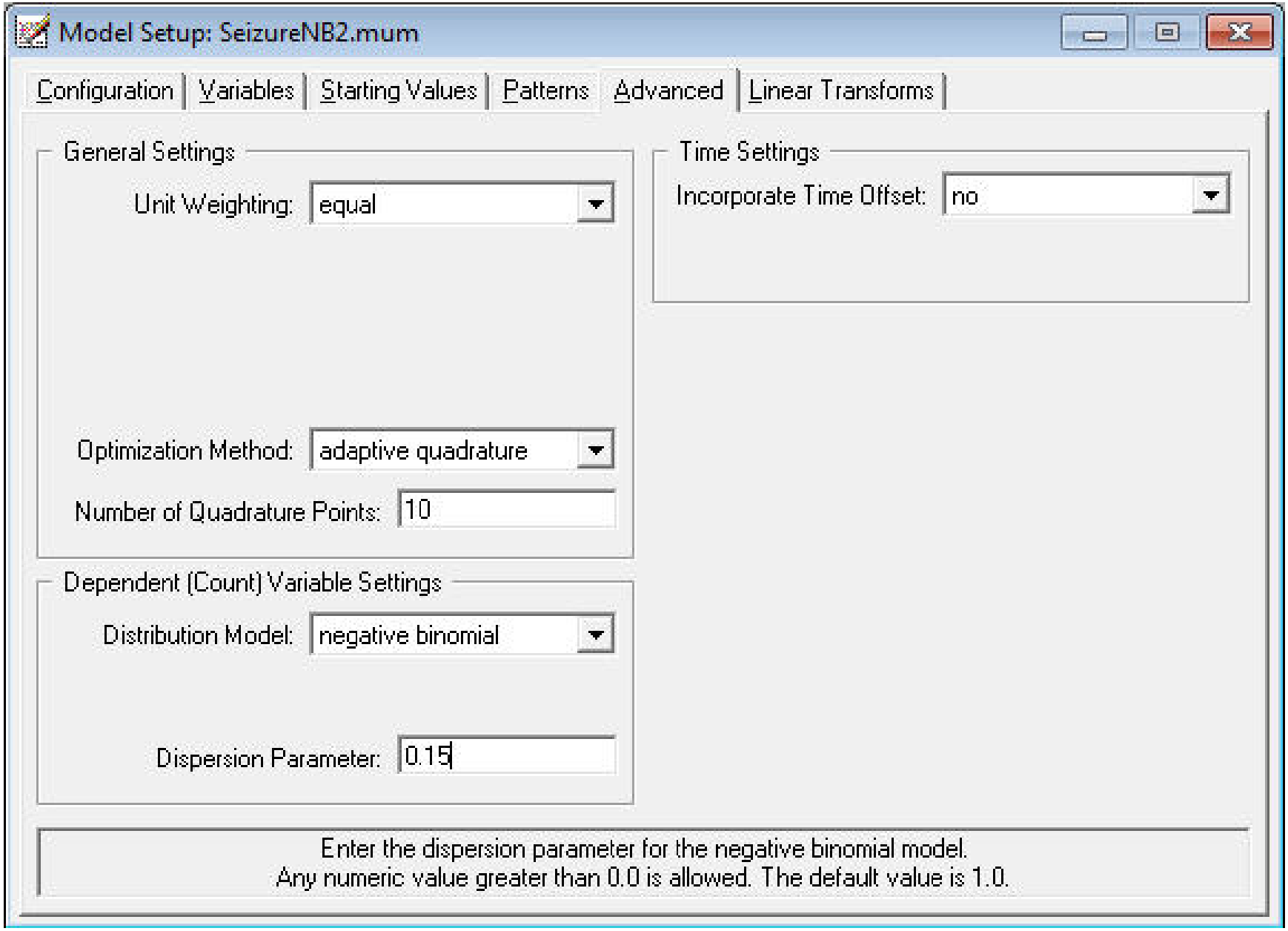
- deviance (-2 logL) = 1334.04 from model without random trends (only random intercept)
- deviance = 1314.21 from model with random intercepts and trends
- $\chi^2_2 \approx 20$, highly significant
- variance of seizure counts changes across time
- Poisson model assumes no overdispersion
- better check what Negative Binomial model yields

