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# Core Guide: Correlation Structures in Mixed Effects Models for Longitudinal Data Analysis

*Part of a series addressing common issues in statistical and epidemiological design and analysis*

## Background

Longitudinal data, also commonly called repeated measures data, is defined as data collected on subjects, or another unit of analysis (e.g., village) repeatedly over time. Whereas a time series usually includes a long time series on a single (or small number of) sequences, repeated measures are typically measured on a relatively large number of subjects over a more limited period of time. Measurements may be approximately equally spaced, as may be the case in carefully controlled laboratory studies or clinical trials, or unequally spaced, as may be the case in electronic health records (EHR) data where subjects are measured when they happen to go to the doctor. Longitudinal data may also be balanced (i.e., having the same number of measures on each subject) or unbalanced. Two primary methods of choice for analyzing the relationship between an outcome and time (and other covariates) are generalized estimating equations (GEE) and mixed-effects models (see Fitzmaurice, Laird, and Ware (2011)[1] for detailed background on each method). The current guide focuses on mixed-effects models, commonly referred to succinctly as "mixed models".

When data are repeatedly measured on the same subject over time, data collected on the same individual are generally positively correlated with each other. For example, my weight today is generally correlated with my weight one month from now, and my current risk of malaria is often correlated with my risk last month, as well as last year at the same time (seasonal effect). However, we assume that data between subjects is independent and uncorrelated, as would (ideally) be the case in an individually-randomized controlled trial (RCT). In a cluster randomized controlled trial, however, we might have correlation among individuals within the same cluster, as well as with repeated measures on the same individual over time. See the recent review articles by Turner et al. for more information about cluster randomized trials.[2,3]

When data are positively correlated within individual, ignoring the correlation in the analysis (e.g., fitting an ordinary least squares linear regression) will lead to inflated type I error rates for time-independent variables (e.g., sex, race) because of underestimated standard errors and inflated type II error rates for time-dependent variables (e.g., the time effect, certain biologic measurements and weight)..[4]

The purpose of the current core guide is to review modeling strategies of longitudinal person-level data in the mixed effects modeling framework in order to account for within-person correlation. We specifically focus on continuous outcomes, and discuss the modeling of different types of within-person correlation structures through the use of random effects, the residual error terms and a combination of both. We discuss different types of error structures and model data described in chapters 7 and 8 of

Fitzmaurice, Laird, and Ware (2011).[1] Mixed effects models for non-Gaussian (e.g., binary) require another set of methods, and interpretation of parameters is more complicated, so will be discussed in a future core guide.

## The Mixed-Effects Model

The mixed-effects model is useful for modeling outcome measurements in any type of grouped (i.e., correlated) data, whether those groups are schools, communities, families, or repeated measures within subjects. In various types of literature, the mixed model has been formulated in both a two-stage and one-stage manner.[5] In this core guide, we focus on the more commonly used one-stage formulation given by:

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Z\gamma} + \boldsymbol{\varepsilon};\;\; \boldsymbol{\varepsilon} \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{R}),\;\; \boldsymbol{\gamma} \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{G}) \qquad (1)$$

where $\boldsymbol{X\beta}$ is the “fixed-effects” part of the model, $\boldsymbol{Z\gamma}$ is the random effects part of the model, and $\boldsymbol{\varepsilon} \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{R})$ is the residual error vector. $\boldsymbol{Y}$ “represents a vector of observed outcome data, $\boldsymbol{\beta}$ is an unknown vector of fixed-effects parameters with known design matrix $\boldsymbol{X}$”, and “$\boldsymbol{\gamma}$ is an unknown vector of random-effects parameters with known design matrix $\boldsymbol{Z}$”.[6] We use **G** to represent the variance-covariance matrix of the random effects and **R** represents the variance-covariance matrix of the residual errors. It follows that the total variance of $\boldsymbol{Y}$ is given by

$$\boldsymbol{V} = \boldsymbol{ZGZ}' + \boldsymbol{R}. \qquad (2)$$

What are the implications of specifying the correlation of repeated measurements on the same individual by including the $\boldsymbol{\gamma}$ vector of random effects (i.e. and then specifying the structure of **G)** and/or changing **R**? It is common for **R** to be specified as the identity matrix so that the residual errors are assumed to be independent of each other. In this case, correlation of repeated measures on the same individual can be accounted for by including random effects $\boldsymbol{\gamma}$ and by specifying a structure for **G**. Another option is to not include random effects and to simply fit a structure on the **R** matrix to account for within-person correlation. Some kinds of simple within-person correlation structures can be specified using either formulation. For example, the commonly used ‘exchangeable’ (or compound symmetry) correlation structure, in which the same correlation is assumed for all pairs of measurements on the same person irrespective of their timing, can be modeled either by (1) including a random intercept for each person (**G** $=\sigma_b^2 \boldsymbol{I}$), or, (2) by not adding random intercepts but instead by setting **R** to be a block diagonal matrix with the same covariance on the off diagonals.

The random effects can include a random intercept and any function of covariates of interest, e.g with a random slope on time. Longitudinal models with both a random intercept and a random slope for time induces a within-individual correlation matrix with correlations that decrease in magnitude the further apart the measurements are on the same person—a common feature of longitudinal data. More complex random effects structures—including adding polynomials for the time effect—are sometimes used. More detail on random effects specification is given in the appendix.

When random effects are added to the model, fixed parameters are interpreted in terms of conditional means. That is, the fixed-effects coefficients are interpreted in terms of changes in subject-specific mean responses, rather than population-averaged mean response (e.g. as would be the case with the GEE approach). However, as Fitzmaurice, Laird, and Ware (2011)[1] show on page 404 of their book, in the case of continuous outcomes (fitted with an identity link function) the population-averaged and conditional models are the same (i.e., we can interpret the coefficients in both a population-level and subject-specific manner). This is not the case for generalized linear mixed models (GLMMs), where the conditional and population-averaged models can differ. This has implications for interpretation when analyzing non-Gaussian data.

Commonly used parameter estimation methods are maxiumum likelihood estimation (MLE) and restricted maximum likelihood estimation (REML). REML should be the estimation method of choice, since the standard errors are biased downward with ML.[7] When fitting regression models to longitudinal data using either approach, it is important to remember that the fixed effects mean structure is inherently linked to the covariance structure. Misspecified covariance structure leads to biased estimates of coefficients in the model of the mean. Thus, it is important to properly specify the covariance structure. Model selection procedures, such as the Akaike Information Criterion (AIC) or likelihood ratio test, can be used to select the most appropriate covariance structure.

