Topics for today:

- *Modeling error covariance structure in an LMM*

Associated reading: Sections 2 and 4 of 'LMM: modeling random effects and error covariance structure' course notes), Hedeker (Chapter 7), SAS Help Documentation (see PROC MIXED, under the REPEATED statement).

*2 Modeling the error covariance structure (**R** matrix)*

2.1 Generalized Least Squares

- Generalized least squares applies to the special case of an LMM where there are no random effects, but the error covariance matrix (**R**) does not necessarily just have the simple independent structure. We can apply the usual LMM methods to such a model, so we will not go into detail in these slides; however the course notes discuss this thoroughly.

2.2 Covariance structures to model 'within-subject' repeated measures

- In this section, we mainly focus on modeling covariances through the **R** matrix, which is generally thought of as the 'within-subject' covariance matrix. For compound symmetry, we see how the same **V** matrix can be modeled by specifying either **G** (through the RANDOM statement) or **R** (through the REPEATED statement).

2.2.1 Types of structures

2.2.1.1 Compound symmetric

- The simplest LMMs have random intercept terms. Usually the random effect term is for subjects, but it could be for other experimental units as well (e.g., hospital, medical instrument). The random intercept just indicates that the experimental units generally differ with respect to the outcome variable. For example, subjects may differ in blood pressure, some generally higher and some generally lower; the random intercept term will fit subject mean blood pressure values.

- Even if the errors between time measurements are modeled as independent, such that $Cov\left(\varepsilon_{ij},\ \varepsilon_{ij'}\right)=0$, the compound symmetric covariance structure is induced for the repeated measures (Y_{ij}) over time. In PROC MIXED, we can model the CS structure in at least three ways, which will yield the same results (as long as the denominator degrees of freedom method, or 'DDFM' is the same, which is an option in the MODEL statement):

```
(1)RANDOM id;
(2)RANDOM intercept / subject=id;
(3)REPEATED / subject=id type=cs;
```

Here, 'id' is the variable to indicate subjects.

2.2.1.2 First-order autoregressive [AR(1)]

- A more realistic covariance structure for repeated measures over time involves the autoregressive covariance structure. In particular, the first-order autoregressive [AR(1)] covariance structure assumes that the covariance for measurements between two time points weakens the further the time points are apart. Remember for discrete time measurements (e.g., days), the AR(1) model for the errors is

$$\varepsilon_{ij} = \phi\varepsilon_{i,j-1} + Z_{ij} \quad , Z_{ij} \sim iid\ N(0, \sigma_Z^2)$$

If we have an experiment or study with 4 time points, the covariance structure is given to the right. The parameter ϕ indicates the correlation between measures taken two days apart within an individual.	$\sigma_\varepsilon^2 \begin{pmatrix} 1 & \phi & \phi^2 & \phi^3 \\ \phi & 1 & \phi & \phi^2 \\ \phi^2 & \phi & 1 & \phi \\ \phi^3 & \phi^2 & \phi & 1 \end{pmatrix}$ where $\sigma_\varepsilon^2 = \frac{\sigma_Z^2}{1-\phi^2}$

2.2.1.3 Unstructured

- This structure is the most flexible one and is the structure that is used in MANOVA. But unlike MANOVA (that is carried out with PROC GLM), the linear mixed model analysis does not drop incomplete records.

- One should also consider the number of parameters when deciding on whether to use the UN structure. If there are many repeated measures, it may be a poor choice, and in some cases the model may not even converge if there are too many parameters.

- The AIC, which penalizes for the number of parameters in the model, can be used as a guide when comparing structures with a real data set. The UN structure for 4 repeated measures is below.

$$\begin{pmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 & \sigma_{34} \\ \sigma_{14} & \sigma_{24} & \sigma_{34} & \sigma_4^2 \end{pmatrix}$$

2.2.1.4 Spatial structures

- When measurements are taken in space or over unequally spaced time points, a distance metric is often useful in calculating covariances. Spatial data may often involve two dimensions if measurements are taken on land surfaces. However, they could also involve three dimensions if altitude (or elevation) also needs to be accounted for in the model.