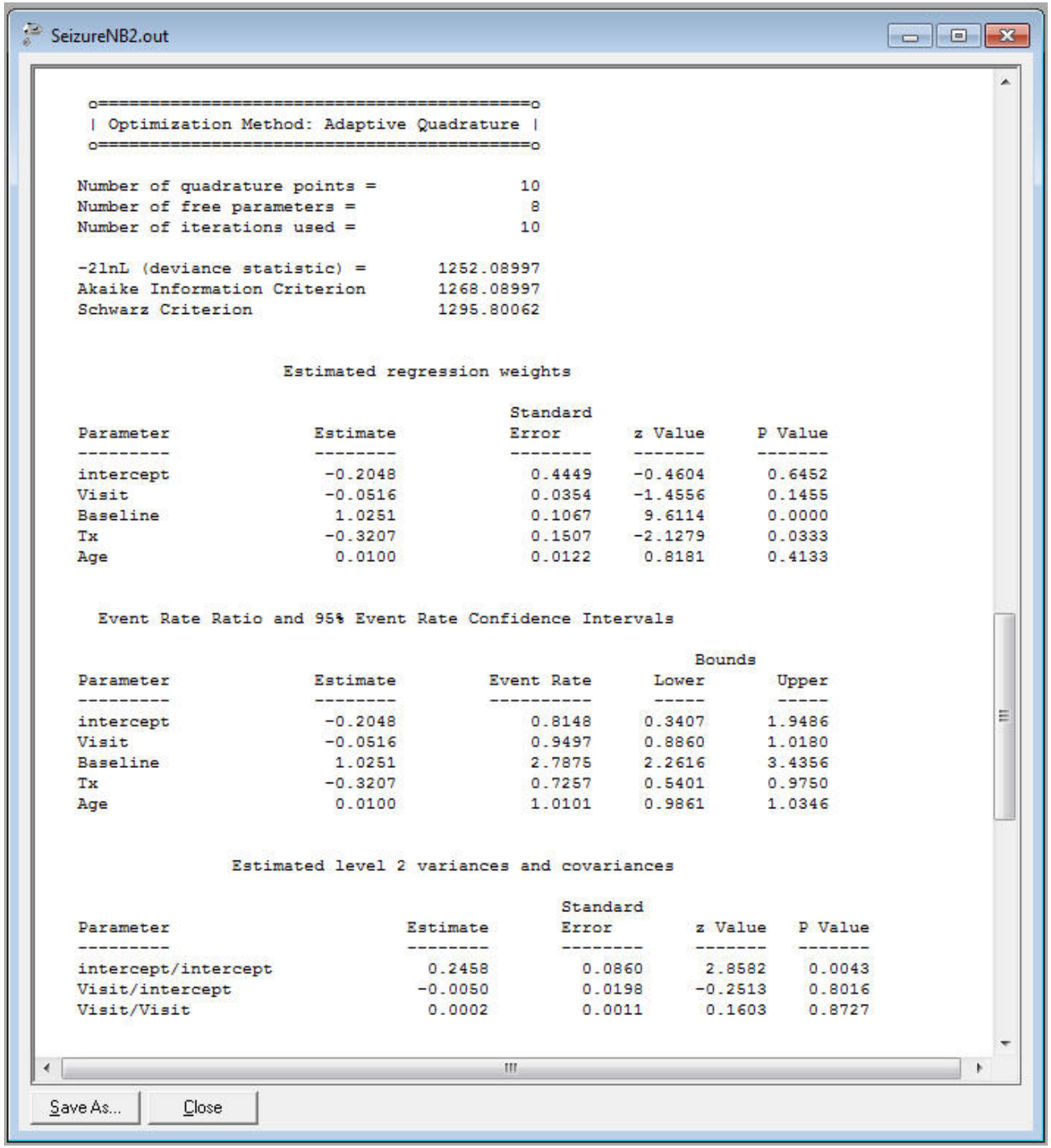
Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Workshop\Count\SeizureNB2.mum
(or C:\SuperMixEn Student Examples\Primer\Count\SeizureNB2.mum)




Model Setup: SeizureNB2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
adaptive quadrature
Number of Quadrature Points:
10
Time Settings
Incorporate Time Offset:
no
Dependent (Count) Variable Settings
Distribution Model:
negative binomial
Dispersion Parameter:
0.15
Enter the dispersion parameter for the negative binomial model.
Any numeric value greater than 0.0 is allowed. The default value is 1.0.

