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1 Bivariate Longitudinal Data

- 1. Often researchers are interested in how two or more longitudinal variables are interrelated. Are the overall levels correlated? Within a subject, do individual ups and downs track each other?
- 2. The correlations between the two responses are called the *cross correlations*. We may test whether the cross correlations are zero or not.
- 3. Occasionally we may consider including the second response as a timevarying covariate in the fixed effects when analyzing the first longitudinal response. We test the coefficient of the longitudinal covariate to see if it is significantly different from zero. If the coefficient is positive, the two variables go up together and down together; if the coefficient is negative, the two variables move in opposite directions. This procedure has a number of drawbacks.
- 4. Pain data: pain rating and log pain tolerance
 - (a) A second longitudinal variable called pain rating. Each subject is asked to rate the pain of each trial on a 1 to 10 scale.
 - (b) We expect an inverse relationship between pain rating and pain tolerance; the less the pain rating, the greater the pain tolerance and vice versa.

- (c) This would show up as a negative coefficient in a model that included pain rating as a predictor for log pain tolerance.
- (d) We might suspect that a subject's average pain rating has no particular meaning, and that average pain rating is uncorrelated with average pain tolerance.
- (e) On the other hand, we might expect the variation up or down in pain rating from the subject's average rating might have some relationship with pain tolerance.
- (f) We need a model that allows us to distinguish between over all subject average pain rating level and random variation from trial to trial.
- 5. Kenya School Lunch Study examples
 - (a) A contrasting example might be when we measure subjects' height and weight repeatedly over time.
 - (b) Subject's average height and weight are likely well correlated, but the random variation in weight might not be particularly correlated with random variation in height.
 - (c) Weight variation might have more to do with daily eating patterns etc., while height variation depends more on slouching and measurement error.

- (d) The observation to observation variation of one measure probably does not have much to do with the other.
- (e) Subject's average nutrition level might predict the slope in an anthropometric response such as height or weight.

2 Bivariate Longitudinal Example

Figure 1 illustrates four different models. Bivariate observations (Y_{ij}, W_{ij}) measured at time $t_{ij} = j$ for j = 1, ..., J = 4 times on each of 8 subjects. The first response, Y_{ij} , is plotted on the horizontal axis and the second response, W_{ij} , is plotted on the vertical axis. Observations from the same subject are plotted using the same symbol; the time sequence of the observations is not indicated. The covariation between Y_{ij} and W_{ij} has two parts. (1) The covariation between subject means of Y_i and W_i . Given the means, (2) observations within a subject (Y_{ij}, W_{ij}) may be correlated.

The language we are using corresponds to a random intercept model for Y_i and another random intercept model for W_i . Each variable, Y or W, has a random subject intercept, and each observation Y_{ij} or W_{ij} has a residual error. Another way of saying that the subject means are correlated is to say that the random intercept for Y_i is correlated with the random intercept of W_i . Similarly, when we say that the observations within a subject are correlated, we mean that the residual errors at a given time j are correlated.



Figure 1: Scatterplots of 4 hypothetical bivariate observations from 8 subjects. Observations within a subject are plotted using the same plotting symbol. Response Y is on the horizontal axis, response W is on the vertical axis. (a) Figure illustrating bivariate longitudinal data with observations within subject positively correlated, and subject averages also positively correlated. (b) Positive correlated between subject averages, observations within subject uncorrelated. (c) Observations within subject correlated, subject averages uncorrelated. (d) Observations within subject uncorrelated and subject averages uncorrelated.

Model	Parameter	Est	SE	t	p
1	rating	055	.025	-2.3	.028
2	rating average	070	.072	97	.34
3	rating deviation	055	.027	-2.1	.043
4	rating deviation	055	.027	-2.1	.045
	rating average	069	.072	-1.0	.34
	deviation - average	.013	.076	.18	.8

Table 1: REML estimates using the unstructured covariance model for four models with pain rating as covariate. All models have 8 parameters for the $CS \times TMT$ interaction effects. Estimates, standard errors and inferences are given only for the pain rating variables. Model 1 has pain rating; model 2 has average pain rating only, model 3 has rating deviation only and model 4 includes both average rating and rating deviation in the model. The last line presents the hypothesis test that the two coefficients are equal in this last model; the estimate and standard error are for the difference in the two coefficients. Models 2 through 4 use data only from the 58 subjects with complete data.

