**Example:** The data are from a randomized, double-blind, parallel-group, multicenter study comparing two oral treatments (denoted A and B) for toe-nail infection. Patients were evaluated for the degree of onycholysis (the degree of separation of the nail plate from the nail-bed) at baseline (week 0) and at weeks 4, 8, 12, 24, 36, and 48 thereafter. The onycholysis outcome variable is binary (none or mild versus moderate or severe). The binary outcome was evaluated on 294 patients comprising a total of 1908 measurements.

**Estimation**

One thing to note with this data is that the parameter estimates markedly change with the number of quadrature nodes: **The following have a random intercepts and slopes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Q=1 Quadrature Node which took T=1.4 seconds to run | | | |  |
| | **Covariance Parameter Estimates** | | | | | --- | --- | --- | --- | | **Cov Parm** | **Subject** | **Estimate** | **Standard Error** | | **UN(1,1)** | **ID** | 5864.32 | 1911.22 | | **UN(2,1)** | **ID** | -151.59 | 98.8156 | | **UN(2,2)** | **ID** | 127.79 | 51.3348 |      | **Solutions for Fixed Effects** | | | | | | | --- | --- | --- | --- | --- | --- | | **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | | **Intercept** | -12.3114 | 1.1700 | 292 | -10.52 | <.0001 | | **Treatment** | -0.1591 | 1.5153 | 1325 | -0.10 | 0.9164 | | **Month** | -10.8162 | 1.8568 | 287 | -5.83 | <.0001 | | **Treatment\*Month** | -1.4697 | 1.2562 | 1325 | -1.17 | 0.2422 |   Q=5 and T=4.18 seconds |  |  |  |  |
| | **Covariance Parameter Estimates** | | | | | --- | --- | --- | --- | | **Cov Parm** | **Subject** | **Estimate** | **Standard Error** | | **UN(1,1)** | **ID** | 291.24 | 101.17 | | **UN(2,1)** | **ID** | -21.3732 | 8.3932 | | **UN(2,2)** | **ID** | 3.2694 | 1.2970 |      | **Solutions for Fixed Effects** | | | | | | --- | --- | --- | --- | --- | | **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | | **Pr > |t|** | | **Intercept** | -6.4800 | 1.1756 | 292 | -5.51 | | <.0001 | | **Treatment** | -0.1972 | 1.2264 | 1325 | -0.16 | | 0.8723 | | **Month** | -1.4157 | 0.3634 | 287 | -3.90 | | 0.0001 | | **Treatment\*Month** | -0.1545 | 0.1913 | 1325 | -0.81 | | 0.4194 | |
| Q=10 and T= 7.4 sec   | **Covariance Parameter Estimates** | | | | | --- | --- | --- | --- | | **Cov Parm** | **Subject** | **Estimate** | **Standard Error** | | **UN(1,1)** | **ID** | 93.1842 | 19.6569 | | **UN(2,1)** | **ID** | -6.1591 | 1.6685 | | **UN(2,2)** | **ID** | 1.0910 | 0.2606 |      | **Solutions for Fixed Effects** | | | | | | | --- | --- | --- | --- | --- | --- | | **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | | **Intercept** | -3.5233 | 1.0978 | 292 | -3.21 | 0.0015 | | **Treatment** | -0.2423 | 1.4467 | 1325 | -0.17 | 0.8670 | | **Month** | -0.9130 | 0.2175 | 287 | -4.20 | <.0001 | | **Treatment\*Month** | -0.2169 | 0.2012 | 1325 | -1.08 | 0.2811 | |  |  |  |  |
| Q=20 and T= 36 sec   | **Covariance Parameter Estimates** | | | | | --- | --- | --- | --- | | **Cov Parm** | **Subject** | **Estimate** | **Standard Error** | | **UN(1,1)** | **ID** | 179.91 | 51.2581 | | **UN(2,1)** | **ID** | -13.4084 | 4.3381 | | **UN(2,2)** | **ID** | 2.1557 | 0.6290 |      | **Solutions for Fixed Effects** | | | | | | | --- | --- | --- | --- | --- | --- | | **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | | **Intercept** | -5.3596 | 1.5727 | 292 | -3.41 | 0.0007 | | **Treatment** | -0.2160 | 1.6621 | 1325 | -0.13 | 0.8966 | | **Month** | -0.8947 | 0.2171 | 287 | -4.12 | <.0001 | | **Treatment\*Month** | -0.5754 | 0.2400 | 1325 | -2.40 | 0.0167 | |  |  |  |  |
| Q=50 and T= 3 minutes and 08 seconds | |  |  |  |