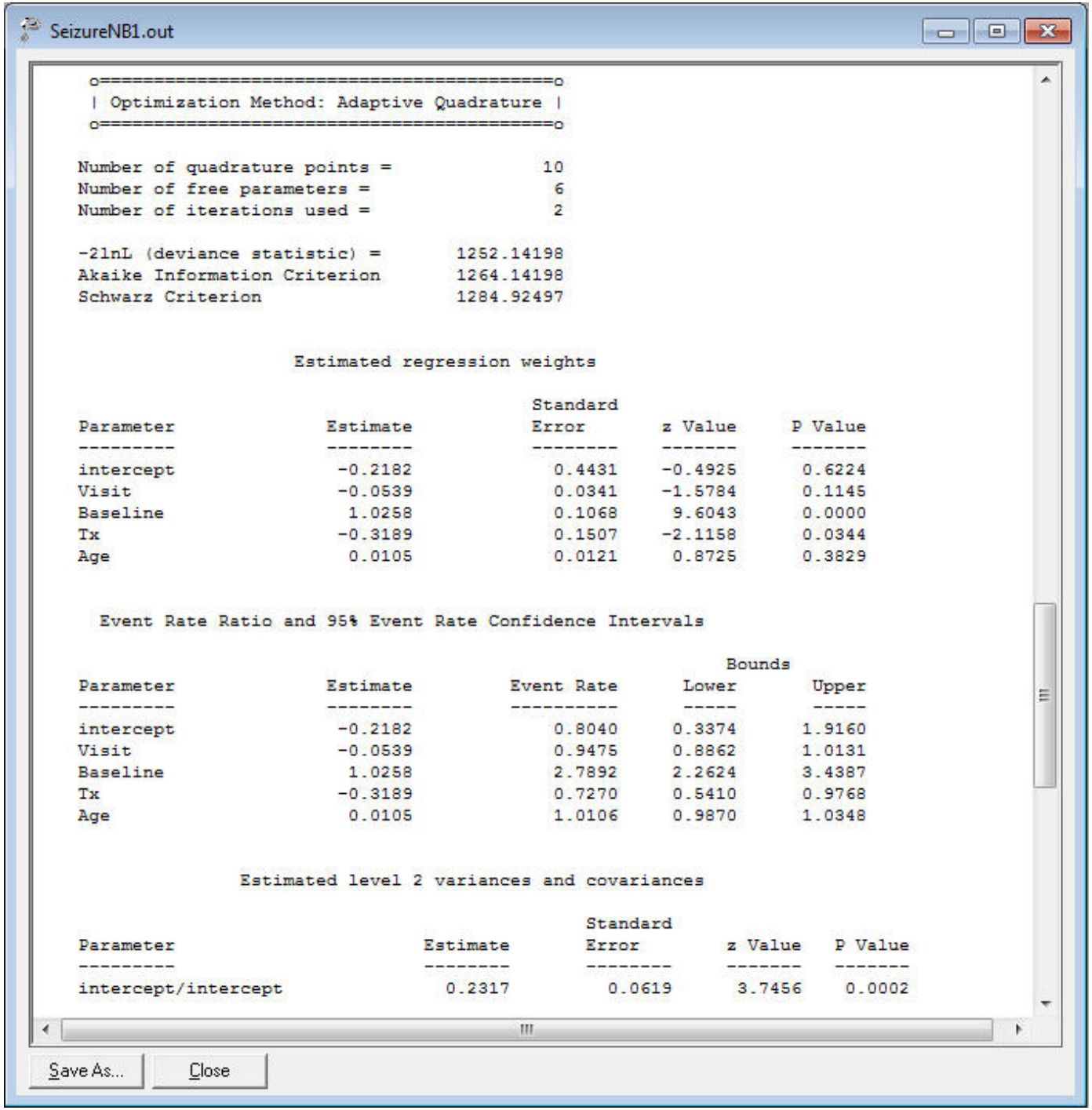

SeizureNB2.out
o===o
| Optimization Method: Adaptive Quadrature |
o===o
Number of quadrature points = 10
Number of free parameters = 8
Number of iterations used = 10
-2lnL (deviance statistic) = 1252.08997
Akaike Information Criterion 1268.08997
Schwarz Criterion 1295.80062
Estimated regression weights
Parameter Estimate Standard Error z Value P Value
intercept -0.2048 0.4449 -0.4604 0.6452
Visit -0.0516 0.0354 -1.4556 0.1455
Baseline 1.0251 0.1067 9.6114 0.0000
Tx -0.3207 0.1507 -2.1279 0.0333
Age 0.0100 0.0122 0.8181 0.4133
Event Rate Ratio and 95% Event Rate Confidence Intervals
Parameter Estimate Event Rate Bounds Lower Upper
intercept -0.2048 0.8148 0.3407 1.9486
Visit -0.0516 0.9497 0.8860 1.0180
Baseline 1.0251 2.7875 2.2616 3.4356
Tx -0.3207 0.7257 0.5401 0.9750