3 Continuous Time Varying Covariates

Bad stats, but fittable using today's software.

- In the log pain tolerance analysis with coping style (CS) by treatment (TMT) interaction, we include the pain rating as a covariate in the analysis.
- Subjects without complete pain rating and pain tolerance data will be dropped from models that involve average pain rating and pain rating deviations.
- 3. We hypothesize that average pain rating is not predictive of log pain tolerance and if we entered it as a time fixed predictor we would not

expect it to be significant.

- 4. Model 2 in table 1 gives the results of using average pain rating as a predictor.
- 5.

rating deviation_{ij} = rating_{ij} - average rating_i.

- 6. Even if average rating should not be predictive of log tolerance, rating deviation should be. Model 3 in table 1 reports the result.
- Finally, we can include both average rating and rating deviation in the model, and this is reported as model 4 in table 1.
- 8. The test that both coefficients are equal is given in the last line of the table and tests the null hypothesis that both effects are the same.
- 9. The results for rating in model 1 and rating deviation in models 3 and 4 are consistent. The higher the subject's pain rating for that trial, the shorter the time of immersion.
- 10. If you reverse the analysis, you don't get the same results.

4 Problems with Using a Response as a Predictor

- 1. Unbalanced data is awkward to handle, for calculating averages, or deviations for example.
- 2. We can not use observations with one response or the other but not both.
- 3. If there is a time trend, then the residuals will show a predictive relationship among the residuals which might be misinterpreted as correlation in the residual variation, when it is actually the time trends of the two variables that are correlated.
- 4. Which response should be treated as the response and which should be treated as the covariate? Fitting four models as in table 1 with pain rating as the response and with pain tolerance gives slightly different results regarding the association. Log tolerance is significant, but log tolerance deviation is borderline not significant; it comes in with *p*-values between .05 and .06 for models 2 and 4. If we were compulsive about using a .05 cutoff for significance we would conclude that there was not a significant relationship between pain rating and log pain tolerance deviations.
- 5. Whichever response is being used as a predictor may be affected by the other covariates in the analysis. Could it be that treatment pre-

dicts pain rating as well as log pain tolerance and that is why the two variables appear related?

- 6. The solution
 - (a) It is preferable that one should model the two responses jointly.
 - (b) Research questions involving two or more continuous longitudinal variables are often best answered in a multivariate longitudinal framework.
 - (c) Treat the two variables as a bivariate response measured repeatedly over time.
 - (d) One advantage of multivariate models is that we can incorporate subjects with different missing observation patterns on each response.

5 The Bivariate Random Intercept Model

- 1. Y_{ij} is the first response measured at time t_{ij} for $j = 1, \ldots n_i$
- 2. W_{ij} be the second response measured at the same times.
- 3. Each response is modeled by its own random intercept model.
- 4. The random effects and error terms will be correlated, inducing correlation between the two responses.

- 5. For covariates, we will assume the same K-vector x_{ij} of covariates at time t_{ij} for both responses and the same matrix X_i , n_i by K of covariates with rows x'_{ij} .
- 6. The Z_i matrices will also be the same.
- 7. Two fixed effects vectors

$$\alpha_Y = (\alpha_{Y1}, \dots, \alpha_{YK})'$$
$$\alpha_W = (\alpha_{W1}, \dots, \alpha_{WK})'$$

Two random intercepts β_{iY} and β_{iW} , each a scalar.

8. Two sets of residual errors

$$\delta_{iY} = (\delta_{iY1}, \dots, \delta_{iYn_i})'$$

$$\delta_{iW} = (\delta_{iW1}, \dots, \delta_{iWn_i})'$$

9. The model

$$Y_{ij} = x'_{ij}\alpha_Y + \beta_{iY} + \delta_{iYj}$$
$$W_{ij} = x'_{ij}\alpha_W + \beta_{iW} + \delta_{iWj}.$$

10.

$$\beta_i = \begin{pmatrix} \beta_{iY} \\ \beta_{iW} \end{pmatrix} \sim N_2 \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} D_{YY} & D_{YW} \\ D_{WY} & D_{WW} \end{pmatrix} \right)$$

