Application of Doubly Repeated Measures Analyses in Drug Trials on Food Intake

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Abstract

Doubly repeated measures designs are commonly used in pharmaceutical and human food intake experiments. This design has strengths in reducing error variance while enabling researchers to study participant behavior over time. Mixed models offer a flexible approach for analyzing such designs by permitting general covariance structures with missing data and unequally spaced assessment times. We illustrate the application of the SAS MIXED procedure in a double-blind randomized trial evaluating the effects of a test drug on food intake and appetite, acutely and after 4 weeks of consumption.

Eighty two participants were randomized into two groups, one receiving a test drug and the other receiving a placebo. Visual acuity scoring (VAS) was used to evaluate appetite and satiety at baseline, week 0 and week 4 before and after breakfast, lunch, and dinner. The week of clinical visit was one repeated factor and the time within each visit was the other repeated factor. The changes from baseline to each assessment week on VAS scores were analyzed as a response variable with the baseline score used as a covariate. This paper will discuss the model fitting strategies and the unique covariance structure in this trial.

Key Words: covariance structure, mixed model, randomized trial, satiety, visual acuity scoring

1. Introduction

Repeated measures refer to response outcomes measured on the same experimental unit on multiple occasions or under multiple conditions. Designs that use repeated measures often enable more efficient estimates due to a reduction in the number of parameters in the error variance (Davis 2002). Repeated measures studies are especially useful for investigating changes in participant behavior over time. Despite advantages, the analyses of repeated measures are often complicated because there are a large number of possible correlation structures among repeated observations made on each experimental unit.

Doubly repeated measures are commonly used in pharmaceutical and human food intake experiments. Doubly repeated measures have two within-subject factors and thus the analysis may become more complex compared to the case of repeated measures on a single within-subject factor. Mixed models provide a flexible approach for analyzing such data by using a mixture of fixed and random effects and permitting a variety of covariance structures with the possibility of missing data and unequally spaced assessment times.

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A double-blind randomized trial was conducted to evaluate the effect of a test drug on food intake, appetite and body weight. Eighty two participants were randomized into two intervention groups, test drug and placebo. Visual acuity scoring (VAS) with a psychometric scale ranging 0 to 100 was used to determine participants' degree of hunger, fullness, and desire to eat. VAS was administrated at baseline, Day 0 and Day 28 before and after breakfast, lunch, and dinner. The test product or a placebo was given to participants at breakfast and lunch at Day 0 and following 28 days. In this study, there is one between-subject factor, the test drug or placebo, and two within-subject factors: the week of clinic visit and the time within each visit. The changes from baseline to follow up on VAS scores were analyzed as a response variable with the baseline score taken as a covariate. The changes from baseline in this study were assumed to be normally distributed. Missing observations were considered to be missing completely at random.

This paper presents the application of SAS PROC MIXED to the analysis of doubly repeated measures in this food intake study. The 'TYPE =' stipulation within the REPEATED option specifies the covariance structure imposed on the residuals. PROC MIXED allows users to choose from many different covariance structures. The most complex is the unstructured covariance model. Repeated measurement data often have patterns in the covariance structure that enable more efficient analyses. The 'GROUP =' option permits different covariance structures at different levels of the GROUP effect. Some model fitting strategies and analytic implications of the different covariance structures are discussed in the following sections.

2. Modeling Correlated Errors

2.1 Direct Product Covariance Structure

There are several approaches to modeling the covariance structure for doubly repeated measures using PROC MIXED. This procedure is fairly flexible for enabling direct product covariance structures for two within-subject factors. First consider the SAS code:

```
Proc Mixed Data=Vast;
  Class Trt Visit Time Subject;
  Model Change = Baseline Time|Visit|Trt / DDFM = KenwardRoger;
  Repeated Visit Time / Subject = Subject Type = UN@UN R Rcorr;
 Run;
```

The analysis invoked using this code assumes an unstructured covariance matrix (UN) for both the levels of visit (factor 1) and the levels of time (factor 2). The 'DDFM = KenwardRoger' specifies using the Kenward-Rogers method for estimating the denominator degrees of freedom for some of the relevant test statistics. This is an especially useful method when there are missing values for some of the data. The estimated covariance and correlation matrices in the PROC MIXED results are given in Table 1 and Table 2, respectively.

