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On the use of PROC MIXED to Estimate Correlation in the Presence of Repeated Measures

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ABSTRACT

The need to assess correlation in settings where multiple measurements are available on each of the variables of interest arises often in biostatistical science. Although several ad hoc approaches can be used, they can easily lead to invalid conclusions (Bland and Altman, 1994) and to a difficult choice of an appropriate measure of the correlation (Hamlett, Ryan, Serrano-Trespalacios and Wolfinger, 2003). While several formal approaches have been proposed (Bland and Altman, 1995, Chinchilli, Martel, Kumanyika and Lloyd, 1996), these are associated with a variety of drawbacks (Hamlett, Ryan, Serrano-Trespalacios and Wolfinger, 2003). Lam et al. (Lam, Webb and O'Donnell, 1999) approached this problem by using maximum likelihood estimation in the case where the replicate measurements are linked over time, for example, by being taken at the same point in time, but the method requires specialized software. We reanalyze the data of Lam et al. (Lam, Webb and O'Donnell, 1999) using PROC MIXED in SAS and generalize their model to encompass other setting not covered in their paper.

INTRODUCTION

In this paper, we demonstrate how to obtain an estimate of the correlation between two variables when multiple measurements are available on each of the variables of interest. We consider the setting where the two variables are linked, for example, if measurements are taken together on different days. We give the necessary code needed to obtain the correlation estimate and apply this code to the data set given in Table 1 (taken from Bland and Altman, 1994) which shows a linked data set of repeated measurements of intramural pH and $PaCO_2$ obtained from gastric pH and blood gas analysis of eight critically ill patients. Note that the number of repeated measurements varies by patient. The case where the repeated measurements are not linked over time is a special case of the linked case.

Table 1. Repeated measures of intramural pH and $PaCO_2$ for 8 critically ill patients

Patient #	pH	$PaCO_2$	Patient #	pH	$PaCO_2$	Patient #	pH	$PaCO_2$
1	6.68	3.97	3	7.34	5.07	6	7.29	5.12
1	6.53	4.12	4	7.36	5.67	6	7.33	4.93
1	6.43	4.09	4	7.33	5.10	6	7.31	5.03
1	6.33	3.97	4	7.29	5.53	6	7.33	4.93
2	6.85	5.27	4	7.30	4.75	7	6.86	6.85
2	7.06	5.37	4	7.35	5.51	7	6.94	6.44
2	7.13	5.41	5	7.35	4.28	7	6.92	6.52
2	7.17	5.44	5	7.30	4.44	8	7.19	5.28
3	7.40	5.67	5	7.30	4.32	8	7.29	4.56
3	7.42	3.64	5	7.37	3.23	8	7.21	4.34
3	7.41	4.32	5	7.27	4.46	8	7.25	4.32
3	7.37	4.73	5	7.28	4.72	8	7.20	4.41
3	7.34	4.96	5	7.32	4.75	8	7.19	3.69
3	7.35	5.04	5	7.32	4.99	8	6.77	6.09
3	7.28	5.22	6	7.38	4.78	8	6.82	5.58
3	7.30	4.82	6	7.30	4.73			

STATISTICAL MODEL

Let (U_{ij}, W_{ij}) be the jth repeated observation $(j = 1, ..., m_i)$ of the variables of interest, say U and W, taken on the ith subject $(i = 1, ..., n)$, in a sample of n individuals and define $N = 2\sum_{i=1}^{n} m_i$ to be the total number of observations.

Assume the pair (U_{ij}, W_{ij}) has a bivariate normal distribution,

$$\begin{bmatrix} U_{ij} \\ W_{ij} \end{bmatrix} \sim BVN\left(\begin{bmatrix} \mu_U \\ \mu_W \end{bmatrix}, \Sigma \right)$$

where m_U and m_W are the overall means of U and W respectively and Σ is the variance-covariance matrix. Assumptions about Σ are important, as this is where we define the correlations of interest.