- 11. D_{YY} the variance of the β_{iY} and D_{WW} the variance of the W random intercepts β_{iW} . The covariance $D_{YW} = D_{WY}$ of the two random effects: the average levels of the two effects are correlated. If they are not correlated, then D_{YW} will be zero. If the covariance D_{YW} is positive, the average levels of Y_i and W_i go up and down together and if D_{YW} is negative, then when Y_i is high, W_i on average will be low. If D_{YW} is positive, that indicates that either case (a) or (b) applies in figure 1, while if D_{YW} is zero, then case (c) or (d) applies.
- 12. Correlated residual errors δ_{iYj} and δ_{iWj} at the same time t_{ij} . Define δ_{ij} , now a 2-vector of residuals to be bivariate normal

$$\delta_{ij} = \begin{pmatrix} \delta_{iYj} \\ \delta_{iWj} \end{pmatrix} \sim N_2 \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{YY} & \sigma_{YW} \\ \sigma_{WY} & \sigma_{WW} \end{pmatrix} \right)$$

13. If σ_{YW} is positive, then the residual errors δ_{iYj} and δ_{iWj} are positively correlated, as illustrated in figure 1(a) and (c). If σ_{YW} is zero, then there is no within subject observation correlation as illustrated in figure 1(b) and (d). In the pain rating example, if σ_{YW} is negative, when log pain tolerance is unusually high for a given subject, then we expect pain rating to be unusually low for that subject.

Parameter	Est	SE	t	p
D_{YY}	2.13	.51	4.2	<.0001
D_{YW}	27	.20	-1.3	.18
D_{WW}	.79	.16	5.0	<.0001
σ_{YY}	.34	.04	9.4	<.0001
σ_{YW}	13	.07	-1.9	.065
σ_{WW}	2.39	.26	9.4	<.0001

Table 2: REML estimates for the covariance parameters for the bivariate random intercept model fit to the $Y = \log$ pain tolerance and W = pain rating data.

14. The bivariate random intercept model allows a decomposition of the covariation of Y and W into two parts: the correlation among the random intercepts which is a subject level correlation and the residual error correlation which occurs at the observation level within a subject.

Pain Rating and Log Pain Tolerance Bivariate random intercept model.

Neither covariance parameter is significant when we include both covariance parameters D_{YW} and σ_{YW} in the model.

The estimated correlation between the random intercepts is

$$-.21 = \frac{-.2740}{(2.1317 \times .7936)^{1/2}}$$

and the estimated correlation between the residuals is

$$-.14 = \frac{-.1279}{(.3432 \times 2.3931)^{1/2}}$$

Μ	Non-zero		$-2 \log$			
#	parameters	df	REML	AIC	BIC	χ^2 test vs. 4
1	D_{YW}, σ_{YW}	6	1568.8	1580.8	1593.8	$\chi^2 = 6, \mathrm{df} = 2,$
						p = .05
2	D_{YW}	5	1572.3	1582.3	1593.1	$\chi^2 = 2.4, df = 1,$
						p = .11
3	σ_{YW}	5	1570.7	1580.8	1591.5	$\chi^2 = 4.1, df = 1,$
						p = .043
4		4	1574.8	1582.8	1591.4	—

Table 3: Model fitting summaries for the bivariate random intercept model fit to the $Y = \log$ pain tolerance and W = pain rating data and three submodels. The first column is the model number, the second column gives the non-zero covariance parameters, and column 3 is the number of covariance parameters. Columns 4 – 6 are -2 log REML, AIC and BIC. The chi-square test in column 7 compares the models to the null model with no correlation.

Sub-models of the Bivariate Random Intercept Model Bivariate random intercept model illustrated in figure 1 and data from three submodels where one or the other or both of D_{YW} and σ_{YW} are zero in (b), (c), (d). All models include the CS and TMT main effects and interaction for both responses.

Both models that include σ_{YW} are significantly better than model 4 with no correlation at all. In the full model neither parameter was quite significant, but the hypothesis test that both parameters are zero is rejected with a *p*value of .05!

If we prefer a more parsimonious model, the full model 1 is not significantly better than model 3 with $D_{YW} = 0$ and model 3 is the model we originally hypothesized a priori as being most plausible.