Age 0.0100 1.0101 0.9861 1.0346
Estimated level 2 variances and covariances
Parameter Estimate Standard Error z Value P Value
intercept/intercept 0.2458 0.0860 2.8582 0.0043
Visit/intercept -0.0050 0.0198 -0.2513 0.8016
Visit/Visit 0.0002 0.0011 0.1603 0.8727
Save As...
Close

Overdispersion? random intercept and trend models

Dispersion parameter	Distribution	Deviance (-2 logL)
0	Poisson	1314.213
.05	Negative Binomial	1262.956
.10	Negative Binomial	1253.284
.15	Negative Binomial	1252.090
.20	Negative Binomial	1254.982

- dispersion = .15 is best, with deviance difference = 62.1
- strong evidence of overdispersion
- deviance = 1252.142 for simpler random intercept NB model with dispersion = .15 (using SeizureNB1.mum)

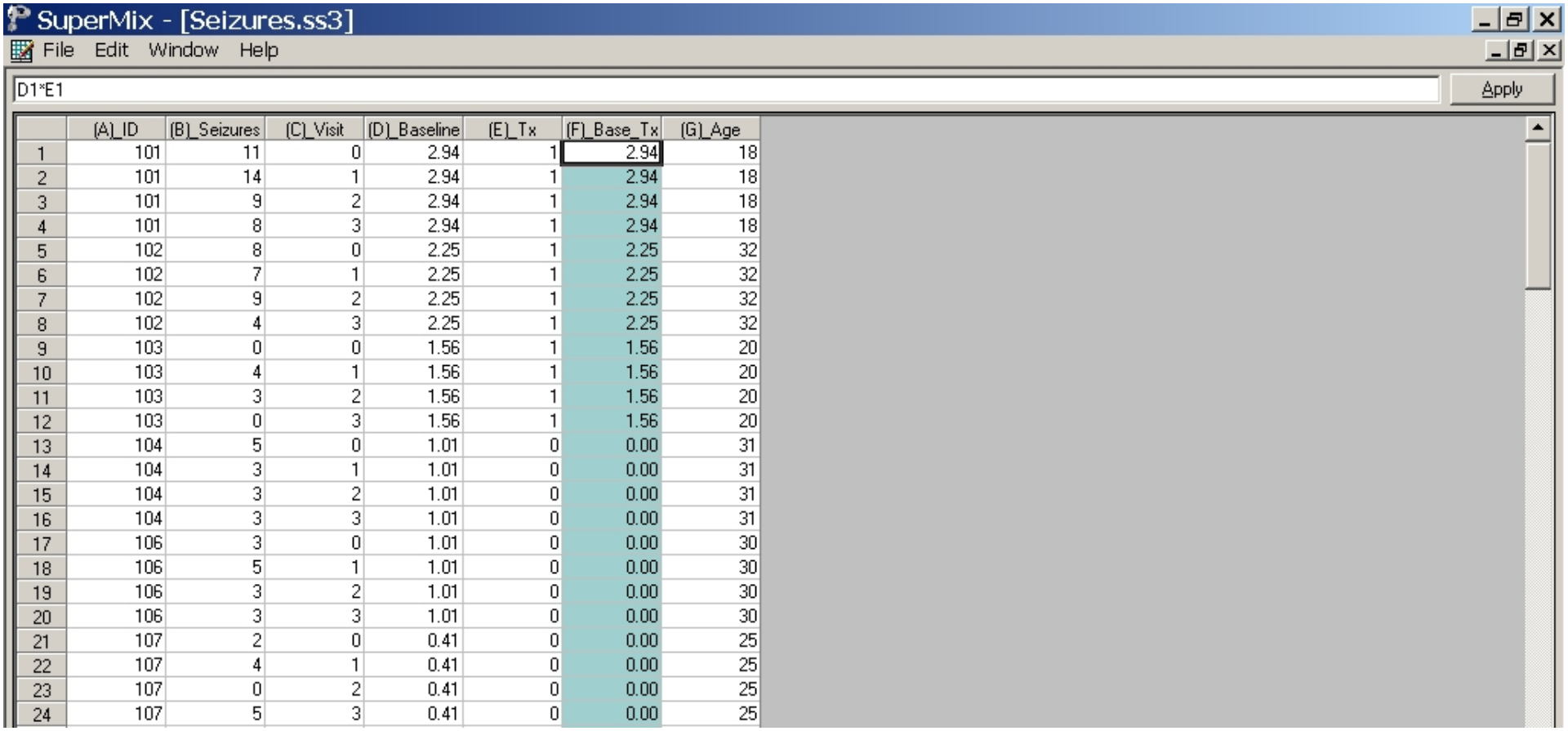
$\Rightarrow$ allowing for overdispersion, no evidence of random subject trends