## Conclusion

We have reviewed the theory behind the modeling of the covariance structure in linear mixed effects models. The choice of modeling the random effects or simply modeling the **R** matrix depends on whether one is interested in the covariance parameters themselves (modeling the random effects) or is treating the covariance as a nuisance to model just in order to avoid bias in the mean parameters (modeling the **R** matrix). The appendix contains detailed examples and code, including more discussion on when to model the random effects or the **R** matrix. This core guide serves as an introduction to modeling the covariance in longitudinal data analysis. For a more in-depth look at the topic, see for example Fitzmaurice, Laird, and Ware (2011).[1]

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*Version: 1.1, last updated September 19, 2017*

## References

1. Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis.* 2nd ed. Hoboken, N.J.: Wiley; 2011.
2. Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1 - Design. *Am J Public Health.* 2017;107(6):907-915.
3. Turner EL, Prague M, Gallis JA, Li F, Murray DM. Review of Recent Methodological Developments in Group-Randomized Trials: Part 2 - Analysis. *Am J Public Health.* 2017;107(7):1078-1086.
4. Dunlop DD. Regression for longitudinal data: a bridge from least squares regression. *The American Statistician.* 1994;48:299+.
5. Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *J Educ Behav Stat.* 1998;23(4):323-355.
6. SAS/STAT 9.2 user's guide. SAS Institute Cary, NC; 2008.
7. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. *SAS for mixed models.* SAS institute; 2007.
8. Wolfinger RD. Heterogeneous variance: covariance structures for repeated measures. *J Agric Biol Environ Stat.* 1996:205-230.
9. Diggle P, Heagerty P, Liang K-Y, Zeger S. *Analysis of longitudinal data.* 2nd ed. Oxford ; New York: Oxford University Press; 2002.

## Appendix

## Modeling correlation structures in common statistical software

In SAS PROC MIXED, which allows the user to fit linear mixed effects models with continuous outcomes, we can model the the covariance structure of the random effects (**G**) using the RANDOM statement, and we can model the covariance structure of of the errors (**R**) using the REPEATED statement (see equation (1)). Hence, we can model the total variability in $\boldsymbol{Y}$ by specifying a structure on either the **G** or **R** matrix, or both. In Stata, using the command `mixed`, the random effects are specified after ||, and the **R** matrix is specified using the option `residuals()` after the random effects part of the model formulation.

We now move on to some examples, using data described and analyzed in chapters 7 and 8 of Fitzmaurice, Laird, and Ware (2011).[1]

## Example 1: Exploring random effects and residual correlation structures

For this first example, we use the exercise therapy trial data, as described on page 180 of Fitzmaurice, Laird, and Ware (2011)[1]:

> In this study, subjects were assigned to one of two weightlifting programs to increase muscle strength. In the first program, hereafter referred to as treatment 1, the number of repetitions of the exercises was increasaed as subjects became stronger. In the second program, hereafter referred to as treatment 2, the number of repetitions was held constant but the amount of weight was increased as subjects became stronger. Measurements of muscle strength were taken at baseline and on days 2, 4, 6, 8, 10, and 12.

To simplify for this illustration, we only consider baseline, day 6, and day 12, referred to as time 0, 1, and 2. The data on n=37 people are plotted in figure 1. It is difficult to get a good idea of the data from the plot (often called a spaghetti plot), although it looks like a good number of people initially increase in strength and then decline by time 2 (day 12). Some other features we notice are that at least one subject is missing the final measurement (e.g. see the data shown in the the upper dashed red line).

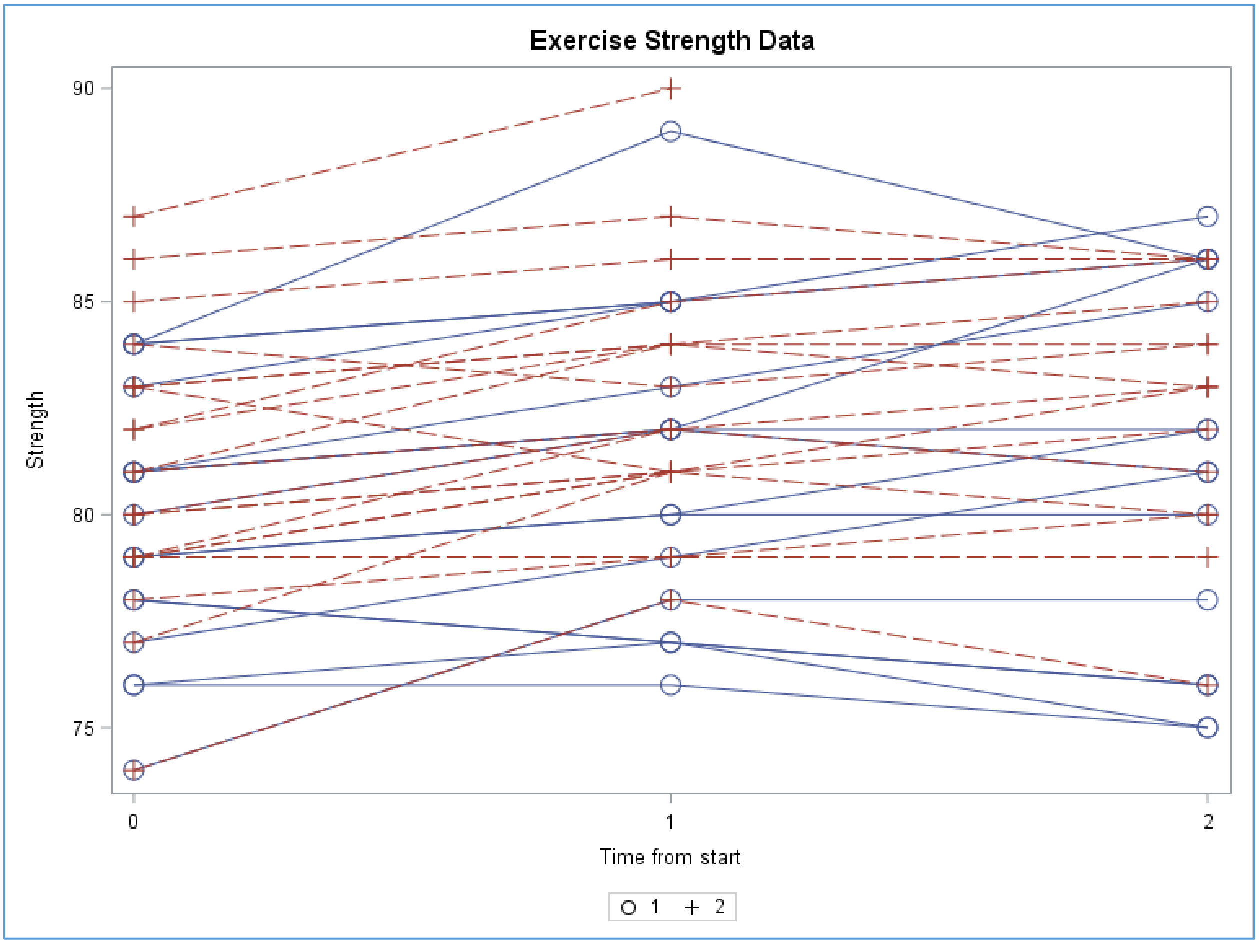


*Figure 1*

Let's look at a simple model with time, treatment group, and the interaction between the two, and examine different covariance structures. Specifically, we model up to three measurements of strength (i.e. at times 0, 1 and 2) for each subject.