Parameter	Est	SE	t
D_{YY}	1.50	.11	14
D_{YW}	1.16	.12	9
D_{WW}	2.46	.23	11
σ_{YY}	1.27	.04	32
σ_{YW}	.34	.06	6
σ_{WW}	5.84	.18	32

Table 4: REML estimates for the covariance parameters for the bivariate random intercept model fit to the Cognitive Y =arithmetic and W = Raven's responses. *P*-values are all significant and less than .0001 and are not reported.

Cognitive Data Jointly analyze Arithmetic and Raven's. Predictors are gender, age_at_baseline, time in years and the time by treatment interaction.

We start with the full bivariate random intercept model. Both covariance parameters D_{YW} and σ_{YW} are highly significant.

6 Bivariate Random Intercept and Slope

Four random effects for each subject, a random intercept and slope for Raven's and a random intercept and slope for arithmetic. The full model allows for all random effects to be correlated, giving a 4 by 4 covariance matrix D.

Residual errors for arithmetic and Raven's are allowed to be correlated when they are observed at the same t_{ij} .

Parm	Name	Est	SE	t	p
D_{11}	AI AI	1.57	.13	12	
D_{21}	RI AI	1.15	.14	8	
D_{22}	RI RI	2.29	.28	8	
D_{31}	AS AI	087	.055	-1.6	.11
D_{32}	AS RI	078	.076	-1.0	.30
D_{33}	AS AS	.15	.04	3.5	.0003
D_{41}	RS AI	.05	.11	.4	.68
D_{42}	RS RI	04	.18	2	.84
D_{43}	RS AS	.11	.07	1.7	.10
D_{44}	RS RS	.77	.20	3.8	
σ_{AA}		1.18	.04	28	
σ_{AR}		.27	.06	4	
σ_{RR}		5.36	.19	28	

Table 5: REML estimates for the covariance parameters for the bivariate random intercept and slope model fit to the Y =arithmetic and W =Raven's. Subscripts on D indicate 1 is the arithmetic random intercept (abbreviated AI), 2 is the Raven's intercept (RI), 3 is the arithmetic random slope (AR), and 4 is the Raven's random slope (RS). The σ parameters are the residual variances and covariances. Name gives the abbreviated name of the variance or correlation. *P*-values less than .0001 are not listed.

The full model is

$$Y_{ij} = x'_{ij}\alpha_Y + \beta_{iY1} + \beta_{iY2}t_{ij} + \delta_{iYj}$$
$$W_{ij} = x'_{ij}\alpha_W + \beta_{iW1} + \beta_{iW2}t_{ij} + \delta_{iWj}.$$
 (1)

 $\beta_i = (\beta_{iY1}, \beta_{iW1}, \beta_{iY2}, \beta_{iW2})'$ be the 4-vector of random effects.

$$\beta_i \sim N_4(\mathbf{0}, D).$$

Cognitive Data Cognitive arithmetic and Raven's data.

A model that omits the covariances between the intercepts and slopes has a $-2 \log \text{REML}$ likelihood of 21374.5 and 4 fewer parameters than the full model. The chi-square statistic is 3.6 which is not significant on 4 degrees of freedom. In this reduced model, the covariance between the random slopes is still not quite significant with a *p*-value of .06; the other covariances are very significant. In this reduced model, the estimated correlation between the residual errors is still .11; the estimated correlation between the intercepts is .62 and the estimated correlation between the slopes is .36. We usually do not like to fit a model where the intercept and slope for the same response are uncorrelated but this reduced model allows a hypothesis test of no correlation between intercepts and slopes and can be fit using current software.

7 Non Simultaneously Measured Observations

Sometimes we have multiple longitudinal sequences measured on the same subjects, but not recorded at the same time.

We can still ask whether random intercepts and/or random slopes are correlated.

We expect nutrition is correlated with anthropometric measures such as weight or height or cognitive measures such as Raven's.

This hypothesis can be tested in a random effects framework where the nutritional variable has a random intercept and weight or Raven's has a random intercept and slope.

Parm	Est	SE	t	p
D_{WW}	8.09	.51	16	
D_{WI}	.085	.043	1.9	.054
D_{II}	.092	.008	12	
Σ_{WW}	.57	.006	97	
Σ_{WI}	—	_	_	
Σ_{II}	.73	.096	8	

Table 6: Bivariate longitudinal analysis of available iron and weight fit using REML estimation. The model has correlated random intercepts and no correlation among residuals. Observations were taken at different times for the two responses.