SeizureNB1.out
o===o
| Optimization Method: Adaptive Quadrature |
o===o
Number of quadrature points = 10
Number of free parameters = 6
Number of iterations used = 2
-2lnL (deviance statistic) = 1252.14198
Akaike Information Criterion 1264.14198
Schwarz Criterion 1284.92497
Estimated regression weights
Parameter Estimate Standard Error z Value P Value
intercept -0.2182 0.4431 -0.4925 0.6224
Visit -0.0539 0.0341 -1.5784 0.1145
Baseline 1.0258 0.1068 9.6043 0.0000
Tx -0.3189 0.1507 -2.1158 0.0344
Age 0.0105 0.0121 0.8725 0.3829
Event Rate Ratio and 95% Event Rate Confidence Intervals
Parameter Estimate Event Rate Bounds Lower Upper
intercept -0.2182 0.8040 0.3374 1.9160
Visit -0.0539 0.9475 0.8862 1.0131
Baseline 1.0258 2.7892 2.2624 3.4387
Tx -0.3189 0.7270 0.5410 0.9768
Age 0.0105 1.0106 0.9870 1.0348
Estimated level 2 variances and covariances
Parameter Estimate Standard Error z Value P Value
intercept/intercept 0.2317 0.0619 3.7456 0.0002
Save As...
Close

Creation of an interaction term

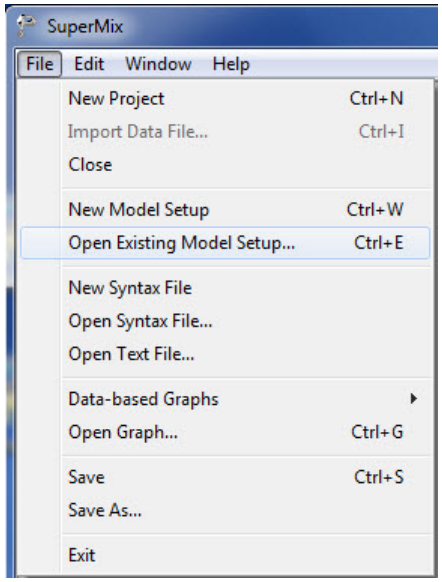
- Thall & Vail (1990) considered treatment by baseline seizure rate interaction (*i.e.*, moderation of treatment effect by baseline seizure rate level)

- This product of Baseline and Tx was created in the SuperMix spreadsheet `Seizures.ss3` as follows:
  - create a new column with header Base_Tx
  - select this column, and input the function D1∗E1 in the formula box
  - click on the Apply button
  - each value of the new variable Base_Tx is equal to the product of the corresponding values of Baseline and Tx