- 'Spatial' structures can also be applied to data collected over other dimensions such as time. For example, say that measurements are taken on subjects on school days only for 3 weeks.

- A spatial structure could be applied to these data that will allow the strength of the correlation between time measurements to change depending on how far apart the time measurements are. Here, it is expected that the correlation between 2 successive school days is stronger than between Friday and Monday, since the latter is spaced apart by 3 days.

- A spatial structure I commonly use is the *spatial power structure* (*SP(POW)(c-list)* in SAS, where *c-list* is replaced with the spatial or temporal variables of interest, e.g., *latitude* and *longitude* for a spatial study, or *day* for a temporal study). This will allow the correlation between measures taken over space or time to decay (or less commonly, to increase) as a function of those variables. The $[j,k]^{th}$ element of the $\mathbf{R}_i$ matrix spatial power structure is: $\sigma_\varepsilon^2 \phi^{d_{jk}}$.

- The *c*-list contains the names of the numeric variables used as coordinates of the location of the observation in space, and d_{jk} is the Euclidean distance between the j^{th} and k^{th} vectors of these coordinates, which correspond to the j^{th} and k^{th} observations in the input data set. The same applies to time, which has one dimension and thus one variable. For the remainder of this section, the application of spatial structures specifically to data collected over time will be considered.

- One appeal of the spatial power structure compared to other spatial covariance structures available is that it is closely tied with the AR(1) structure for data collected in discrete units of time. For such data, $d_{jk} = |j-k|$, where j and k are time-specific indices such as the day of the study.

- Going back to the example above where data are collected on successive school days for 3 weeks, let j (or k)=1, 2,…,21 denote successive days in the study, including weekends; d_{jk} denotes the number of days between day j and day k. These data could be modeled with either the spatial structure or the AR(1) structure.

- In order to use the AR(1) structure, the data set should include all days (even weekends), with missing values put in for the outcome on the weekend days. This will allow for proper spacing between measures on days, so that the correlation between Friday and Monday will be estimated as $\hat{\phi}^3$ instead of $\hat{\phi}$. There are 2 covariance parameters in the **R** matrix for both the AR(1) and SP(POW) structures.

- When time is a discrete unit (such as days), the AR(1) and SP(POW) structures may actually yield the same results if consecutive-day records are included with the AR(1) approach, using missing values as necessary. But there are clear advantages to using the SP(POW) structure over AR(1) if a covariate in the model has a missing values for all subjects on at least one day. This is described in more detail in the Software and Computational Issues chapter.

- The spatial exponential structure is an alternative to model unequally spaced longitudinal data. The $[j,k]^{th}$ element of the $\mathbf{R}_i$ matrix spatial exponential structure is:

$$\sigma_\varepsilon^2 e^{-d_{jk}/\theta}$$

For practice: There is also a close tie between the AR(1) and spatial exponential structures for discrete time data. Determine the relationship between ϕ in the AR(1) model and θ in the SP(EXP) model for discrete time data.

- Spatial structures are even more useful when the time (or space) variables are more continuous in nature and spaces in between measurements vary widely.

- For example, with the Complement data introduced early on, measurements were taken immediately before and after an exercise or allergen challenge (minutes apart), then at 1, 6 and 24 hours after the test. In this case, the time measurements are at 0, ~0.08h, 1h, 6h, 24h; the intervals between time points differ greatly and there is really no good way to employ the AR(1) structure here. The spatial structure is really the only choice to accurately model the repeated measures.