In SAS, using a REPEATED statement with compound symmetry (CS) structure (also referred to as an exchangeable structure) will give the same results as using a RANDOM statement with only a random intercept specified. When using the REPEATED statement only, the term $\boldsymbol{\gamma}$ is excluded from model (1) and within-person correlation is accounted for by specifying **R** to be an exchangeable correlation matrix. In contrast, when using the RANDOM statement only, **R** is assumed to be an identity matrix and, instead, $\boldsymbol{\gamma}$ is a vector of random intercepts. The SAS code is given as follows:

**SAS code snippet 1:**

```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      repeated time / type=CS subject=id R=2;
run;
```

**SAS code snippet 2:**

```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      random INTERCEPT / subject=id G V=2;
run;
```

The equivalent Stata code is given by the following. Note that **in SAS, restricted maximum likelihood (REML) is the default, but in Stata, maximum likelihood (ML) is the default, so the reml option must be specified in Stata.** In addition, we use the fvset command to change the reference category for program and time to match the default reference category used in SAS.

```
fvset base 2 program
fvset base 2 time
```

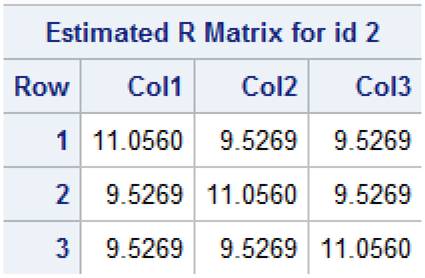
**Stata code snippet 1:**

```
/* equivalent of SAS repeated statement with compound symmetry
(exchangeable) structure on the residuals */
mixed strength i.program i.time i.program#i.time, reml || id: , noconstant
residuals(exch, t(time)) variance
```

**Stata code snippet 2:**

```
/* equivalent of SAS random statement with random intercept */
mixed strength i.program i.time i.program#i.time, reml || id:
```

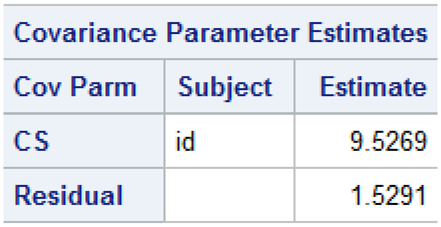
**SAS code snippet 1** (and equivalently, **Stata code snippet 1**), which excludes the $\boldsymbol{\gamma}$ vector, gives the following for the residual correlation structure for person 2, which in this case equals the total variance for person 2 since the random effects are 0. Person 2 was chosen for illustration. In practice, this R matrix will be the same for every individual, although smaller if a person is missing data at a time point. This is model is not conditioned on any random effects.



| Estimated R Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 11.0560 | 9.5269 | 9.5269 |
| 2 | 9.5269 | 11.0560 | 9.5269 |
| 3 | 9.5269 | 9.5269 | 11.0560 |

*Code Output 1*

And the covariance parameter estimates are:



| Covariance Parameter Estimates | | |
|---|---|---|
| Cov Parm | Subject | Estimate |
| CS | id | 9.5269 |
| Residual | | 1.5291 |

*Code Output 2*

The notation is as follows for the CS structure:

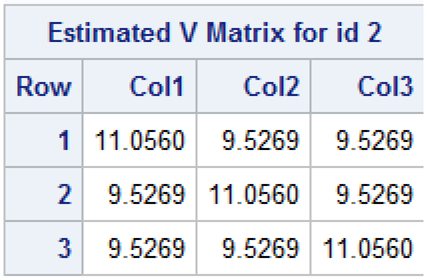
$$\begin{bmatrix} \sigma^2 + \sigma_b & \sigma_b & \sigma_b \\ \sigma_b & \sigma^2 + \sigma_b & \sigma_b \\ \sigma_b & \sigma_b & \sigma^2 + \sigma_b \end{bmatrix}$$

where $\sigma_b$ is the CS parameter (9.5269) and sigma-squared is the residual parameter. Thus, based on the off-diagonals, we estimate a covariance of 9.5269 between two measurements on the same person, regardless of time lapsed. Based on the diagonal elements, we estimate a constant residual variance of 9.5269 + 1.5291 = 11.056. Also, all subjects have the same covariance structure. Since the random effects are zero in this model, the total variance of $\boldsymbol{Y}$ is equal to the **R** matrix. That is, $\boldsymbol{V} = \boldsymbol{R}$.

In **SAS code snippet 2** (and equivalently, **Stata code snippet 2**), we fit a random intercept model. In this model, we obtain the same structure on the total variance matrix (i.e, **V** matrix) as the model fit without random effects but with a compound symmetry structure on the residuals (**SAS code snippet 1**). It can be easily shown from the formula for **V** that in the random intercept model we end up with (if we call the random intercept variance $\sigma_b$)

$$\boldsymbol{V} = \sigma_1 + \sigma^2 \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} \sigma^2 + \sigma_b & \sigma_b & \sigma_b \\ \sigma_b & \sigma^2 + \sigma_b & \sigma_b \\ \sigma_b & \sigma_b & \sigma^2 + \sigma_b \end{bmatrix},$$

which is the compound symmetry structure. Indeed, from **SAS code snippet 2**, which specifies a random intercept for each person, we obtain the following **V** matrix in **code output 3**.