Following Lam et al. (Lam, Web and O'Donnell, 1999) we assume

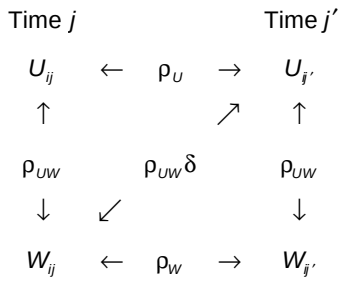
$$\Sigma = \begin{bmatrix} s_U^2 & s_U s_W r_{UW} \\ s_U s_W r_{UW} & s_W^2 \end{bmatrix}$$

where s_U^2 and s_W^2 are the variances of U and W respectively, and r_{UW} is their correlation, our main parameter of interest. For notational convenience, it will be useful to define the covariance term $s_U s_W r_{UW} = s_{UW}$. Full specification of the model also requires assumptions regarding the relationships between U's and W's measured at different times. Like Lam et al. (Lam, Web and O'Donnell, 1999) we assume that correlations between measurements taken at two different times, j and j', $j \neq j'$, are given by:

$$\begin{aligned} \text{Corr}\,(U_{ij}, U_{ij'}) &= r_U \\ \text{Corr}\,(W_{ij}, W_{ij'}) &= r_W \\ \text{Corr}\,(U_{ij}, W_{ij}) &= r_{UW} \\ \text{Corr}\,(U_{ij}, W_{ij'}) &= r_{UW} d \end{aligned}$$

Heuristically, we would expect the term d to generally be less than 1, indicating that correlations between variables measured at different times are lower in magnitude than those taken at the same time. The assumed correlation structure is depicted in Figure 1.

Figure 1. Correlation Structure



In order to better visualize the covariance structure, it is helpful to write out the full covariance matrix for the entire set of $2m_i$ repeated measurements for the ith subject:

$$V_i = \text{Cov}\begin{pmatrix} U_{i1} \\ W_{i1} \\ U_{i2} \\ W_{i2} \\ \vdots \\ U_{in_i} \\ W_{in_i} \end{pmatrix} = \begin{pmatrix} \sigma_U^2 & \sigma_{UW} & \sigma_U^2\rho_U & \sigma_{UW}\delta & \cdots & \sigma_U^2\rho_U & \sigma_{UW}\delta \\ \sigma_{UW} & \sigma_W^2 & \sigma_{UW}\delta & \sigma_W^2\rho_W & \cdots & \sigma_{UW}\delta & \sigma_W^2\rho_W \\ \sigma_U^2\rho_U & \sigma_{UW}\delta & \sigma_U^2 & \sigma_{UW} & \vdots & \sigma_U^2\rho_W & \sigma_{UW}\delta \\ \sigma_{UW}\delta & \sigma_W^2\rho_W & \sigma_{UW} & \sigma_W^2 & \vdots & \sigma_{UW}\delta & \sigma_W^2\rho_W \\ \vdots & \vdots & \cdots & \cdots & \ddots & \vdots & \vdots \\ \sigma_U^2\rho_U & \sigma_{UW}\delta & \sigma_U^2\rho_U & \sigma_{UW}\delta & \cdots & \sigma_U^2 & \sigma_{UW} \\ \sigma_{UW}\delta & \sigma_W^2\rho_W & \sigma_{UW}\delta & \sigma_W^2\rho_W & \cdots & \sigma_{UW} & \sigma_W^2 \end{pmatrix}.$$

Note the block structure of this matrix, with submatrices corresponding to Σ down the main diagonal. The covariance matrix will have the same structure for each subject, except that the dimension will vary, due to the unequal number of repeated measurements between subjects.

MODEL FITTING IN SAS

The statistical model described above can be formulated as a linear mixed effects model and fitted using PROC MIXED in SAS.

MIXED MODEL FORMULATION

Let $Y_i = \left[U_{i1},\ W_{i1},\ \ldots,\ U_{im_i},\ W_{im_i}\right]'$ be the $2m_i$ dimensional vector of observations on subject i, and $Y = \left[Y_1,\ Y_2,\ \ldots,\ Y_n\right]'$ be the N dimensional vector of total observations. For the ith subject, we consider the linear mixed effects model given by

$$Y_i = X_i\beta + Z_i\gamma_i + \varepsilon_i \qquad (1)$$

where X_i and Z_i are the fixed and random design matrices respectively, β is a vector of fixed effects, γ_i is a vector of random effects and ε_i is the random error.