- If the variable measuring time is called *hours*, then to employ the spatial exponential structure, we would include:

```
repeated / subject=subject type= sp(exp)(hours);
```

  Example: Sleep data. I previously introduced the Sleep data and showed how the correlation of responses over time could actually be measured reasonably well using only random effects. Here, we reexamine the data

and apply a more intuitive model for the data that uses a spatial exponential covariance structure for **R**. This structure should work well here since the time points are unequally spaced. There are two possible approaches: (a) to use only the specified **R** matrix instead of using the random effects, and (b) to use the specified **R** matrix in addition to the random effects. Here are code and fitted values of **V** to the right (the rest of the output is suppressed). Note that for model (a), only the 'r' option is available in the REPEATED statement, but when the model does not have random effects (i.e., no RANDOM statement), **V**=**R**.

SAS Code:

```
*(a) Linear, SP POW for R;
proc mixed data=sleep_nc;
 class id;
 model y = time / solution;
 repeated / type=sp(pow)(time)
subject=id r; run;


*(b) linear, UN for G, SP POW for R;
proc mixed data=sleep_nc;
 class id;
 model y = time / solution;
 repeated
  / type=sp(pow)(time) subject=id;
 random intercept time
  / type=un subject=id v; run;
```

Partial output:

```
a. Estimated R Matrix for id 1021

Row Col1 Col2 Col3 Col4 Col5
1 7.8974 7.2631 6.6797 5.1960 3.1440
2 7.2631 7.8974 7.2631 5.6498 3.4186
3 6.6797 7.2631 7.8974 6.1432 3.7172
4 5.1960 5.6498 6.1432 7.8974 4.7786
5 3.1440 3.4186 3.7172 4.7786 7.8974

b.  Estimated V Matrix for id 1021

Row Col1 Col2 Col3 Col4 Col5
1 6.7495 5.9558 5.5501 5.1267 4.8557
2 5.9558 6.7030 5.9400 5.2836 5.1548
3 5.5501 5.9400 6.7177 5.4850 5.4545
4 5.1267 5.2836 5.4850 7.1298 6.3672
5 4.8557 5.1548 5.4545 6.3672 9.6088
```

- Model (a) yields an AIC of 1015.8, while (b) yields 1003.6, demonstrating improvements over previous models with random effects only (recall that the model with linear random effects and UN structure yielded an AIC of 1014.9).

- The estimated correlation parameter based on the spatial power structure is 0.9197, which expresses the correlation between errors 1 month apart for a subject. For model a, this would be the same as the correlation between responses 1 month apart, since there are no random effects in the model. However for model (b), correlation between responses 1 month apart is not the same as for errors 1 month apart. Can you argue why?

  For practice: write out the full models for the associated code given above.

- There are other spatial structures that can be used as well (see SAS Help Documentation). Since the spatial structures are similar in their form, one may wonder which one to use. In some cases they may provide similar fits. In other cases, fitting one spatial structure may not lead to convergence, while it will for another. If multiple spatial structures lead to fits where convergence criteria are met, then the AIC can be used to select the optimal one. In practice, thus far I have only used the spatial exponential and spatial power structures.

2.2.1.5 Toeplitz

- This is sort of a cross between the AR(1) structure and UN structure. It is a little more flexible than the AR(1) structure, but more constrained (i.e., has fewer parameters) than the UN structure. Here is an example of the Toeplitz structure for 4 time points.

$$\begin{pmatrix} \sigma^2 & \sigma_1 & \sigma_2 & \sigma_3 \\ \sigma_1 & \sigma^2 & \sigma_1 & \sigma_2 \\ \sigma_2 & \sigma_1 & \sigma^2 & \sigma_1 \\ \sigma_3 & \sigma_2 & \sigma_1 & \sigma^2 \end{pmatrix}$$

2.2.1.6 Direct Product (Kronecker)

- For some data sets, we may need to account for repeated measures over two dimensions. For example, say that strength measurements are taken on each leg for subjects over 3 time points. There are 2 'repeated measures' in space (i.e., body part) as well as 3 repeated measures over time. The covariance matrix to account for all repeated measures would then have size 6×6. Instead of dealing with this big messy matrix, it is easier to define it in pieces and then take the Kronecker product.