Anthropometry and Nutrition The nutrition, cognitive and anthropometry measures are measured at different times.

Available iron and weight, and fit the bivariate random intercept model without correlation between the residual errors.

8 Unstructured Covariance Models for Bivari-

ate Responses

- 1. Unstructured Covariance Model
- 2. Independent Model, Each separately with Unstructured Covariance
- 3. Product Correlation

We have J(2J+1) variance parameters.

		Pain Rating Log Pain Tolerar					nce		
		1	2	3	4	1	2	3	4
	1	4.73	3.02	2.20	1.40	62	34	78	44
Pain	2	.64	4.75	2.08	1.49	31	31	48	38
Rating	3	.48	.45	4.49	2.27	21	.22	41	04
	4	.32	.34	.54	4.00	12	.02	23	21
Log	1	29	14	10	06	1.00	.75	.95	.58
Pain	2	15	13	.10	.01	.70	1.14	.88	.76
Tolerance	3	31	19	17	10	.82	.71	1.35	.90
	4	19	17	02	10	.55	.68	.74	1.11

Table 7: Estimated covariance matrix (upper half) and correlation matrix (lower half) for the pain data using the unstructured covariance model for bivariate longitudinal data. The long diagonal (in bold) gives the estimated variances for pain rating at each trial and then for log pain tolerance. The upper left and lower right quadrants give the covariance/correlation matrix of the pain ratings and log pain tolerances respectively. The bold face correlations in the lower left quadrant identify the correlations between simultaneously assessed pain rating and log pain tolerance.

			$-2 \log$			
#	model	df	REML	AIC	BIC	chi-square
1	Bivar RI	6	1568.8	1580.8	1593.8	$\chi^2 = 44.4, df = 30, p = .044$
2	Ind RI	4	1574.8	1582.8	1591.4	$\chi^2 = 50.4, df = 32, p = .02$
3	PCRI	4	1576.4	1584.4	1593.0	$\chi^2 = 52.0, df = 32, p = .014$
4	FA1	15	1617.2	1647.2	1679.6	$\chi^2 = 92.8, df = 21, p = .000$
5	FA2	23	1551.3	1597.3	1647.0	$\chi^2 = 26.9, df = 13, p = .013$
4	PCUN	12	1553.4	1577.4	1603.3	$\chi^2 = 29.0, df = 24, p = .22$
5	INDUN	20	1540.5	1580.5	1623.7	$\chi^2 = 16.1, df = 16, p = .45$
6	UN	36	1524.4	1596.4	1674.2	_

Table 8: REML log likelihood, AIC and BIC for several models fit to the bivariate pain data. The chi-square test compares each model to the unstructured covariance model. Model 1 is the bivariate random intercept model, model 2 is the independent random intercepts model and model 3 is the product correlation random intercept model. Model 4 is the product correlation unstructured model (PCUN), 5 is the independent unstructured model (INDUN) and 6 is the unstructured model.

8.1 Unstructured Within Response, Independent Responses

Test independence by comparing UN to the model where there is a separate unstructured covariance model for each response and no correlation between responses. This bivariate independent unstructured (INDUN) model has J(J+1) covariance parameters.

8.2 Product Correlation Models

The *product correlation* unstructured (PCUN) model allows for the same correlation structure for each response and essentially the same variance structure for the two responses.

 Σ_Y be the covariance matrix of the first response.

 Σ_W be the covariance matrix of the second response.

$$\Sigma_W = v_1 \Sigma_Y$$

where v_1 is an unknown scale parameter to be estimated. The correlation between W_{ij} and W_{il} is equal to the correlation between Y_{ij} and Y_{il}

$$\operatorname{Corr}(W_{ij}, W_{il}) = \operatorname{Corr}(Y_{ij}, Y_{il}).$$

The ratio of two variances at different times is also the same

$$\frac{\operatorname{Var}(W_{ij})}{\operatorname{Var}(W_{il})} = \frac{\operatorname{Var}(Y_{ij})}{\operatorname{Var}(Y_{il})}.$$

The variances $\operatorname{Var}(W_{ij})$ and $\operatorname{Var}(Y_{ij})$ are different, because of the v_1 parameter.