It is assumed that $\gamma_i \sim N(0, G)$, ε_i is a $2m_i$ x $2m_i$ matrix of random errors distributed as $N(0, R_i)$ and $\mathrm{cov}(\gamma_i, \varepsilon_i) = 0$. We will discuss appropriate assumptions for G and R_i presently.

From (1), we have

$$E(Y_i) = X_i\beta \text{ and } \mathrm{Var}(Y_i) = Z_iGZ_i' + R_i$$

The challenge is to determine X_i, Z_i, G and R_i so that we can fit the model with the given variance-covariance structure describe in the previous section.

Since there are two variables of interest, namely U and W, this suggest that X_i would have three columns, allowing for an intercept term. Each row of X_i would correspond to the intercept term and whether the observation was taken on the U or W variable. Hence, X_i would consist of zeros and ones, as indicated below. The length of X_i is $2m_i$. Thus we have,

$$\beta = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{pmatrix} \text{ and } X_i = \begin{pmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ . & . & . \\ . & . & . \\ . & . & . \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix}$$

Note that X_i is not of full rank, thus restrictions need to be imposed to make the parameters estimable. Usually, we set $\beta_2 = 0$. The solution for β gives the means μ_U and μ_W.

In order to determine Z_i, G and R_i it is useful to note that the matrix V_i can be rewritten as the sum of two parts, one, a matrix of constants whose values depend on whether the corresponding pair is two U's, two W's or a $U-W$ pair, and the other which is block diagonal, with blocks corresponding to pairs measured at the same time. Specifically V_i can be written as,

$$V_i = \begin{pmatrix} \sigma_U^2\rho_U & \sigma_{UW}\delta & \sigma_U^2\rho_U & \sigma_{UW}\delta & \cdots & \sigma_U^2\rho_U & \sigma_{UW}\delta \\ \sigma_{UW}\delta & \sigma_W^2\rho_W & \sigma_{UW}\delta & \sigma_W^2\rho_W & \cdots & \sigma_{UW}\delta & \sigma_W^2\rho_W \\ \sigma_U^2\rho_U & \sigma_{UW}\delta & \sigma_U^2\rho_U & \sigma_{UW}\delta & \vdots & \sigma_U^2\rho_U & \sigma_{UW}\delta \\ \sigma_{UW}\delta & \sigma_W^2\rho_W & \sigma_{UW}\delta & \sigma_W^2\rho_W & \vdots & \sigma_{UW}\delta & \sigma_W^2\rho_W \\ \vdots & \vdots & \cdots & \cdots & \ddots & \vdots & \vdots \\ \sigma_U^2\rho_U & \sigma_{UW}\delta & \sigma_U^2\rho_U & \sigma_{UW}\delta & \cdots & \sigma_U^2\rho_U & \sigma_{UW}\delta \\ \sigma_{UW}\delta & \sigma_W^2\rho_W & \sigma_{UW}\delta & \sigma_W^2\rho_W & \cdots & \sigma_{UW}\delta & \sigma_W^2\rho_W \end{pmatrix} + \begin{pmatrix} \eta & \xi & 0 & 0 & \cdots & 0 & 0 \\ \xi & \nu & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \eta & \xi & \vdots & 0 & 0 \\ 0 & 0 & \xi & \nu & \vdots & 0 & 0 \\ \vdots & \vdots & \cdots & \cdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & \eta & \xi \\ 0 & 0 & 0 & 0 & \cdots & \xi & \nu \end{pmatrix} \qquad (2)$$

where $\eta = \sigma_U^2(1-\rho_U)$, $\nu = \sigma_W^2(1-\rho_W)$ and $\xi = \sigma_{UW}(1-\delta)$.