  Example 1: For the scenario described above, say that repeated measures over space can be modeled with the UN structure and repeated measures over time can be modeled with the AR(1) structure:

  Structure for space: $\mathbf{R}_{i1} = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}$

  Structure for time: $\mathbf{R}_{i2} = \sigma_\varepsilon^2 \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix}$

The combined (Kronecker product structure):

$$\mathbf{R}_i = \mathbf{R}_{i1} \otimes \mathbf{R}_{i2} = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix} \otimes \sigma_\varepsilon^2 \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} = \begin{pmatrix} \sigma_1^2 \mathbf{R}_{i2} & \sigma_{12} \mathbf{R}_{i2} \\ \sigma_{12} \mathbf{R}_{i2} & \sigma_2^2 \mathbf{R}_{i2} \end{pmatrix}$$

$$= \begin{pmatrix} \sigma_1^2 \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} & \sigma_{12} \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} \\ \sigma_{12} \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} & \sigma_2^2 \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} \end{pmatrix} = \begin{pmatrix} \sigma_1^2 & \sigma_1^2\phi & \sigma_1^2\phi^2 & \sigma_{12} & \sigma_{12}\phi & \sigma_{12}\phi^2 \\ \sigma_1^2\phi & \sigma_1^2 & \sigma_1^2\phi & \sigma_{12}\phi & \sigma_{12} & \sigma_{12}\phi \\ \sigma_1^2\phi^2 & \sigma_1^2\phi & \sigma_1^2 & \sigma_{12}\phi^2 & \sigma_{12}\phi & \sigma_{12} \\ \sigma_{12} & \sigma_{12}\phi & \sigma_{12}\phi^2 & \sigma_2^2 & \sigma_2^2\phi & \sigma_2^2\phi^2 \\ \sigma_{12}\phi & \sigma_{12} & \sigma_{12}\phi & \sigma_2^2\phi & \sigma_2^2 & \sigma_2^2\phi \\ \sigma_{12}\phi^2 & \sigma_{12}\phi & \sigma_{12} & \sigma_2^2\phi^2 & \sigma_2^2\phi & \sigma_2^2 \end{pmatrix}$$

- Note: the σ_ε^2 on the AR(1) structure is not included because it becomes redundant once we take the direct product, i.e., it is absorbed into parameters in the other matrix. Available Kronecker structures in SAS include: UN@AR(1), UN@CS and UN@UN. (The symbol '@' is used to denote '$\otimes$' since the latter is not on the keyboard!)

- Example 2: Let's discuss how a Kronecker product structure could be used with the Mt. Kilimanjaro data, considering that measurements were taken daily, but also during AM and PM.

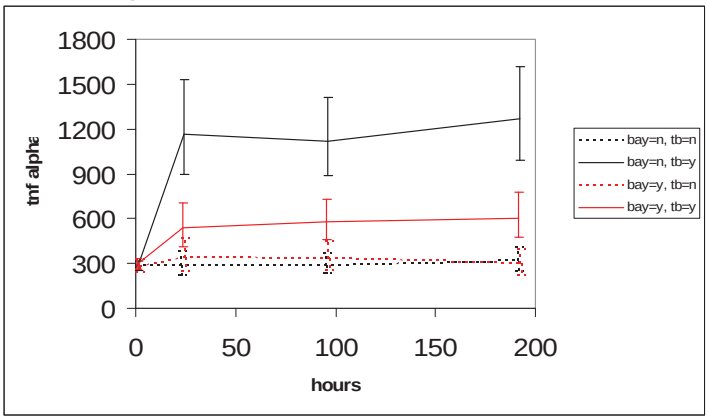
- A real application from my work (first shown in the Introduction notes): *Nuclear factor-kappa B increases survival of Mycobacterium tuberculosis in human macrophages*; Nicole E. Feldman, Kathryn Chmura, Xiyuan Bai, Danielle Cook, Matthew Strand, Corinne M. Floyd, Seiji Murakami, Loretta Gaido,Dennis R. Voelker, Edward D. Chan; Impact of research on clinical medicine and basic science:
  - Novel ways to kill *Mycobacterium tuberculosis* are needed in light of increasing drug resistance.
  - Our research with a human macrophage cell line and with two types of primary human macrophages demonstrate inhibition of NFκB activation is associated with increased macrophage apoptosis and decreased survival of intracellular *M. tuberculosis*.
  - These findings represent an important advance in understanding the host immune response to tuberculosis.
  - In the basic science experiment associated with this article, a sample was first taken from each subject.