The diagonals of Table 1 are the estimated variances of the errors associated with 6 time measurements for 2 visits. The variances for outcomes observed after meals are consistently larger than before meals, but variances for outcomes observed within measurement times over two follow-up assessments are compatible. Thus, compound symmetry (CS) for Visit may be a reasonable choice for the covariance structure for the

Visit. Leaving the covariance unstructured for Time, this would be invoked by choosing Type=UN@CS. The estimated covariance and correlation matrices for this specification are given in Table 3 and Table 4, respectively.

Table 1: Estimated covariance matrix for a model using the direct product code UN@UN to indicate unstructured covariance configurations for both within-subject factors: Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	675.1	139.5	119.1	-46.5	207.3	-9.6
2	139.5	401.3	57.0	-38.4	52.2	86.5
3	119.1	57.0	486.2	-5.7	132.2	32.1
4	-46.5	-38.4	-5.7	189.5	-4.7	-20.8
5	207.3	52.2	132.2	-4.7	566.2	-104.6
6	-9.6	86.5	32.1	-20.8	-104.6	305.9
7	163.0	33.7	28.7	-11.2	50.0	-2.3
8	33.7	96.9	13.8	-9.3	12.6	20.9
9	28.7	13.8	117.4	-1.4	31.9	7.8
10	-11.2	-9.3	-1.4	45.7	-1.1	-5.0
11	50.0	12.6	31.9	-1.1	136.7	-25.3
12	-2.3	20.9	7.8	-5.0	-25.3	73.8

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	163.0	33.7	28.7	-11.2	50.0	-2.3
2	33.7	96.9	13.8	-9.3	12.6	20.9
3	28.7	13.8	117.4	-1.4	31.9	7.8
4	-11.2	-9.3	-1.4	45.7	-1.1	-5.0
5	50.0	12.6	31.9	-1.1	136.7	-25.3
6	-2.3	20.9	7.8	-5.0	-25.3	73.8
7	581.6	120.2	102.6	-40.0	178.6	-8.3
8	120.2	345.8	49.1	-33.1	44.9	74.5
9	102.6	49.1	418.9	-4.9	113.9	27.7
10	-40.0	-33.1	-4.9	163.3	-4.1	-17.9
11	178.6	44.9	113.9	-4.1	487.8	-90.1
12	-8.3	74.5	27.7	-17.9	-90.1	263.5

Table 2: Estimated correlation matrix for a model using the direct product code UN@UN to indicate unstructured covariance configurations for both within-subject factors: Row/Columns 1-6 correspond to the measurements made across 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.000	0.268	0.208	-0.130	0.335	-0.021
2	0.268	1.000	0.129	-0.139	0.109	0.247
3	0.208	0.129	1.000	-0.019	0.252	0.083
4	-0.130	-0.139	-0.019	1.000	-0.014	-0.086
5	0.335	0.109	0.252	-0.014	1.000	-0.251
6	-0.021	0.247	0.083	-0.086	-0.251	1.000

7	0.260	0.070	0.054	-0.034	0.087	-0.006
8	0.070	0.260	0.034	-0.036	0.028	0.064
9	0.054	0.034	0.260	-0.005	0.066	0.022
10	-0.034	-0.036	-0.005	0.260	-0.004	-0.022
11	0.087	0.028	0.066	-0.004	0.260	-0.065
12	-0.006	0.064	0.022	-0.022	-0.065	0.260

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	0.260	0.070	0.054	-0.034	0.087	-0.006
2	0.070	0.260	0.034	-0.036	0.028	0.064
3	0.054	0.034	0.260	-0.005	0.066	0.022
4	-0.034	-0.036	-0.005	0.260	-0.004	-0.022
5	0.087	0.028	0.066	-0.004	0.260	-0.065
6	-0.006	0.064	0.022	-0.022	-0.065	0.260
7	1.000	0.268	0.208	-0.130	0.335	-0.021
8	0.268	1.000	0.129	-0.139	0.109	0.247
9	0.208	0.129	1.000	-0.019	0.252	0.083
10	-0.130	-0.139	-0.019	1.000	-0.014	-0.086
11	0.335	0.109	0.252	-0.014	1.000	-0.251
12	-0.021	0.247	0.083	-0.086	-0.251	1.000