We can see that the first of these two matrices can be expressed as Z_iGZ_i', with appropriate choices for Z_i and G, and the second as R_i. Inspection of the first matrix reveals that there are only three different components, namely, $\sigma_U^2\rho_U$, $\sigma_{UW}\delta$ and

$\sigma_W^2\rho_W$ in this matrix. This implies that G is 2×2 and thus, γ_i is 2×1. Therefore, Z_i is $2m_i \times 2$, comprising of zeros and ones. Similarly, we can see that R_i is $2m_i \times 2m_i$, with 2×2 blocks along the main diagonal.

Hence we have,

$$G = \begin{pmatrix} \sigma_U^2\rho_U & \sigma_{UW}\delta \\ \sigma_{UW}\delta & \sigma_W^2\rho_W \end{pmatrix},\ \gamma_i = \begin{pmatrix} \gamma_1 \\ \gamma_2 \end{pmatrix},\ R_i = I_{m_i} \otimes \begin{pmatrix} \eta & \xi \\ \xi & \nu \end{pmatrix}, \text{ and } Z_i = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ . & . \\ . & . \\ . & . \\ 1 & 0 \\ 0 & 1 \end{pmatrix},$$

where I_{m_i} is the identity matrix of size m_i.

G and R_i can be set up through judicious use of the random and repeated statements in PROC MIXED. Consider first the matrix on the left hand side of equation (2). Careful scrutiny indicates that the matrix can be constructed by assigning $U-$ and $W-$ specific random effects to individual i, and allowing these random effects to be correlated. This can be achieved by declaring a variable which we call "*Vtype*" (i.e., the indicator of whether a particular observation is an U or a W) to be random across individual subjects. Covariance between $U-$ and $W-$ specific random effects can be achieved by specifying an unstructured covariance matrix. Now consider the second matrix on the right hand side of equation (2). This structure is relatively straightforward and can be achieved by declaring the variable "*Vtype*" to be repeated within each individual-specific replicate (i.e., declaring subject to be replicate nested within individual), and using an unstructured covariance matrix for R_i.

In order to use PROC MIXED, the data must be entered in univariate form, that is, each row of data must correspond to a different measurement. A variable needs to be defined, which indicates whether each line of data corresponds to an $U-$ or $W-$ observation. As indicated above, this is the variable *Vtype*. A variable which we call *Replicate* is used to keep track of the repeated measurements within subjects. Note that the *Replicate* variable will be nested within subjects.

Appropriate SAS data format is illustrated below by Example 1, for the data in Table 1, taken from Bland and Altman (Bland and Altman, 1994) where pH is chosen as *Vtype*=1 and $PaCO_2$ is chosen as *Vtype*=2. *Response* is the value of *Vtype*=1 or *Vtype*=2 and *Persnum* is the patient number. It is of no significance that pH is chosen as *Vtype*=1 and $PaCO_2$ as *Vtype*=2, since the coding scheme was arbitrary.

Example 1.

```
input Persnum Vtype Response Replicate;
datalines;
1 1 6.68 1
1 2 3.97 1
1 1 6.53 2
1 2 4.12 2
1 1 6.43 3
1 2 4.09 3
1 1 6.33 4
1 2 3.97 4
.
.
.
8 1 6.82 8
8 2 5.58 8
;
```

The SAS code to obtain the parameter estimates is given by,

SAS code:

```
proc mixed method=ml;
class persnum vtype replicate;
model response = vtype / solution ddfm=kr;
```

```
random vtype /type=un subject=persnum v vcorr;
repeated vtype / type=un subject=replicate(persnum);
run;
```

where, *Persnum* corresponds to patient number, *Vtype* refers to the two variables, which are coded as 1 and 2, *Response* corresponds to the values of the two variables and *Replicate* corresponds to the number of repeated measurements for each patient, which need not be the same. The CLASS statement specifies *Persnum* , *Treatment* and *Replicate* as classification (categorical) effects and the MODEL statement specifies the mean (regression) model for the data. SOLUTION requests that the fixed effects (specified on the righthand side of the equal sign in the model statement, before /) estimates be printed and DDFM = *KR* specifies the Kenward-Roger (Kenward and Roger, 1997) method for computing the denominator degrees of freedom for the fixed effects. Note that while this latter option is not necessary, it tends to yield more reliable results in general (see the SAS manual (SAS Institute Inc., 1999) for more details).