- Three types of macrophages were then isolated (if possible) into different cultures.
- Each culture was then split into four parts; each part was assigned a different treatment: MTB=Y, Bay=Y; MTB=Y, Bay=N; MTB=N, Bay=Y; MTB=N, Bay=N. (The 'Bay' treatment is an inhibitor of NFκB activation.)
- The experiment units were then observed 1, 4 and 8 days after treatment.
- Outcome measures on each experimental unit were tumor necrosis factor-alpha (TNF-alpha), interferon-gamma, and interleukin-8 expressions.
- [TNF-alpha is a protein manufactured by white blood cells to stimulate and activate the immune system in response to infection or cancer. Overproduction of this compound can lead to disease where the immune systems acts *against* healthy tissues, such as arthritis or psoriasis. Some treatments for these diseases utilize drugs that bind and inactivate TNF-alpha, thereby reducing unhealthy inflammation.]

The SAS code associated with this experiment follows, with a key emphasis on the REPEATED statement.

```
proc mixed data=chan;
class id bay tb time;
model y=time bay tb time*bay time*tb bay*tb time*bay*tb
  / ddfm=satterth solution outp=outter;
repeated time bay*tb / subject=id type=un@cs;
estimate 'bay vs no bay for tb at time 1'
 bay 1 -1 bay*time 1 0 0 0 -1 0 0 0
 bay*tb 0 1 0 -1 bay*tb*time 0 0 0 0 1 0 0 0 0 0 0 0 -1 0 0 0;
estimate 'bay vs no bay for tb at time 24'
 bay 1 -1 bay*time 0 1 0 0 0 -1 0 0 bay*tb 0 1 0 -1
 bay*tb*time 0 0 0 0 0 1 0 0 0 0 0 0 0 -1 0 0;
estimate 'bay vs no bay for tb at time 96'
 bay 1 -1 bay*time 0 0 1 0 0 0 -1 0 bay*tb 0 1 0 -1
 bay*tb*time 0 0 0 0 0 0 1 0 0 0 0 0 0 0 -1 0;
estimate 'bay vs no bay for tb at time 192'
 bay 1 -1 bay*time 0 0 0 1 0 0 0 -1 bay*tb 0 1 0 -1
 bay*tb*time 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 -1;
lsmeans bay*tb*time / pdiff; run;
```

- To illustrate the results, below is the TNF_alpha expression for the primary human alveolar macrophages. The estimated means are connected by lines, with bars extending to *Mean–SE* and *Mean+SE*.



- For this example, we have an UN@CS structure for TIME and BAY*TB. For simplicity, just consider BAY*TB=TREATMENT. We have 4 times and 4 treatments. Thus, the structure for TIME will be a 4×4 unstructured matrix; the structure for TREATMENT will be a 4×4 compound symmetric structure. The complete structure will be 16×16. I used UN structure for TIME due to the unequally spaced time measurements.

2.2.1.7 Other structures

- A LOCAL statement can be added as an option in the REPEATED statement (after the slash) that will add residual variance down the diagonal. I have found this useful as an addition to the AR(1) structure for some applications.

- There are many other structures available to model correlated responses within subjects or clusters. For more detail, see the SAS Help Documentation > SAS/STAT > The MIXED Procedure > Syntax > REPEATED Statement.

  For practice: write the **R** matrix when the AR(1) structure is specified and the LOCAL option is included as an option.