Table 3: Estimated covariance matrix for a model using the direct product code UN@CS to indicate an unstructured covariance configuration for Time and Compound Symmetry for Visit: Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	619.0	125.0	110.2	-40.3	185.7	-10.3
2	125.0	377.7	54.1	-35.9	50.1	80.5
3	110.2	54.1	461.0	-5.2	125.1	33.9
4	-40.3	-35.9	-5.2	175.9	-5.0	-19.7
5	185.7	50.1	125.1	-5.0	522.9	-96.6
6	-10.3	80.5	33.9	-19.7	-96.6	289.5
7	161.1	32.5	28.7	-10.5	48.3	-2.7
8	32.5	98.3	14.1	-9.3	13.1	21.0
9	28.7	14.1	120.0	-1.4	32.6	8.8
10	-10.5	-9.3	-1.4	45.8	-1.3	-5.1
11	48.3	13.1	32.6	-1.3	136.1	-25.2
12	-2.7	21.0	8.8	-5.1	-25.2	75.3

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	161.1	32.5	28.7	-10.5	48.3	-2.7
2	32.5	98.3	14.1	-9.3	13.1	21.0
3	28.7	14.1	120.0	-1.4	32.6	8.8
4	-10.5	-9.3	-1.4	45.8	-1.3	-5.1
5	48.3	13.1	32.6	-1.3	136.1	-25.2
6	-2.7	21.0	8.8	-5.1	-25.2	75.3
7	619.0	125.0	110.2	-40.3	185.7	-10.3
8	125.0	377.7	54.1	-35.9	50.1	80.5

9	110.2	54.1	461.0	-5.2	125.1	33.9
10	-40.3	-35.9	-5.2	175.9	-5.0	-19.7
11	185.7	50.1	125.1	-5.0	522.9	-96.6
12	-10.3	80.5	33.9	-19.7	-96.6	289.5

Table 4: Estimated correlation matrix for a model using the direct product code UN@CS to indicate an unstructured covariance configuration for Time and Compound Symmetry for Visit: Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.000	0.259	0.206	-0.122	0.326	-0.024
2	0.259	1.000	0.130	-0.139	0.113	0.244
3	0.206	0.130	1.000	-0.018	0.255	0.093
4	-0.122	-0.139	-0.018	1.000	-0.016	-0.087
5	0.326	0.113	0.255	-0.016	1.000	-0.248
6	-0.024	0.244	0.093	-0.087	-0.248	1.000
7	0.260	0.067	0.054	-0.032	0.085	-0.006
8	0.067	0.260	0.034	-0.036	0.029	0.063
9	0.054	0.034	0.260	-0.005	0.066	0.024
10	-0.032	-0.036	-0.005	0.260	-0.004	-0.023
11	0.085	0.029	0.066	-0.004	0.260	-0.065
12	-0.006	0.063	0.024	-0.023	-0.065	0.260

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	0.260	0.067	0.054	-0.032	0.085	-0.006
2	0.067	0.260	0.034	-0.036	0.029	0.063
3	0.054	0.034	0.260	-0.005	0.066	0.024
4	-0.032	-0.036	-0.005	0.260	-0.004	-0.023
5	0.085	0.029	0.066	-0.004	0.260	-0.065
6	-0.006	0.063	0.024	-0.023	-0.065	0.260
7	1.000	0.259	0.206	-0.122	0.326	-0.024
8	0.259	1.000	0.130	-0.139	0.113	0.244
9	0.206	0.130	1.000	-0.018	0.255	0.093
10	-0.122	-0.139	-0.018	1.000	-0.016	-0.087
11	0.326	0.113	0.255	-0.016	1.000	-0.248
12	-0.024	0.244	0.093	-0.087	-0.248	1.000

In repeated measures, there is a tendency for measurements made close together across time to be more highly correlated than measurements made farther apart. Covariance structures that can accommodate changes in correlation over time, such as first-order autoregressive (AR(1)), heterogeneous variance autoregressive (ARH(1)) and antedependence structures (TOEPH) (Little et al 2006), may be more appropriate than CS. However, note that with only two post baseline visits, ARH(1) and CS structures are identical.