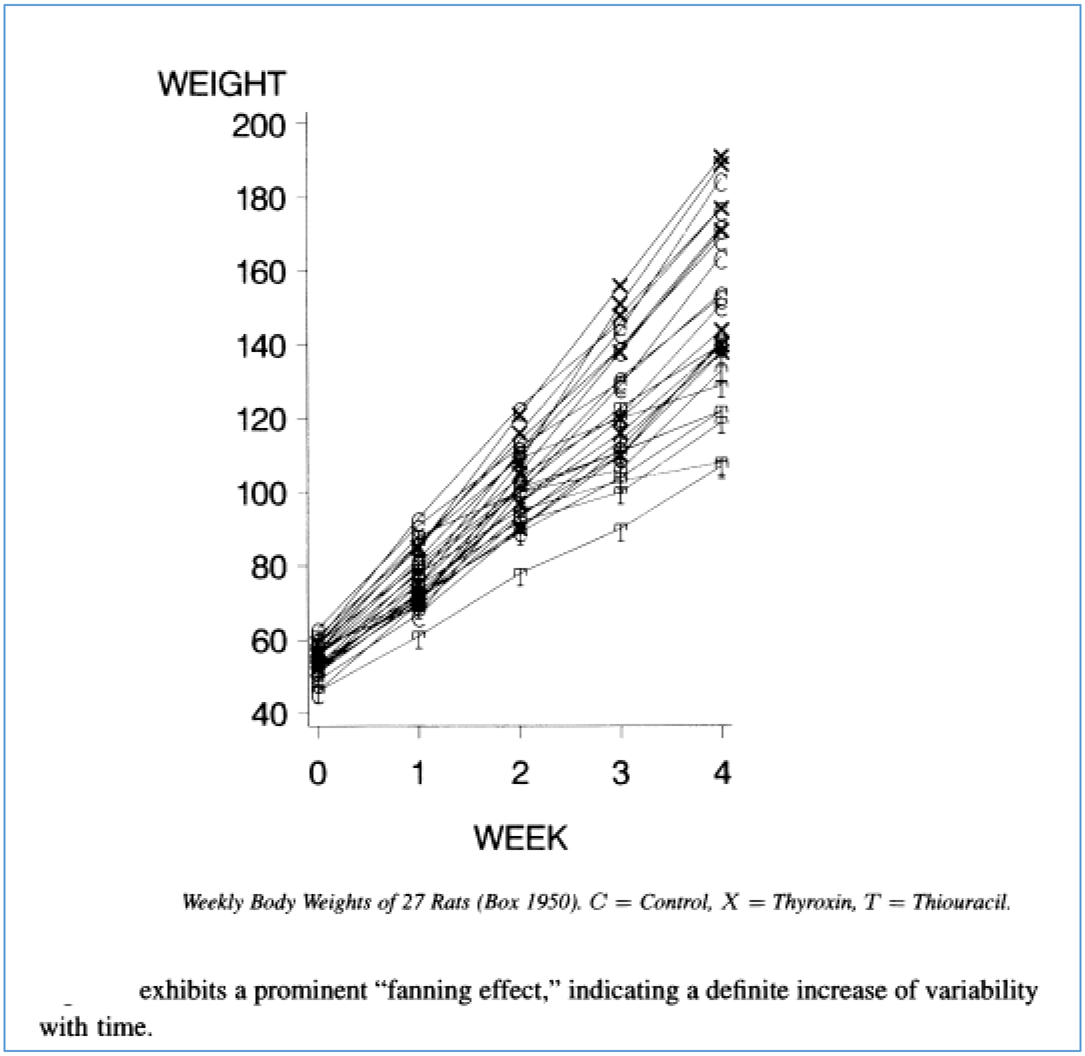
| Estimated V Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 11.0560 | 9.5269 | 9.5269 |
| 2 | 9.5269 | 11.0560 | 9.5269 |
| 3 | 9.5269 | 9.5269 | 11.0560 |

*Code Output 3*

This is the same as the structure when fitting the model using the REPEATED statement with compound symmetry structure (**code output 1**). The difference comes in the interpretation of the fixed-effects mean model, since with the first model we have a population averaged interpretation, but with the second model (with the RANDOM statement) we have a population averaged and conditional interpretation. However, the value of the means and standard deviations of the fixed effects are the same across both models.

In longitudinal models with subjects (participants) measured at more than two time points, compound symmetry is usually not realistic. First, covariance between measures on the same person often decays over time. For example, my weight tomorrow is probably much more related to my weight today than is my weight one year from now. Additionally, commonly seen in longitudinal studies is an increase in variance over time. For example, from page 206 of Wolfinger (1996)[8], when we examine the body weights of 27 rats in three treatment groups over time, a clear increase in variability of body weights is seen as time increases (**figure 2**).

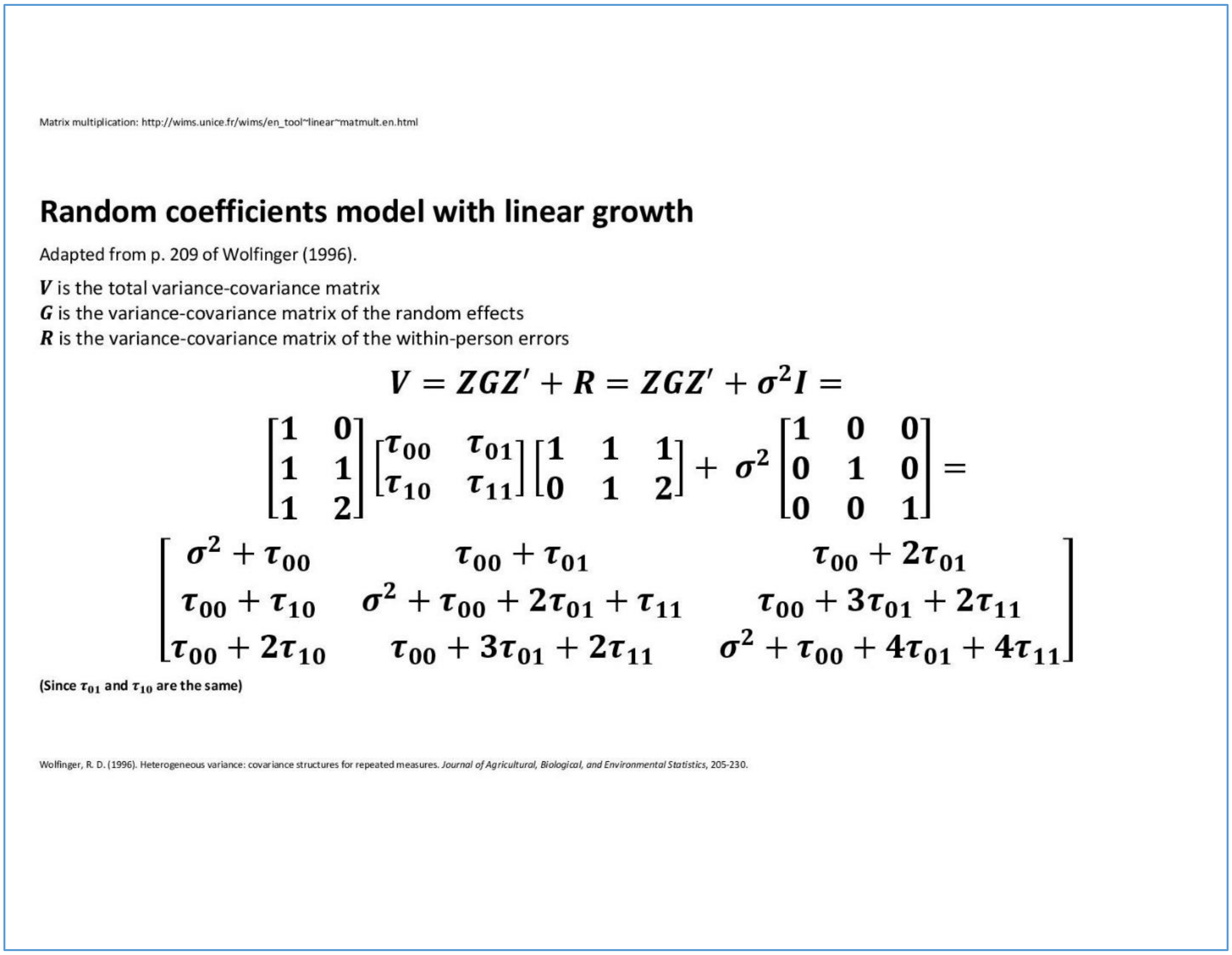
In this case, we may wish to fit a random effects model with a random intercept and random slope for time, in order to account for increasing variance in outcome measurements over time. How does this compare to an autoregressive(1) structure on the **R** matrix, to which this is often compared?