2.2.2 Choosing a covariance structure

- With so many covariance structures to choose from, it might seem overwhelming to choose a structure.

- There are theoretical and empirical approaches to choosing a structure.

- On the theoretical side, the covariance structure should make sense.
  - If there are measures taken over time, consider the AR(1) or possibly a spatial structure.
  - If there are a limited number of measurements taken over space or across treatments, the UN structure might be tried and compared with simpler structures, down to the CS structure.
  - So once the list is narrowed down to those that make sense for the given type of data, one can then compare AIC values between fit models to make a final decision.

- As discussed, the choice of structure for **R** needs to be balanced with how random effects are specified. Sometimes the more random effects that are included in the model, the less complex the **R** structure necessary.

- The bottom line is that there are many ways to model clustered data using combinations of random effects and specified **R** matrices, and sometimes modeling fitting needs to be done in order to determine the best model.

- However, it is helpful to narrow the list of possible covariance models down beforehand based on what seems reasonable for the given data, both for the sake of time, and also because a priori information can be as valuable of a statistic as one purely based on data.

2.2.3 Structures for other models

- Some procedures, such as PROC GENMOD in SAS are used to model non-normal outcomes, which we will learn more about later.

- Non-normal longitudinal data can be modeled using PROC GENMOD with generalized estimating equations (GEE), which is invoked when a REPEATED statement is included in the code.

- Unfortunately, there are not nearly as many covariance structures to choose from in modeling the repeated measures. For example, the spatial structures are not available. However, gaps between measures can be handled more easily with PROC GENMOD compared with PROC MIXED, by filling in records in the data set with missing values. Thus, the AR(1) structure can often be suitably employed for unequally spaced data. This is discussed in more detail in the 'missing data' notes.

3 Putting it together: specifying **G** *and* **R** *in the same model*

We will discuss next time (hopefully!)

4 Examining the covariance structure

- In this set of notes we've learned different ways to account for correlated data. Although the most direct way to model repeated measures is through the error covariance matrix (i.e., **R**), we can actually model correlated data over time by adding random effect terms as well. In fact, there may be multiple ways to model the *Var*(**Y**) adequately. The modeled covariance matrix is

$$\hat{Var}(\mathbf{Y}) = \mathbf{Z}\hat{\mathbf{G}}\mathbf{Z}^t + \hat{\mathbf{R}}$$

which demonstrates that a combination of **G** and **R** are used for the final estimate of the covariance structure for **Y**.

- For models with covariates that involve only time trends (e.g., linear and quadratic trends for time), we can get a sense of how well our specified structure is working by comparing numerical (i.e., estimated) forms of $\mathbf{V}=Var(\mathbf{Y})$ with the sample covariance matrix.

- The sample covariance is **S** (as previously defined) and can obtained using PROC CORR for data in multivariate format. Consider the *Sleep data* with time variables Y1, Y2, Y3, Y6 and Y12 (where the number indicates the month in the averaging). Let's compare this with the modeled covariance that we obtained by fitting various mixed models. For simplicity, only the lower diagonal is shown.

- On the following slide to the left are sample ($\mathbf{S}_i$) and model-based $\mathbf{V}_i=Var(\mathbf{Y}_i)$ covariance matrices, and on the right are relative differences to the sample covariance matrix, $\mathbf{S}_i$. 'Mean (median) error' is the average (median) of the absolute values of the relative difference values on the right.