PROC MIXED allows three direct product structures for two within-subject factors: UN*UN, UN*CS, and UN*AR(1). We can choose two covariance structures: CS or AR(1) structure for Time and UN for Visit or we can interchange the order of two factors in the repeated statement to select CS or AR(1) for Visit and UN for Time. Although examination of the residual error correlation matrix (see Table 2) did not indicate a need to investigate potential covariance structures other than UN, we reversed the order of Visit and Time in the Repeated option and chose the CS structure for Time for illustration purposes. The resulting estimated covariance and correlation matrices are given in Table 5 and Table 6.

```
Proc Mixed Data=Vast;
  Class Trt Visit Time Subject;
  Model Change = Baseline Time|Visit|Trt /DDFM = KenwardRoger;
  Repeated Visit Time / Subject = Subject Type = UN@CS R Rcorr;
 Run;
```

Table 5: Estimated correlation matrix for a model using the direct product code UN@CS to indicate an unstructured covariance configuration for Visit and Compound Symmetry for Time: Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	415.3	35.0	35.0	35.0	35.0	35.0
2	35.0	415.3	35.0	35.0	35.0	35.0
3	35.0	35.0	415.3	35.0	35.0	35.0
4	35.0	35.0	35.0	415.3	35.0	35.0
5	35.0	35.0	35.0	35.0	415.3	35.0
6	35.0	35.0	35.0	35.0	35.0	415.3
7	107.7	9.1	9.1	9.1	9.1	9.1
8	9.1	107.7	9.1	9.1	9.1	9.1
9	9.1	9.1	107.7	9.1	9.1	9.1
10	9.1	9.1	9.1	107.7	9.1	9.1
11	9.1	9.1	9.1	9.1	107.7	9.1
12	9.1	9.1	9.1	9.1	9.1	107.7

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	107.7	9.1	9.1	9.1	9.1	9.1
2	9.1	107.7	9.1	9.1	9.1	9.1
3	9.1	9.1	107.7	9.1	9.1	9.1
4	9.1	9.1	9.1	107.7	9.1	9.1
5	9.1	9.1	9.1	9.1	107.7	9.1
6	9.1	9.1	9.1	9.1	9.1	107.7
7	395.8	33.4	33.4	33.4	33.4	33.4
8	33.4	395.8	33.4	33.4	33.4	33.4
9	33.4	33.4	395.8	33.4	33.4	33.4
10	33.4	33.4	33.4	395.8	33.4	33.4
11	33.4	33.4	33.4	33.4	395.8	33.4
12	33.4	33.4	33.4	33.4	33.4	395.8

Table 6: Estimated correlation matrix for a model using the direct product code UN@CS to indicate an unstructured covariance configuration for Visit and Compound Symmetry for Time: Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1, Row/Column 7-12 correspond to the measurements made across the 6 times in visit 2.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.000	0.084	0.084	0.084	0.084	0.084
2	0.084	1.000	0.084	0.084	0.084	0.084
3	0.084	0.084	1.000	0.084	0.084	0.084
4	0.084	0.084	0.084	1.000	0.084	0.084
5	0.084	0.084	0.084	0.084	1.000	0.084
6	0.084	0.084	0.084	0.084	0.084	1.000
7	0.266	0.022	0.022	0.022	0.022	0.022
8	0.022	0.266	0.022	0.022	0.022	0.022
9	0.022	0.022	0.266	0.022	0.022	0.022
10	0.022	0.022	0.022	0.266	0.022	0.022
11	0.022	0.022	0.022	0.022	0.266	0.022
12	0.022	0.022	0.022	0.022	0.022	0.266

Row	Col7	Col8	Col9	Col10	Col11	Col12
1	0.266	0.022	0.022	0.022	0.022	0.022
2	0.022	0.266	0.022	0.022	0.022	0.022
3	0.022	0.022	0.266	0.022	0.022	0.022
4	0.022	0.022	0.022	0.266	0.022	0.022
5	0.022	0.022	0.022	0.022	0.266	0.022
6	0.022	0.022	0.022	0.022	0.022	0.266
7	1.000	0.084	0.084	0.084	0.084	0.084
8	0.084	1.000	0.084	0.084	0.084	0.084
9	0.084	0.084	1.000	0.084	0.084	0.084
10	0.084	0.084	0.084	1.000	0.084	0.084
11	0.084	0.084	0.084	0.084	1.000	0.084
12	0.084	0.084	0.084	0.084	0.084	1.000

Table 7 contains a summary of analyses of the model fit demonstrating results using different direct product covariance structures for two within-subject factors. Using three information criteria, Akaike's information criterion (AIC), AIC corrected (AICc), and Bayesian information criterion (BIC), the "best" model is selected as UN structure for Time and CS structure for Visit in which estimates are required for 22 covariance parameters (Moser and Macchiavelli 2002). Using -2 times the log likelihood as the criteria yields the same conclusion. The other two covariance models explained less variation than the unstructured model.