*Weekly Body Weights of 27 Rats (Box 1950). $C$ = Control, $X$ = Thyroxin, $T$ = Thiouracil.*

exhibits a prominent “fanning effect,” indicating a definite increase of variability with time.

Figure 2. extracted from Wolfinger (1996).[8]



Matrix multiplication: http://wims.unice.fr/wims/en_tool~linear~matmult.en.html

## Random coefficients model with linear growth

Adapted from p. 209 of Wolfinger (1996).

***V*** is the total variance-covariance matrix
***G*** is the variance-covariance matrix of the random effects
***R*** is the variance-covariance matrix of the within-person errors

$$\boldsymbol{V = ZGZ' + R = ZGZ' + \sigma^2 I =}$$

$$\begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 2 \end{bmatrix} \begin{bmatrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 \\ 0 & 1 & 2 \end{bmatrix} + \sigma^2 \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} =$$

$$\begin{bmatrix} \sigma^2 + \tau_{00} & \tau_{00} + \tau_{01} & \tau_{00} + 2\tau_{01} \\ \tau_{00} + \tau_{10} & \sigma^2 + \tau_{00} + 2\tau_{01} + \tau_{11} & \tau_{00} + 3\tau_{01} + 2\tau_{11} \\ \tau_{00} + 2\tau_{10} & \tau_{00} + 3\tau_{01} + 2\tau_{11} & \sigma^2 + \tau_{00} + 4\tau_{01} + 4\tau_{11} \end{bmatrix}$$

**(Since $\tau_{01}$ and $\tau_{10}$ are the same)**

Wolfinger, R. D. (1996). Heterogeneous variance: covariance structures for repeated measures. *Journal of Agricultural, Biological, and Environmental Statistics*, 205-230.

*Image 1. adapted from Wolfinger (1996).[8]*

Wolfinger (1996)[8] calls the linear mixed effects model with random intercept and random (linear) slope by time the "random coefficients model with linear growth", abbreviated RCL. If we performed the matrix algebra on an example with three time periods (**image 1**), we might find that the covariance between random effects (indicated by $\tau_{01}$ in the above figure) is constrained to be 0, and the covariance remains constant across the top row and first column. If the covariance between random effects is negative (i.e., someone with a low intercept [starting point] has a greater slope, and vice versa) which is often the case in longitudinal studies, then the modeled covariance decays over time.

Additionally, since $\tau_{00}$ and $\tau_{01}$ are variances and hence must be greater than or equal to zero (and in practice will be greater than zero), the RCL model assumes increased variance over time, regardless of whether one fits a covariance between the random effects or not.

First, we fit an RCL model on the exercise data with the random effects covariance constrained to zero (**code snippets 3**).

**SAS code snippet 3:**

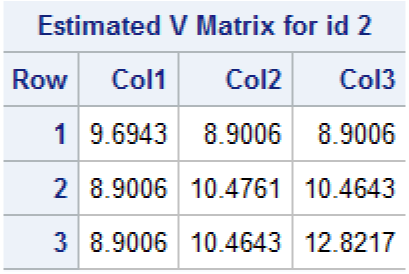
```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      random INTERCEPT time_cont / subject=id G GCORR V=1,2 VCORR;
run;
```

The equivalent Stata code is:

**Stata code snippet 3:**

```
/* equivalent of SAS random statement with random intercept and slope but
no covariance */
mixed strength i.program i.time i.program#i.time, reml || id: time
```

Note that we've added a variable time_cont (time treated as a continuous variable) to the random part of the model in SAS. Time must be treated as continuous rather than categorical in the random part of the model to obtain the desired properties, even if the fixed part of the model contains time as a categorical variable. In Stata, time is treated as categorical by adding i. in front of the variable name. The **V** matrix (total variance-covariance) for person 2 is thus,

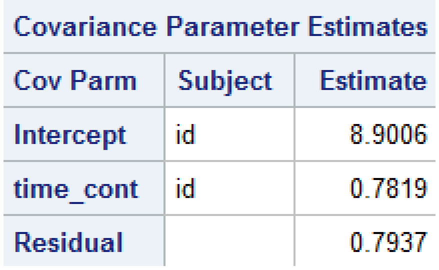


Estimated V Matrix for id 2

| Row | Col1 | Col2 | Col3 |
|---|---|---|---|
| 1 | 9.6943 | 8.9006 | 8.9006 |
| 2 | 8.9006 | 10.4761 | 10.4643 |
| 3 | 8.9006 | 10.4643 | 12.8217 |

*Code Output 4*

The random effects parameters ($\tau_{00}$ and $\tau_{01}$) and the residual error ($\sigma^2$) are as follows:



Covariance Parameter Estimates

| Cov Parm | Subject | Estimate |
|---|---|---|
| Intercept | id | 8.9006 |
| time_cont | id | 0.7819 |
| Residual | | 0.7937 |

*Code Output 5*

If we fit an unstructured covariance matrix to the random effects, allowing for a covariance between random intercept and slope, we fit the following code (**code snippets 4**).