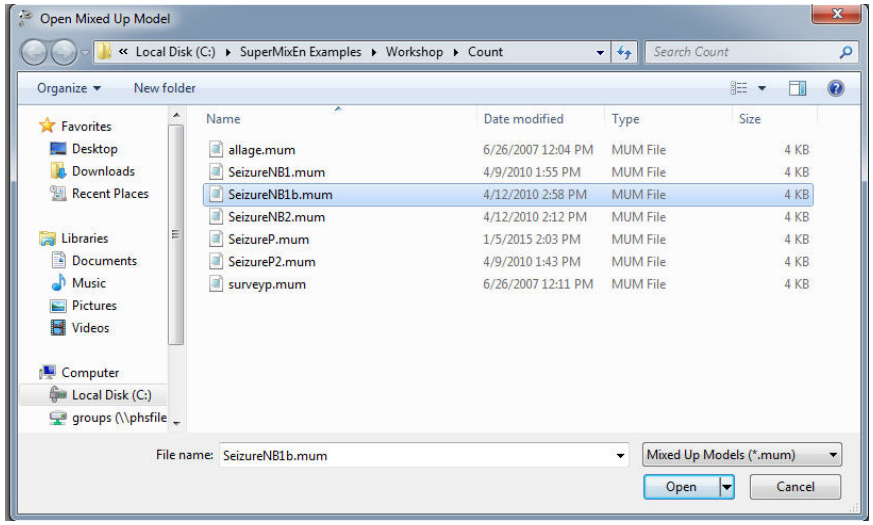


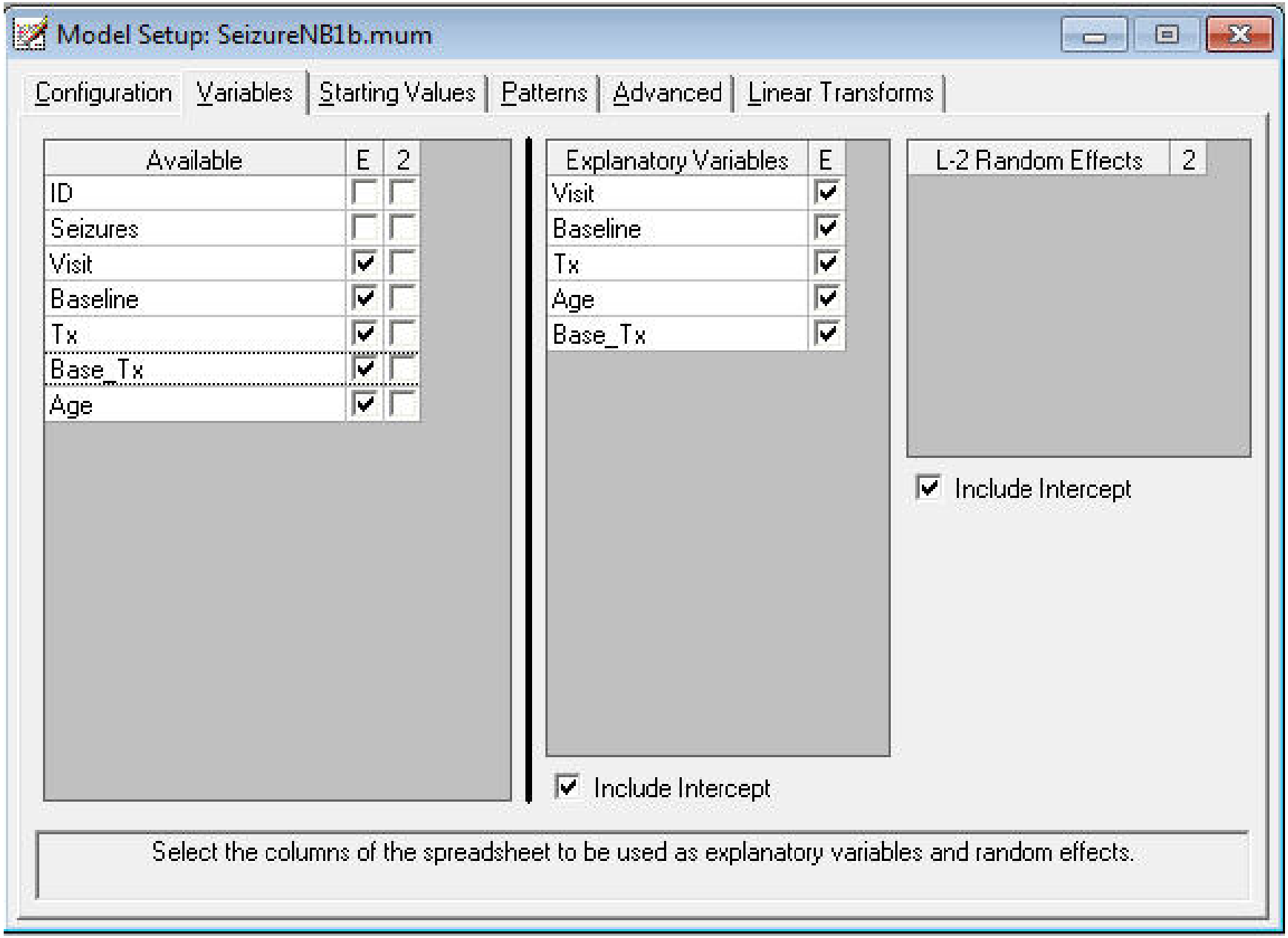
	(A)_ID	(B)_Seizures	(C)_Visit	(D)_Baseline	(E)_Tx	(F)_Base_Tx	(G)_Age
1	101	11	0	2.94	1	2.94	18
2	101	14	1	2.94	1	2.94	18
3	101	9	2	2.94	1	2.94	18
4	101	8	3	2.94	1	2.94	18
5	102	8	0	2.25	1	2.25	32
6	102	7	1	2.25	1	2.25	32
7	102	9	2	2.25	1	2.25	32
8	102	4	3	2.25	1	2.25	32
9	103	0	0	1.56	1	1.56	20
10	103	4	1	1.56	1	1.56	20
11	103	3	2	1.56	1	1.56	20
12	103	0	3	1.56	1	1.56	20
13	104	5	0	1.01	0	0.00	31
14	104	3	1	1.01	0	0.00	31
15	104	3	2	1.01	0	0.00	31
16	104	3	3	1.01	0	0.00	31
17	106	3	0	1.01	0	0.00	30
18	106	5	1	1.01	0	0.00	30
19	106	3	2	1.01	0	0.00	30
20	106	3	3	1.01	0	0.00	30
21	107	2	0	0.41	0	0.00	25
22	107	4	1	0.41	0	0.00	25
23	107	0	2	0.41	0	0.00	25
24	107	5	3	0.41	0	0.00	25