Figure 1 below is a graph of the least squares means across 6 time points over two visits generated by PROC MIXED using the "best" selected model. The significant treatment effect indicates the active drug curbed hunger levels below levels in the control group averaged over the 6 time points.

Table 7. Model fit summary for doubly repeated measures modeled using the direct covariance product.

Model		-2logL	Parms	AIC	AICC	BIC
Visit=UN	Time=UN	5458.7	24	5504.7	5506.5	5552.1
Visit=CS	Time=UN	5460.4	22	5504.0	5506.1	5549.7
Visit=AR(1)	Time=UN	5460.4	22	5504.0	5506.1	5549.7
Visit=UN	Time=CS	5545.0	4	5553.0	5553.0	5561.2
Visit=UN	Time=AR(1)	5552.9	4	5560.9	5561.0	5569.2

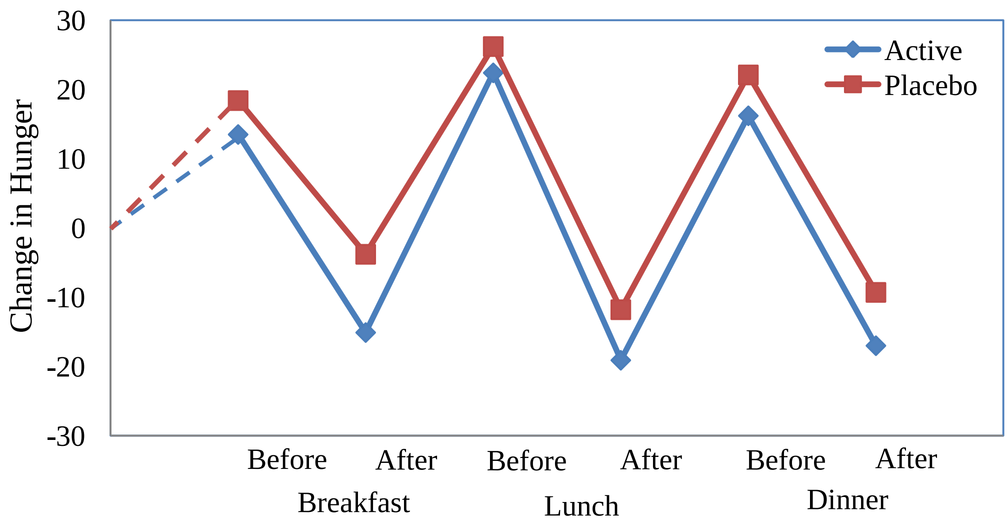

Figure 1: Least square means across 6 time points over 2 visits, covariance structure being modeled using direct product of two covariance structures, UN for Time and CS for Visit.

2.2 GROUP = Optional Statement

Although it is convenient to model direct product structures for two within-subject factors, this approach has limited applications due to only three structures being available. PROC MIXED also permits specifying a single effect while using group specification to model doubly repeated measures. Since the visits are separated by a longer interval (28 days) than time variable (within a day), we considered other options available in PROC MIXED. The analysis resulting from the following code assumes separate covariance structures for different visits, with the UN for various time measurements.

```
Proc Mixed Data=Vast;
  Class Trt Visit Time Subject;
  Model Change = Baseline Time|Visit|Trt / DDFM = KenwardRoger;
  Repeated Time / Subject = Subject*Visit GROUP = Visit Type = UN R Rcorr;
Run;
```

The estimated covariance matrices for two visits are given in Table 8. The number of estimated covariance parameters is 42.

Table 8: Estimated covariance structure matrix for a model using separated UN by two time visits. Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1 (up) and in visit 2 (bottom).