**SAS code snippet 4:**

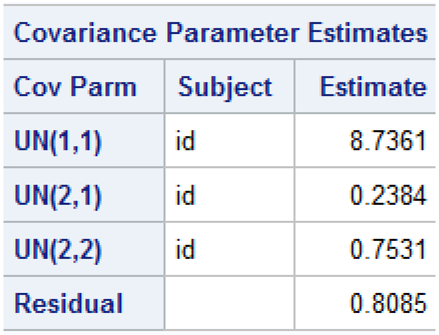
```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      random INTERCEPT time_cont / type=un subject=id G GCORR V=1,2 VCORR;
run;
```

The equivalent Stata code is:

**Stata code snippet 4:**

```
/* equivalent of SAS random statement with random intercept and slope and
covariance between the two */
mixed strength i.program i.time i.program#i.time, reml || id: time,
covariance(un)
```

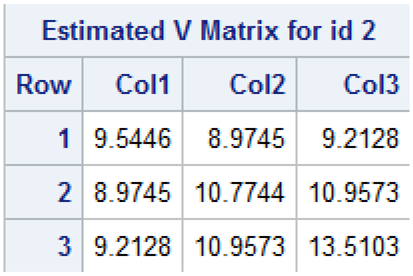
For this particular data, from **code snippets 4** we obtain a positive covariance between the random intercept and slope, indicating that those with a higher intercept (starting point) actually have a greater slope than those with lower intercept (starting point).



| Covariance Parameter Estimates | | |
|---|---|---|
| Cov Parm | Subject | Estimate |
| UN(1,1) | id | 8.7361 |
| UN(2,1) | id | 0.2384 |
| UN(2,2) | id | 0.7531 |
| Residual | | 0.8085 |

*Code Output 6*

Thus, we obtain the variance-covariance matrix for person 2:



| Estimated V Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 9.5446 | 8.9745 | 9.2128 |
| 2 | 8.9745 | 10.7744 | 10.9573 |
| 3 | 9.2128 | 10.9573 | 13.5103 |

*Code Output 7*

Thus, we model the covariance as initially decaying but then increasing.

Now let’s try fitting a first-order autoregressive (AR(1)) model on the residuals, and an ARH(1), which is heterogeneous first-order autoregressive and allows the variance to differ over time at the expense of having to estimate more parameters.

The AR(1) covariance structure is given by:

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{bmatrix}$$

This allows the covariance to decay over time (since ρ is a correlation which is less than or equal to 1), while we still only have to fit two parameters for the covariance structure.

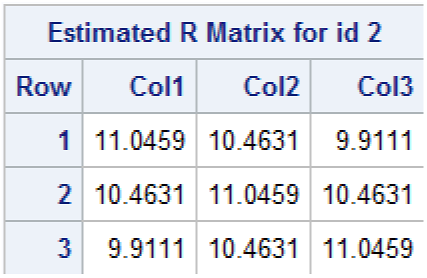
For AR(1):

**SAS code snippet 5:**

```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      repeated time / type=AR(1) subject=id R=1,2 RCORR;
run;
```

**Stata code snippet 5:**

```
/* equivalent of SAS repeated statement with AR(1) structure */
mixed strength i.program i.time i.program#i.time, reml || id: , noconstant
residuals(ar, t(time)) variance
```



| Estimated R Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 11.0459 | 10.4631 | 9.9111 |
| 2 | 10.4631 | 11.0459 | 10.4631 |
| 3 | 9.9111 | 10.4631 | 11.0459 |

*Code Output 8*

The variance is thus the same across time and the covariance is constrained to decay over time.  The RCL model showed that this may not be the most appropriate structure for the data.

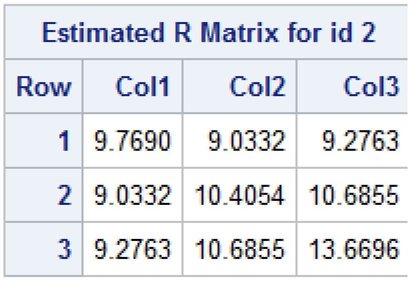
The ARH(1) covariance structure is given by

$$\begin{bmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho & \sigma_1\sigma_3\rho^2 \\ \sigma_2\sigma_1\rho & \sigma_2^2 & \sigma_2\sigma_3\rho \\ \sigma_3\sigma_1\rho^2 & \sigma_3\sigma_2\rho & \sigma_3^2 \end{bmatrix}$$

**SAS code snippet 6:**

```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      repeated time / type=ARH(1) subject=id R=1,2 RCORR;
run;
```

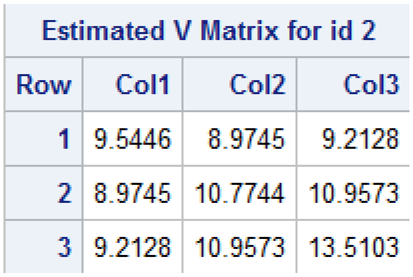
Unfortunately, at this time there is no Stata equivalent of the ARH structure.



| Estimated R Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 9.7690 | 9.0332 | 9.2763 |
| 2 | 9.0332 | 10.4054 | 10.6855 |
| 3 | 9.2763 | 10.6855 | 13.6696 |

*Code Output 9*

This is much more flexible, as the variance is allowed to differ for each time point, thus allowing the covariance between time points to vary and even increase. This is very similar to, but not quite the same as, the **V** matrix from the RCL model, which was



| Estimated V Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 9.5446 | 8.9745 | 9.2128 |
| 2 | 8.9745 | 10.7744 | 10.9573 |
| 3 | 9.2128 | 10.9573 | 13.5103 |

*Code Output 10*

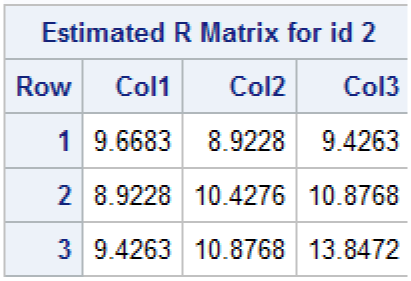
Now let’s see what an unstructured covariance gets us. Fitting an unstructured covariance matrix for **R** allows the most flexibility by fitting each variance and covariance separately at the expense of losing many more degrees of freedom to estimation compared to simpler structures. The unstructured matrix can be prohibitive to estimate, especially as the number of time points is 5 or more.

**SAS code snippet 7:**

```
proc mixed data=long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      repeated time / type=un subject=id R=1,2 RCORR;
run;
```

**Stata code snippet 6:**

```
/* equivalent of SAS repeated statement with UN structure */
mixed strength i.program i.time i.program#i.time, reml || id: , noconstant
residuals(un, t(time)) variance
```



Estimated R Matrix for id 2

| Row | Col1 | Col2 | Col3 |
|---|---|---|---|
| 1 | 9.6683 | 8.9228 | 9.4263 |
| 2 | 8.9228 | 10.4276 | 10.8768 |
| 3 | 9.4263 | 10.8768 | 13.8472 |

*Code Output 11*

Since this most flexible covariance structure indicates increasing variance and covariance, it would seem that a covariance structure with increasing variance and slightly increasing covariance over time would be the most appropriate fit. In fact, this is so similar to the RCL model and the heterogeneous autoregressive model that it indicates that estimating extra parameters may not be worth it. How can we test this?