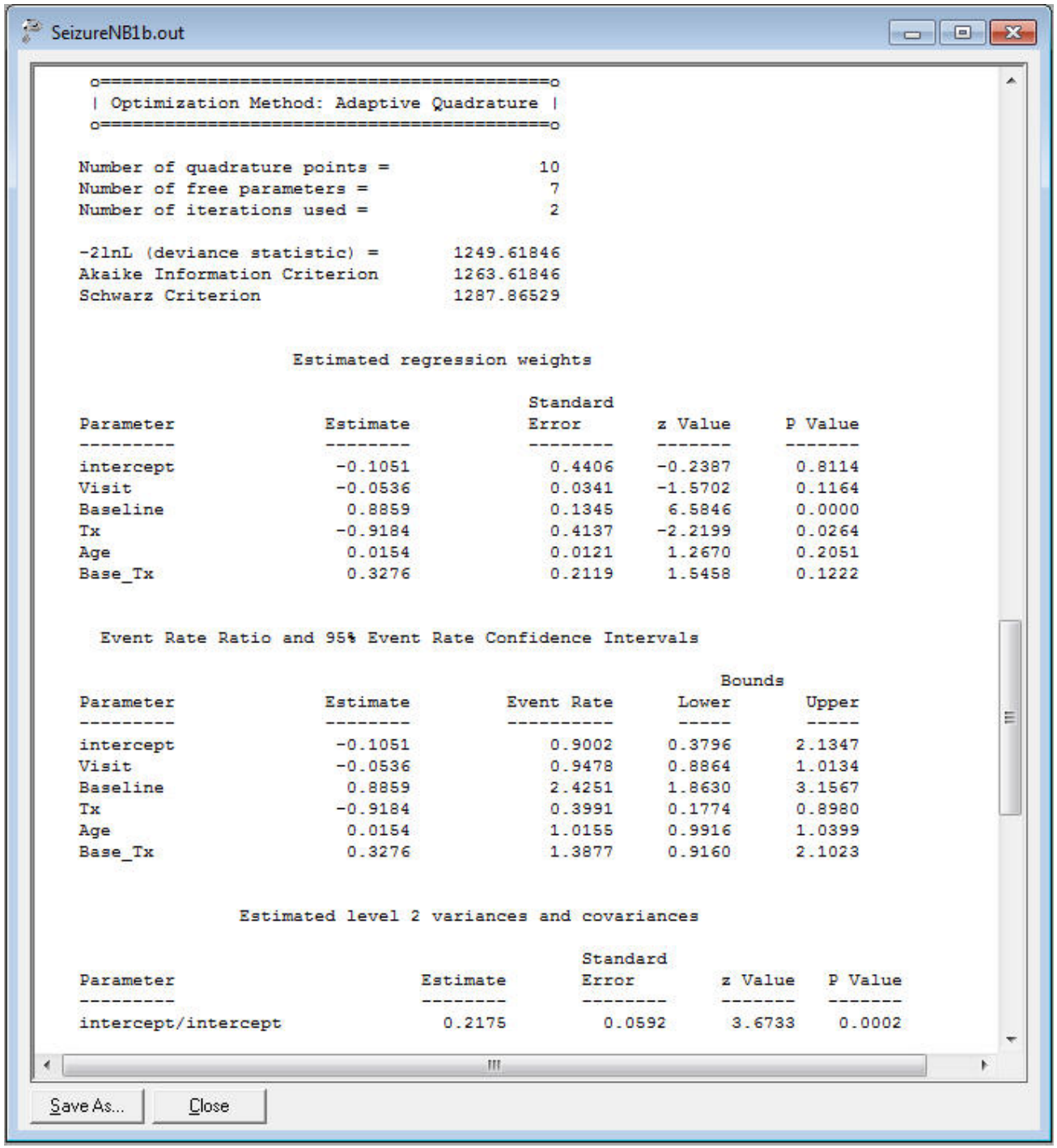
Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Workshop\Count\SeizureNB1b.mum
(or C:\SuperMixEn Student Examples\Primer\Count\SeizureNB1b.mum)