The cross-covariance between observations Y_{ij} and W_{il} taken at different times t_{ij} and t_{il} is

$$\operatorname{Cov}(Y_{ij}, W_{il}) = v_2 \Sigma_{jl}$$

where v_2 is a further unknown parameter to be estimated. Since $\Sigma_{jl} = \Sigma_{lj}$,

$$\operatorname{Cov}(Y_{ij}, W_{il}) = \operatorname{Cov}(Y_{il}, W_{ij}),$$

where the j and l subscripts are switched on the right hand side compared to the left hand side of the equation. Similarly, it is not too hard to show that the cross correlations follow the same property

$$\operatorname{Corr}(Y_{ij}, W_{il}) = \operatorname{Corr}(Y_{il}, W_{ij}) = \frac{v_2}{v_1^{1/2}} \frac{\Sigma_{jl}}{(\Sigma_{jj} \Sigma_{ll})^{1/2}}.$$
 (2)

The cross correlation between Y_{ij} and W_{il} is the same as between Y_{il} and W_{ij} . Unlike what we can potentially see with the unstructured covariance, there can not be a temporal lead dog. In the product correlation model we can not have the situation where Y_{i1} is highly correlated with (hence highly

			Pain I	Rating		Log	g Pain	Tolera	nce
	1	5.25	3.68	3.83	2.32	34	24	25	15
Pain	2	.67	5.70	3.65	2.96	24	36	23	19
Rating	3	.67	.61	6.22	3.78	25	23	40	24
	4	.44	.54	.66	5.27	15	19	24	34
Log	5	16	10	10	07	.89	.62	.65	.39
Pain	6	10	16	10	08	.67	.96	.62	.50
Tolerance	7	10	10	16	10	.67	.61	1.05	.64
	8	07	08	10	16	.44	.54	.66	.89

Table 9: REML fit values from the product correlation unstructured (PCUN) model. Correlations are below, variances are on, and covariances are above the long diagonal. The covariance/correlation matrix for pain rating and separately for log pain tolerance are in bold.

predictive of) W_{i2} , but that W_{i1} does not predict Y_{i2} . This is possible with the unstructured covariance matrix.

When j = l, (2) simplifies to

$$\operatorname{Corr}(Y_{ij}, W_{ij}) = \frac{v_2 \Sigma_{jj}}{(v_1 \Sigma_{jj} \Sigma_{jj})^{1/2}} = \frac{v_2}{v_1^{1/2}}.$$
(3)

In the product correlation model, the two observations at the same time Y_{ij} and W_{ij} have the highest correlation in absolute value among all pairs Y_{ij} and W_{il} . This can be seen by comparing the last two equations and realizing that the second term in equation (2) is a correlation and so is less than one in absolute value, and this term is missing in the contemporaneous correlation (3).

There are J(J+1)/2 parameters in Σ_Y plus 2 additional parameters v_1 and v_2 respectively the variance factor v_1 for W over Y and the cross-

covariance factor v_2 . The unstructured covariance model has J(2J + 1) parameters. We can test the PCUN versus the UN model with a chi-square statistic with $J(2J + 1) - (J(J + 1)/2 + 2) = 1.5J^2 + J/2 - 2$ degrees of freedom.

Another product correlation model is the product correlation random intercept (PCRI) model. The covariance matrix Σ_Y is now a RI covariance model with two parameters, and $\Sigma_W = v_1 \Sigma_Y$, and the *J* by *J* covariance matrix $\text{Cov}(Y_i, W_i) = v_2 \Sigma_Y$ for a total of 4 parameters. The correlations within Y_i or within W_i are assumed the same, but the variances are different between Y_i and W_i . The correlation between Y_{ij} and W_{ij} at the same time is larger than the correlation between Y_{ij} and W_{il} at different time points.

8.3 Data Structure

- 1. Data structure for the pain data, a single data set in long form with 8 observations for each subject.
- 2. A single variable 'response' which is the pain rating for the first four observations and is the log pain tolerance for the second four observations.
- A separate variable 'type' tells which type of response each observation is. For the pain data this was "r" or "t" for rating or tolerance.