In her highly cited paper on SAS PROC MIXED, Singer (1998)[5] uses a goodness of fit statistic such as AIC to compare covariance structures. That is, we can fit several different covariance structures with the same fixed-effects structure and compare AICs.

For the above models, we obtain the following AICs.

| Structure | AIC |
|---|---|
| CS | 438.7 |
| AR(1) | 432.1 |
| ARH(1) | 432.8 |
| UN | 436.6 |

Thus, it appears that the AR(1) and ARH(1) fit the best, based on the AIC. Although the ARH(1) is less parsimonious, its flexibility in this case is appealing, so we select the ARH(1) for the final covariance structure. Alternatively, we could fit the RCL model, which is even more parsimonious and is similar to the structure of the ARH(1) model.

Next, let’s fit a model where we apply structure to both **G** and **R**.

## Example 2: Fitting structure on both the random effects and residual error

In this example, we discuss the use of time as a continuous variable, and the modeling of data using both **G** and **R** matrices. Diggle, Heagerty, Liang, Zeger [9] distinguish three forms of correlation:

- **Random effects:** "When units are sampled at random from a population, various aspects of their behaviour may show stochastic variation between units" [9]. The variation in these random effects corresponds to the **G** matrix.
- **Serial Correlation**: "At least part of any unit's observed measurement profile may be a response to time-varying stochastic processes operating within that unit" [9]. This variation can be modeled directly by placing structure on **R**.
- **Measurement Error:** This is composed of random variation within the measurement process.

When discussing when it may be appropriate to fit a model with both random effects and serial correlation modeled (that is, specifying the structure on both **G** and **R**), Diggle, Heagerty, Liang, Zeger [9] note that while "serial correlation would appear to be a natural feature of any longitudinal data model, in specific applications its effects may be dominated by the combination of random effects and measurement error." That is, it may be the case the researcher has already accounted well enough for the correlation structure simply by including random effects.

Fitzmaurice, Laird, and Ware (2011)[1] also discuss this issue in their textbook on page 197. Using the term $b_i$ to refer to the random effects and $\varepsilon_{ij}$ to refer to the errors, they state that in modeling structure on both the **G** and **R** matrices

> would raise two potential complications. First, the $\varepsilon_{ij}$'s would no longer have a simple interpretation as measurement or sampling errors. This would alter the interpretation of the $\varepsilon_{ij}$'s, and hence $b_i$, implying that the $\varepsilon_{ij}$'s include a component of model misspecification at the individual level. Second, there can be subtle issues of model identification when $R_i$ is assumed to have a non-diagonal covariance pattern since there may be insufficient information in the data at hand to support separate estimation of both $G$ and a non-diagonal $R_i$. For example, it is not possible to estimate both $G$ and an unstructured $R_i$.

The authors later state on page 228 that "there can be identifiability problems with the hybrid model [i.e., the model with both random effects and error structure] unless the random effects structure is kept very simple (e.g., random intercepts only). That is, there may be insufficient information in the data at hand to support separate estimation of randomly varying slopes, serially correlated residuals, and measurement errors".[1]

**SAS code snippet 8:**

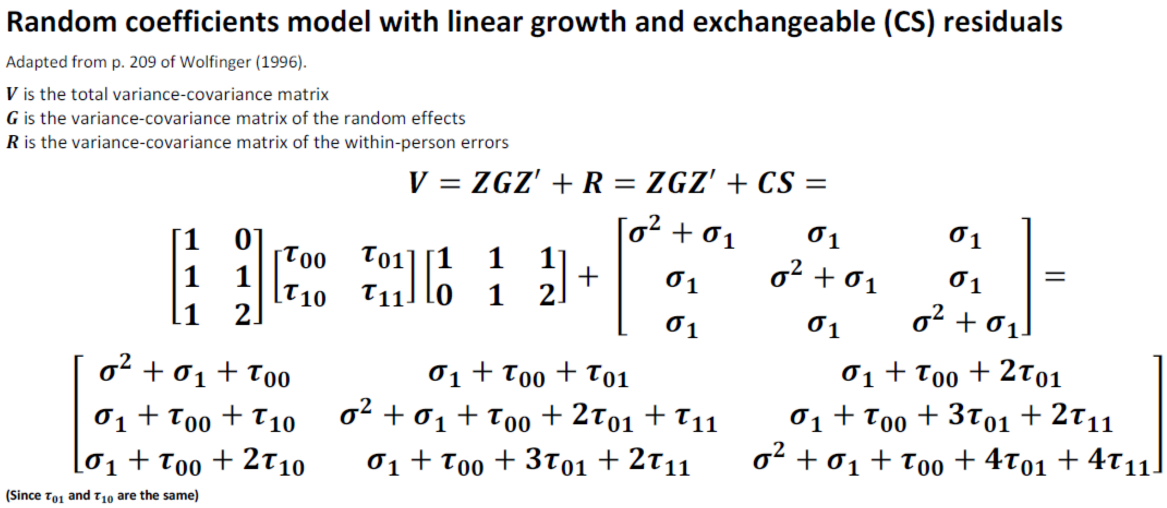
```
/* RANDOM INTERCEPT AND SLOPE WITH UNSTRUCTURED COVARIANCE MATRIX FOR THE
RANDOM EFFECTS */
proc mixed data=in.long_final;
      class id program time;
      model strength=program time program*time / s chisq;
      random INTERCEPT time_cont / type=un subject=id G GCORR V=1,2 VCORR;
      repeated time / type=CS subject=id R=2,3,4;
run;
```

**Stata code snippet 7:**

```
/* equivalent of SAS random statement with random intercept and slope and
covariance between the two, and structure on the residuals */
mixed strength i.program i.time i.program#i.time, reml || id: time,
covariance(un) residuals(exch, t(time)) variance
```

These give slightly different results for the covariance parameter estimates.

The matrix for this model is:



**Random coefficients model with linear growth and exchangeable (CS) residuals**

Adapted from p. 209 of Wolfinger (1996).