| **Covariance Parameter Estimates** | | | |
| --- | --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** | **Standard Error** |
| **UN(1,1)** | **ID** | 76.1561 | 20.9446 |
| **UN(2,1)** | **ID** | -5.5172 | 1.8133 |
| **UN(2,2)** | **ID** | 1.1002 | 0.3236 |

| **Solutions for Fixed Effects** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **Intercept** | -2.6926 | 0.9627 | 292 | -2.80 | 0.0055 |
| **Treatment** | -0.07782 | 1.2446 | 1325 | -0.06 | 0.9502 |
| **Month** | -0.8318 | 0.1827 | 287 | -4.55 | <.0001 |
| **Treatment\*Month** | -0.3521 | 0.1873 | 1325 | -1.88 | 0.0603 |

**GEE vs GLMM**

Now let’s fit the same model using GEE.

**proc** **gee** data=toenail descend;

class id;

model Response=Treatment Month Treatment\*Month /d=bin link=logit;

repeated subject=ID/corr=UN corrw;

**run**;

Let’s look at the results:

| **Analysis Of GEE Parameter Estimates** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Empirical Standard Error Estimates** | | | | | | |
| **Parameter** | **Estimate** | **Standard Error** | **95% Confidence Limits** | | **Z** | **Pr > |Z|** |
| **Intercept** | -0.7625 | 0.1695 | -1.0947 | -0.4304 | -4.50 | <.0001 |
| **Treatment** | 0.0451 | 0.2550 | -0.4548 | 0.5449 | 0.18 | 0.8597 |
| **Month** | -0.1277 | 0.0260 | -0.1786 | -0.0768 | -4.92 | <.0001 |
| **Treatment\*Month** | -0.0866 | 0.0480 | -0.1807 | 0.0075 | -1.80 | 0.0713 |

For the GLMM with Q=50 we had

| **Solutions for Fixed Effects** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **Intercept** | -2.6926 | 0.9627 | 292 | -2.80 | 0.0055 |
| **Treatment** | -0.07782 | 1.2446 | 1325 | -0.06 | 0.9502 |
| **Month** | -0.8318 | 0.1827 | 287 | -4.55 | <.0001 |
| **Treatment\*Month** | -0.3521 | 0.1873 | 1325 | -1.88 | 0.0603 |

How to explain the differences





The parameter vector in the GEE model needs to be interpreted completely different from the parameter vector in the GLMM:

* GEE: marginal interpretation
* GLMM: conditional interpretation, conditionally upon level of random effects

• In general, the model for the marginal average is not of the same parametric form as the conditional average in the GLMM.

• The coefficients for a logistic mixed model with normally distributed random intercepts, can be approximated by again a logistic GEE model

Where σ is the standard deviation of the random intercepts and c = 0.5881. In the toenail example we had random intercepts and slopes.

If we change to random intercepts only we get:

| **Covariance Parameter Estimates** | | | |
| --- | --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** | **Standard Error** |
| **UN(1,1)** | **ID** | 16.0531 | 3.0441 |

| **Solutions for Fixed Effects** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **Intercept** | -1.6183 | 0.4343 | 292 | -3.73 | 0.0002 |
| **Treatment** | -0.1609 | 0.5840 | 1612 | -0.28 | 0.7830 |
| **Month** | -0.3910 | 0.04438 | 1612 | -8.81 | <.0001 |
| **Treatment\*Month** | -0.1368 | 0.06801 | 1612 | -2.01 | 0.0444 |

For the Toenail example σ was 4.001 with makes . Using this we get

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect** | **GLMM Estimate** | **GLMM/2.559** | **GEE** |
| **Intercept** | -1.6183 | -0.632 | -0.7625 |
| **Treatment** | -0.1609 | -0.063 | 0.0451 |
| **Month** | -0.3910 | -0.153 | -0.1277 |
| **Treatment\*Month** | -0.1368 | -0.053 | -0.0866 |

In general the coefficients from GLMM are larger in absolute value than those from GEE.