As indicated earlier, the RANDOM and REPEATED statements are used to set up the structure of the G and R_i matrices. Declaring SUBJECT = *Persnum* after the specification of *Vtype* as random instructs PROC MIXED to make the $N \times N$ variance-covariance matrix for the entire data vector to be block diagonal, with block corresponding to patient. The size of the blocks depends on the number of measurements each patient has. These patient blocks are in themselves block diagonal of size 2×2 with structure specified by TYPE=option. TYPE=UN specifies a general variance-covariance matrix and makes the patient-specific U and W random effects correlated.

On the REPEATED statement line, SUBJECT = *Replicate(Persnum)* instructs PROC MIXED to make the $N \times N$ variance-covariance matrix for the entire data vector to be a diagonal matrix of 2×2 blocks. Each of these 2×2 blocks has the structure specified by the TYPE=option. In this case, TYPE=UN specifies a general variance-covariance matrix.

Specifying V and VCORR options results in the estimated response variances-covariances and correlations (our estimates of interest) be printed respectively. By default, the first block, determined by the SUBJECT=effect is printed. However, the default can be changed by specifying a specific value V and VCORR (see the SAS manual (SAS Institute, Inc., 1999)).

PROC MIXED allows specification of a METHOD=option to specify the method of estimation for the covariance parameters. If no METHOD=option is given in the PROC MIXED statement, the covariance parameters are estimated using Restricted Maximum Likelihood (REML) estimation, the default option.

Similarly, in the MODEL statement you can specify the method of computation for the denominator degrees of freedom by using the DDFM=option. If no DDFM= option is given in the MODEL statement, for the SAS code given here, the CONTAINMENT option is used. For further details on the METHOD=option and DDFM=option, see the SAS manual (SAS Institute, Inc., 1999).

EXAMPLE

Table 1 provided by Bland and Altman (Bland and Altman, 1994) and reproduced in Lam et al. (Lam, Webb and O'Donnell, 1999) shows linked repeated measurements of intramural pH and $PaCO_2$ for eight subjects.

Lam et al. (Lam, Webb and O'Donnell, 1999) obtained parameter estimates (Table 2) for the data, using a Maximum Likelihood (ML) estimation program. These results can be reproduced using the above SAS code, by specifying METHOD=ML in the PROC MIXED statement. The main difference between ML and REML (the default option) is that ML gives biased estimates of the covariance parameters, where as, REML does not. Selected portions of the SAS output are given in Tables 3-5, where labels have been added for clarity.

Table 2. Parameter estimates from Lam et al. (Lam, Webb and O'Donnell, 1999) for the pH(U)-$PaCO_2$(W) data in Table 1

Parameter	Estimate
μ_U	7.1151
μ_W	5.0082
σ_U^2	0.0862
σ_W^2	0.6799
ρ_U	0.8659
ρ_W	0.6254
ρ_{UW}	-0.0100
δ	-10.4724

The results in Table 2 are obtained from Tables 3 to 5. Table 3 gives the results obtained from the SAS code for the V matrix and Table 4 gives the corresponding correlations associated with the V matrix. From Table 3, 0.0862 and 0.6799 are the

overall estimated variances $\left(\sigma_U^2;\ \sigma_W^2\right)$ of U and W respectively. From Table 4, the estimated correlation between U and W $\left(\rho_{UW}\right)$ is -0.0010. For $j \neq j'$, the estimated correlation between U_{ij} and $U_{ij'}$ $\left(\rho_U\right)$ is 0.8659 and the estimated correlation between W_{ij} and $W_{ij'}$ $\left(\rho_W\right)$ is 0.6254. The estimated correlation between $U_{ij'}$ and W_{ij} $\left(\rho_{UW}\delta\right)$ is 0.1042 and thus, the estimate of δ is -10.4724 (0.1042/-0.00995). The means μ_U and μ_W are obtained from Table 5. In SAS, when the variables are categorical, the highest value is taken as the point of reference, which in our case is the variable labeled as 2 ($PaCO_2$(W)). The estimate for μ_U is 7.1151, which is the sum of the estimated values for the intercept and $PaCO_2$(W). The estimate for μ_W is 5.0082, the intercept value.