Sample covariance matrix, $\mathbf{S}_i$	Relative difference for the modeled covariance, relative to $\mathbf{S}_i$
y1 6.50 y2 5.83 6.90 y3 5.13 6.35 7.20 y6 5.24 5.49 5.56 7.48 y12 4.42 4.97 5.31 6.91 9.05	
Estimate of $\mathbf{V}_i$ based on linear random effects model (4 cov. parms)	mean error=4.8%; median error=5.9%
1 7.01 2 5.80 6.83 3 5.70 5.67 6.74 4 5.37 5.47 5.57 6.95 5 4.73 5.07 5.41 6.43 9.58	7.8% -0.5% -1.0% 11.1% -10.7% -6.4% 2.5% -0.4% 0.2% -7.1% 7.0% 2.0% 1.9% -6.9% 5.9%
Estimate of $\mathbf{V}_i$ based on quadratic random effects model (6 cov. parms*)	mean error=3.4%; median error=2.3%
1 6.85 2 5.68 6.80 3 5.60 5.70 6.87 4 5.29 5.59 5.86 7.57 5 4.32 4.93 5.48 6.81 9.09	5.4% -2.6% -1.4% 9.2% -10.2% -4.6% 1.0% 1.8% 5.4% 1.2% -2.3% -0.8% 3.2% -1.4% 0.4%
Estimate of $\mathbf{V}_i$ based on quadratic r. e.'s plus spatial model (7 cov. parms*)	mean error=3.0%; median error=3.6%
1 6.48 2 5.77 6.65 3 5.42 5.99 6.90 4 5.05 5.47 5.89 7.96 5 4.35 4.98 5.55 6.86 9.11	-0.3% -1.0% -3.6% 5.7% -5.7% -4.2% -3.6% -0.4% 5.9% 6.4% -1.6% 0.2% 4.5% -0.7% 0.7%

*1 covariance parameter dropped from **G** during fit.

- The fitted covariance structures were obtained via the 'v' option in the RANDOM statement. Note that if no random effects are included in the model, then the fitted values for **V** and **R** are the same, and can be obtained by specifying the 'r' option in the REPEATED statement.

- The difference between the sample covariance matrix and the modeled covariance gets progressively better as more covariance parameters are added to the model. However, this is not to say that we should just keep adding more parameters. As with modeling in general, there is a tradeoff between the benefit of modeling data by adding parameters, and the drawbacks of overfitting.

- The relatively decent fit without using a time-sensitive covariance structure for **R** demonstrates that repeated measures can actually be modeled via the **G** matrix relatively well; the more complex **G** is, the better the fit. Fitting an unstructured (UN) covariance matrix for **R** but no random effects does improve the fit, and in this case the sample covariance matrix and estimated **V** from the model are essentially the same. We next discuss covariance structures for **R**. (Here I've dropped the *i* subscript on the matrices for convenience, although we typically do present the subject version.)

- Here is a table that summarizes the AIC and number of parameters for different models. Since REML estimation was used, only covariance parameters are penalized for in the AIC (SAS specific). This is not an exhaustive list of models tried; there may be other reasonable models to fit.

	Fixed-effect model	-2 ResLogL	Number of cov. parm's	AIC
(1) Up to linear random effects, UN structure for G	Linear	1006.9	4	1014.9
(2) Model (1), plus spatial power structure for R	Linear	993.6	5	1003.6
(3) Up to quadratic random effects, UN structure for G	Quadratic	1012.7	6*	1024.7
(4) Model (3), plus spatial power structure for R	Quadratic	999.5	7*	1013.5
(5) UN structure for R	Linear	976.9	15	1006.9
(6) UN structure for R	Quadratic	985.3	15	1015.3

*1 dropped from **G** during fit

- The results overall indicate the following:
  - A linear model for fixed effects is adequate.
  - The spatial power structure helps, added onto the random intercept and linear terms for subjects.
  - If one is concerned about getting an accurate estimate of **V**, then the UN structure could be used (along with the linear fixed effect model, i.e., model 5), in which case random effects are not needed since the structure for **V** is already saturated.

- Overall, I would probably use model (2) for the data, since it has a reasonable number of parameters and best AIC; the fitted covariance structure for **V** (not shown on the previous page) has a mean error for elements of 4.8% and median error of 3.8%. This is a reasonable fit for **V**, and will provide relatively accurate inference for fixed effects in the model. Also, incorporating up to linear random effects will also allow us to examine subject differences in CPAP adherence trends as well as conduct subject-specific tests of significance.