Model Setup: SeizureNB1b.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
Seizures
Visit
Baseline
Tx
Base_Tx
Age
Explanatory Variables
E
Visit
Baseline
Tx
Age
Base_Tx
Include Intercept
L-2 Random Effects
2
Include Intercept
Select the columns of the spreadsheet to be used as explanatory variables and random effects.


SeizureNB1b.out
o===o
| Optimization Method: Adaptive Quadrature |
o===o
Number of quadrature points = 10
Number of free parameters = 7
Number of iterations used = 2
-2lnL (deviance statistic) = 1249.61846
Akaike Information Criterion 1263.61846
Schwarz Criterion 1287.86529
Estimated regression weights
Parameter Estimate Standard Error z Value P Value
intercept -0.1051 0.4406 -0.2387 0.8114
Visit -0.0536 0.0341 -1.5702 0.1164
Baseline 0.8859 0.1345 6.5846 0.0000
Tx -0.9184 0.4137 -2.2199 0.0264
Age 0.0154 0.0121 1.2670 0.2051
Base_Tx 0.3276 0.2119 1.5458 0.1222
Event Rate Ratio and 95% Event Rate Confidence Intervals
Parameter Estimate Event Rate Bounds Lower Upper
intercept -0.1051 0.9002 0.3796 2.1347
Visit -0.0536 0.9478 0.8864 1.0134
Baseline 0.8859 2.4251 1.8630 3.1567
Tx -0.9184 0.3991 0.1774 0.8980
Age 0.0154 1.0155 0.9916 1.0399
Base_Tx 0.3276 1.3877 0.9160 2.1023
Estimated level 2 variances and covariances
Parameter Estimate Standard Error z Value P Value
intercept/intercept 0.2175 0.0592 3.6733 0.0002
Save As...
Close

Baseline by Tx interaction?

not really significant ($p = .122$), but

$\hat{\beta}_{\text{Tx}} = -.9184$ and $\hat{\beta}_{\text{Base\_Tx}} = .3276$ suggests that mean seizure rate for progabide group is either higher or lower than placebo group, depending on baseline seizure level

- Tx effect $= -.9184$ when (log) Baseline $= 0$
  (remember baseline seizure rate is expressed in log units)

- Tx effect $= 0$ when (log) Baseline $= .9184/.3276 = 2.8$
  (or $\exp 2.8 = 16.4$ in raw baseline seizure values)

- Tx effect > 0 when baseline seizure rate > 16.4

Summary

- Poisson overdispersion can be handled by
  - random effects
  - inclusion of overdispersion parameter (Negative Binomial regression)
  - random effects and overdispersion (mixed Negative Binomial regression)
- Zero-inflated models (ZIP, ZINB) are in Supermix update
- Supermix can handle 3-level models (repeated observations within subjects within clusters) and uses full-likelihood solutions throughout