Table 3. Estimated variance-covariance matrix for the pH(U)-$PaCO_2$(W) data in Table1, for Patient #1

	U_1	W_1	U_2	W_2	U_3	W_3	U_4	W_4
U_1	0.0862	-0.0024	0.0747	0.0252	0.0747	0.0252	0.0747	0.0252
W_1	-0.0024	0.6799	0.0252	0.4252	0.0252	0.4252	0.0252	0.4252
U_2	0.0747	0.0252	0.0862	-0.0024	0.0747	0.0252	0.0747	0.0252
W_2	0.0252	0.4252	-0.0024	0.6799	0.0252	0.4252	0.0252	0.4252
U_3	0.0747	0.0252	0.0747	0.0252	0.0862	-0.0024	0.0747	0.0252
W_3	0.0252	0.4252	0.0252	0.4252	-0.0024	0.6799	0.0252	0.4252
U_4	0.0747	0.0252	0.0747	0.0252	0.0747	0.0252	0.0862	-0.0024
W_4	0.0252	0.4252	0.0252	0.4252	0.0252	0.4252	-0.0024	0.6799

Table 4. Estimated correlation matrix between pH(U) and $PaCO_2$(W) data in Table 1, for Patient #1

	U_1	W_1	U_2	W_2	U_3	W_3	U_4	W_4
U_1	1.0000	-0.0100	0.8659	0.1042	0.8659	0.1042	0.8659	0.1042
W_1	-0.0100	1.0000	0.1042	0.6254	0.1042	0.6254	0.1042	0.6254
U_2	0.8659	0.1042	1.0000	-0.0100	0.8659	0.1042	0.8659	0.1042
W_2	0.1042	0.6254	-0.0100	1.0000	0.1042	0.6254	0.1042	0.6254
U_3	0.8659	0.1042	0.8659	0.1042	1.0000	-0.0100	0.8659	0.1042
W_3	0.1042	0.6254	0.1042	0.6254	-0.0100	1.0000	0.1042	0.6254
U_4	0.8659	0.1042	0.8659	0.1042	0.8659	0.1042	1.0000	-0.0100
W_4	0.1042	0.6254	0.1042	0.6254	0.1042	0.6254	-0.0100	1.0000

Table 5. Regression results for the pH(U)-$PaCO_2$(W) data in Table 1

Effect	Estimate	SE	DF	t-value	Pr > |t|
Intercept	5.0082	0.2432	7.25	20.57	<0.0001
pH	2.1069	0.2528	7.18	8.34	<0.0001
$PaCO_2$	0	.	.	.	

CONCLUSION

In this paper we demonstrated how to obtain an estimate of the correlation between two variates, say U and W in the presence of repeated measures or replicates. We considered the case where U and W are linked, under the assumption that the two variates follow a multivariate normal distribution. PROC MIXED in SAS was used to estimate the correlation. The mixed model formulation is very easy to apply using PROC MIXED in SAS.

In the situation where the replicates are not linked, i.e., no time effect, PROC MIXED can still be used to obtain an estimate of the correlation. The unlinked case is a special case of the linked one with δ set equal to one, in the correlation structure depicted in Figure 1, and ξ set equal to zero in R_i .The code is the same as that described above, except that the REPEATED statement is replaced by,

```
repeated vtype / type=un(1) subject=replicate(persnum);
```

where TYPE=UN(1) specifies a variance-covariance matrix whose off-diagonal element is zero. Equivalently, one can use the following code for the repeated statement,

```
repeated / group=vtype;
```

where GROUP= *Vtype* specifies heterogeneity of variances between observations with *Vtype*=1 and *Vtype*=2 (i.e., for U and W).

If the data are skewed, thereby violating the normality assumption, a transformation, such as the log for example, might be appropriate before applying the SAS PROC MIXED procedure.

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