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	494.2					
2	94.4	463.1				
3	120.1	80.1	563.4			
4	2.1	-31.2	3	163.7		
5	130.9	84.8	164	-10.6	494.7	
6	-30	81.6	81.5	-14.9	-76.2	341.4

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	400.5					
2	48.9	400.5				
3	48.9	48.9	400.5			
4	48.9	48.9	48.9	400.5		
5	48.9	48.9	48.9	48.9	400.5	
6	48.9	48.9	48.9	48.9	48.9	400.5

Employing still another approach, PROC MIXED will estimate the covariance structure using information pooled over two visits if we leave out the ‘GROUP =’ option. The resulting number of estimated covariance parameters is 21, as shown in Table 9.

```
Proc Mixed Data=Vast;
  Class Trt Visit Time Subject;
  Model Change = Baseline Time|Visit|Trt / DDFM = KenwardRoger;
  Repeated Time / Subject = Subject*Visit Type = UN R Rcorr;
Run;
```

Table 9: Estimated covariance structure matrix for a model using UN, ‘GROUP =’ option being omitted. Row/Columns 1-6 correspond to the measurements made across the 6 times pooled over two visits.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	604.4					
2	151.6	413.8				
3	130.8	69.4	461.3			
4	-30.4	-27.5	1.9	168.2		
5	219.7	65.3	139.1	-4	542	
6	-15	81.5	34.3	-7.7	-84.1	285

We can replace the covariance structure UN with CS, AR(1), or SP(POW) in search of improvement in model fitness. The analysis further assumes identical covariance structures among the visits if the 'GROUP = Visit' option is omitted. The number of estimated covariance parameters would be 4 and 2, as indicated in Table 10 and Table 11 respectively.

We can choose appropriate covariance structures for Time by specifying 'Subject = Subject*Visit' or select covariance structures for Visit by specifying 'Subject = Subject*Time'. Table 12 below lists fitness indices from analyses using different covariance structures. The "best" model is selected as identical UN structure for Time for both visits in which estimates are required for 21 covariance parameters, or CS structure for Visit at 12 Time measurement over 2 visits in which estimates are required for 12 covariance parameters.

Table 10: Estimated covariance structure matrix for a model using separated CS by two time visits. Row/Columns 1-6 correspond to the measurements made across the 6 times in visit 1 (up) and in visit 2 (bottom).

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	417					
2	40.7	417				
3	40.7	40.7	417			
4	40.7	40.7	40.7	417		
5	40.7	40.7	40.7	40.7	417	
6	40.7	40.7	40.7	40.7	40.7	417

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	400.5					
2	48.9	400.5				
3	48.9	48.9	400.5			
4	48.9	48.9	48.9	400.5		
5	48.9	48.9	48.9	48.9	400.5	
6	48.9	48.9	48.9	48.9	48.9	400.5

Table 11: Estimated covariance structure matrix for a model using CS, 'GROUP =' option being omitted. Row/Columns 1-6 correspond to the measurements made across the 6 times pooled over two visits.

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	409.4					
2	44.5	409.4				
3	44.5	44.5	409.4			
4	44.5	44.5	44.5	409.4		
5	44.5	44.5	44.5	44.5	409.4	
6	44.5	44.5	44.5	44.5	44.5	409.4

Table 12. Model fit summary for doubly repeated measures modeled using the “Group” option.

	Group	-2logL	Parms	AIC	AICC	BIC
Time = UN	Y	5460.3	42	5544.3	5550.6	5657.7
Time = UN	N	5478.9	21	5520.9	5522.5	5577.6
Time = CS	Y	5565.4	4	5573.4	5573.5	5584.2
Time = CS	N	5565.7	2	5569.7	5569.7	5575.1
Visit = UN	Y	5484.3	18	5520.3	5521.4	5589.5
Visit = UN	N	5553.5	3	5559.5	5559.5	5571.0
Visit = CS	Y	5493.0	12	5517.0	5517.5	5563.2
Visit = CS	N	5553.6	2	5557.6	5557.6	5565.3

3. Final Comments

Analytical efficiency can be gained by taking advantage of structured patterns in the underlying covariance matrix for model residuals in studies involving repeated measures. This paper discussed some model fitting strategies and the unique covariance structures in a food intake trial. PROC MIXED enables doubly repeated measures analysis with direct product covariance structures or specifying a single effect while using the ‘GROUP =’ option. Our considerations have not dealt with the many diagnostic analyses that should be incorporated into the usual analysis of repeated measures data. Residuals should be examined for the bell shaped distribution. The effects of influential observations and outliers should be examined as well. In addition, three or more repeated measures arise in many situations and additional software is needed to fully exploit the covariance patterns for these types of data. In the future, we will fit random coefficients regression models to accommodate unequally spaced time measurements in analyzing doubly repeated measures designs.

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