***V*** is the total variance-covariance matrix
***G*** is the variance-covariance matrix of the random effects
***R*** is the variance-covariance matrix of the within-person errors

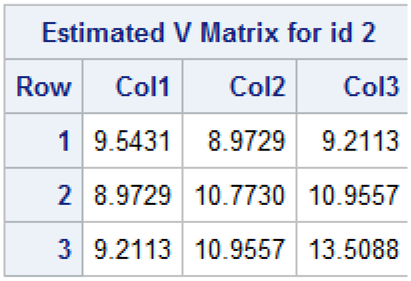
$$\boldsymbol{V = ZGZ' + R = ZGZ' + CS =}$$

$$\begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 2 \end{bmatrix} \begin{bmatrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 \\ 0 & 1 & 2 \end{bmatrix} + \begin{bmatrix} \sigma^2 + \sigma_1 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma^2 + \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma^2 + \sigma_1 \end{bmatrix} =$$

$$\begin{bmatrix} \sigma^2 + \sigma_1 + \tau_{00} & \sigma_1 + \tau_{00} + \tau_{01} & \sigma_1 + \tau_{00} + 2\tau_{01} \\ \sigma_1 + \tau_{00} + \tau_{10} & \sigma^2 + \sigma_1 + \tau_{00} + 2\tau_{01} + \tau_{11} & \sigma_1 + \tau_{00} + 3\tau_{01} + 2\tau_{11} \\ \sigma_1 + \tau_{00} + 2\tau_{10} & \sigma_1 + \tau_{00} + 3\tau_{01} + 2\tau_{11} & \sigma^2 + \sigma_1 + \tau_{00} + 4\tau_{01} + 4\tau_{11} \end{bmatrix}$$

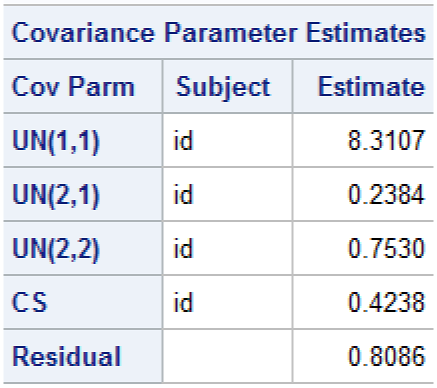
**(Since $\tau_{01}$ and $\tau_{10}$ are the same)**

So we can see by fitting this model, we've added an extra parameter ($\sigma_1$) to the total **V** matrix.



| Estimated V Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 9.5431 | 8.9729 | 9.2113 |
| 2 | 8.9729 | 10.7730 | 10.9557 |
| 3 | 9.2113 | 10.9557 | 13.5088 |

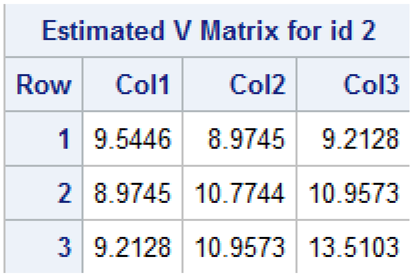
*Code Output 12*



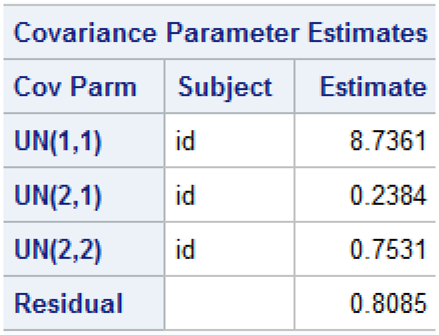
| Covariance Parameter Estimates | | |
|---|---|---|
| Cov Parm | Subject | Estimate |
| UN(1,1) | id | 8.3107 |
| UN(2,1) | id | 0.2384 |
| UN(2,2) | id | 0.7530 |
| CS | id | 0.4238 |
| Residual | | 0.8086 |

*Code Output 13*

Let's compare this to the random effects-only model.



| Estimated V Matrix for id 2 | | | |
|---|---|---|---|
| Row | Col1 | Col2 | Col3 |
| 1 | 9.5446 | 8.9745 | 9.2128 |
| 2 | 8.9745 | 10.7744 | 10.9573 |
| 3 | 9.2128 | 10.9573 | 13.5103 |



| Covariance Parameter Estimates | | |
|---|---|---|
| Cov Parm | Subject | Estimate |
| UN(1,1) | id | 8.7361 |
| UN(2,1) | id | 0.2384 |
| UN(2,2) | id | 0.7531 |
| Residual | | 0.8085 |

We can see that the **V** matrix does not differ much between the two models. In the model in which we estimated a structure on both **G** and **R**, we added an extra parameter ($\sigma_1 = 0.4238$), but the estimate of the random intercept variance decreased to compensate ($\tau_{00} = 8.7361$ in the model without the compound symmetry (CS) structure on **R**, and $\tau_{00} = 8.3107$ in the model with the CS structure).

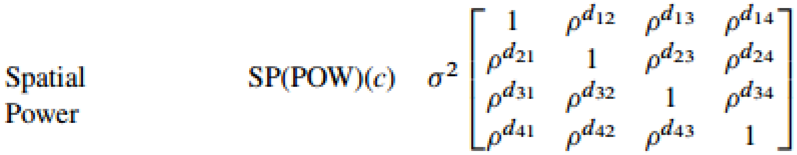
In this case, the extra complexity did not gain us anything. In fact, the AIC for this model (435.5) is higher than for the random intercept and slope only model (432.8). And what Diggle, Heagerty, Liang, Zeger [9] stated is true in this case. The random effects structure alone accounted well enough for total variance structure.

## Continuous time

For time which is truly considered continuous, such as data collected from electronic health records (EHR), some of the structures mentioned above are not appropriate.  For example, it doesn't make sense to use the autoregressive structure, as we will fit the same covariance between time 1 and 2 (etc.) for each individual, regardless of whether time 1 and 2 are 1 day apart for one individual or 1 year apart for another.

In such cases modeling random effects for intercept and slope (and possibly polynomials of slope) offers the flexibility of modeling an individual-specific intercept and slope while taking into account the within-subject correlation, regardless of the number of measurements on each individual or the time difference between measurements.

In addition, if modeling the residual covariance matrix, **R**, is of interest with continuous time, SAS allows the user to fit a spatial covariance structure.  (Stata does not have this option.)  This includes the spatial power covariance structure, shown below for an individual with four measurements.[6]



Spatial Power    SP(POW)($c$)    $\sigma^2 \begin{bmatrix} 1 & \rho^{d_{12}} & \rho^{d_{13}} & \rho^{d_{14}} \\ \rho^{d_{21}} & 1 & \rho^{d_{23}} & \rho^{d_{24}} \\ \rho^{d_{31}} & \rho^{d_{32}} & 1 & \rho^{d_{34}} \\ \rho^{d_{41}} & \rho^{d_{42}} & \rho^{d_{43}} & 1 \end{bmatrix}$

Each $d_{xy}$ above is the "distance" (time difference in this case; Euclidian distance in the case of spatial data) between time point x and time point y.  Thus, we allow the correlation to vary to the power of the distance.  Thus, correlation decreases over time, but the decrease depends on the time difference between two measurements.  This is the analog of an AR(1) structure for continuous time and spatial data.

See chapter 8 of Fitzmaurice, Laird, and Ware (2011)[1] for a detailed discussion of modeling when time is continuous.