LINEAR MODELS FOR LONGITUDINAL DATA

Modeling the Variance-Covariance-Correlation

- Models for longitudinal data involve a **mean model** and a **variance-covariance-correlation** model
- Reasons to build / test the covariance model:
  - make correct and efficient inferences on the mean model, or
  - because the covariance model is of direct interest
  - Here, we focus primarily on the first motivation
- We have already discussed two broad classes of covariance model
- **Unstructured** correlation model:
  - different correlation for each pair of times
  - requires balanced data
  - yields a large number of variance-covariance parameters
- **Covariance pattern** models, e.g.:
  - exchangeable or compound-symmetry

- exponential
- others (later notes and Fitzmaurice et al. Section 7.4)

- Recall that

$$Y_{ij} = \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \epsilon_{ij}$$

and that the variance-covariance-correlation model applies to the ϵ_{ij}'s (i.e., represents the variance-covariance among the Y_{ij}'s **after** removing effects of whatever is in $\boldsymbol{x}_{ij}$

- Specifically, the v-c-c model will be a model for V_i in

$$\boldsymbol{\epsilon}_i \sim N(0, V_i)$$

- We will parameterize this model by $\boldsymbol{\gamma}$, writing $V_i = V_i(\boldsymbol{\gamma})$

- **Examples:**
  - $\boldsymbol{\gamma} = (\sigma^2, \rho)'$ in the exchangeable correlation model
  - $\boldsymbol{\gamma} = (\nu^2, \tau^2)'$ in the exchangeable correlation model (alternative parameterization)

- $\boldsymbol{\gamma} = (\delta^2, \alpha)'$ in the exponential correlation model
- $\boldsymbol{\gamma} = (\sigma_{11}, \sigma_{12}, \ldots)'$ in the unstructured correlation model (all variances and covariances, each representing its own parameter)

- The **general linear model** for longitudinal data can be written

$$\boldsymbol{Y} = X\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

where

$$\boldsymbol{\epsilon} \sim MVN(0, V)$$

where V is the **variance-covariance** matrix of $\boldsymbol{\epsilon}$ and we have concatenated all $\boldsymbol{Y}_i$'s, X_i's and $\boldsymbol{\epsilon}_i$'s from all subjects

- With **correlated data**, V is of the **block diagonal** form:

$$\mathbf{V} = \begin{pmatrix} \mathbf{V_1} & 0 & \ldots \\ 0 & \mathbf{V_2} & \ldots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

Estimation of the Variance-Covariance-Correlation Model
ML and ReML

- Inference on the mean model parameters β is an extension of general linear model theory (WLS, to be presented later)
- Inference on the **variance-covariance-correlation** model is also such an extension
- Basic approaches to estimation of $\boldsymbol{\gamma}$:
  - maximum likelihood for joint estimation of β and $\boldsymbol{\gamma}$
  - restricted maximum likelihood for estimation of $\boldsymbol{\gamma}$
  - Software:
    - SAS: proc mixed
    - Stata: xtmixed
    - R: lme4 package, etc.

- Conceptually, the easiest thing to do is **maximum likelihood**:
  - Recall, the **general linear model** for longitudinal data is

$$\boldsymbol{Y} = X\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

    where

$$\boldsymbol{\epsilon} \sim MVN(0, V(\boldsymbol{\gamma}))$$

    the log-likelihood is

$$L(\boldsymbol{\beta}, \boldsymbol{\gamma}) = -\frac{1}{2}N\log(2\pi) - \frac{1}{2}\log|V| - \frac{1}{2}(\boldsymbol{y} - X\boldsymbol{\beta})'V^{-1}(\boldsymbol{y} - X\boldsymbol{\beta})$$

  - This contains (mean model) parameters $\boldsymbol{\beta}$ and **covariance model** parameters $\boldsymbol{\gamma}$
  - Maximize $L(\boldsymbol{\beta}, \boldsymbol{\gamma})$ with respect to both $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ $\rightarrow$ **joint estimation** of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$
  - This is what SAS `proc mixed method=ml` does (default is ReML)

- Maximum likelihood (ML) allows LRTs and Wald-type confidence intervals
- However ML is not the best approach to estimation of γ; ReML is a better approach

ReML for Covariance Parameters

- Recall: When we estimate $\sigma^2 = \mathrm{var}(Y)$ for i.i.d. Y
  - Maximum likelihood estimator is divided by N and is biased:

$$\hat{\sigma}^2_{MLE} = \frac{\sum_{i=1}^{N}(y_i - \bar{y})^2}{N}$$

  - Note: if we had known $\mu = \mathrm{E}(Y)$ instead of replacing μ by $\bar{y}$, then MLE would have been unbiased
  - We need to use $\hat{\sigma}^2_{unbiased} = \frac{\sum_{i=1}^{N}(y_i - \bar{y})^2}{N-1}$ to obtain unbiased estimator

- Recall: When we do OLS regression for independent observations,

$$\boldsymbol{Y} = X\boldsymbol{\beta} + \boldsymbol{\epsilon},$$

where

$$\boldsymbol{\epsilon} \sim MVN(0, \sigma^2 I_N),$$

- MLE for σ^2 is divided by N and is biased:

$$\hat{\sigma}^2_{MLE} = \frac{(\boldsymbol{y} - X\hat{\boldsymbol{\beta}})'(\boldsymbol{y} - X\hat{\boldsymbol{\beta}})}{N},$$

  we can show that

$$\mathrm{E}(\hat{\sigma}^2_{MLE}) = \frac{N-p}{N}\sigma^2$$

  where $p = \text{rank}(X) =$ number of coefficients in $\boldsymbol{\beta}$ (if X is full rank)

- Bias arises because MLE has not taken into account that $\boldsymbol{\beta}$ is also estimated, and replace $\boldsymbol{\beta}$ by $\hat{\boldsymbol{\beta}}$ in estimation of σ^2
- Need to divide by $N - p$ to obtain unbiased estimator

• ReML – **Restricted (or Residual/Reduced) Maximum Likelihood** estimation extends this idea to correct bias by ML

  - Does not include $\boldsymbol{\beta}$ in likelihood

- Here is how ReML works:
  - Recall that $\boldsymbol{Y}$ is the entire vector of responses, and that

$$\boldsymbol{Y} = X\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

$$\mathrm{E}(\boldsymbol{Y}) = X\boldsymbol{\beta}$$

$$\boldsymbol{\epsilon} \sim MVN(0, V),$$

    which leads to the log-likelihood

$$L(\boldsymbol{\beta}, \boldsymbol{\gamma}) = -\frac{1}{2}\log|V| - \frac{1}{2}(\boldsymbol{y} - X\boldsymbol{\beta})'V^{-1}(\boldsymbol{y} - X\boldsymbol{\beta})$$

  - Suppose that we had a matrix K such that $K'X = 0$

    Hence

$$K'\boldsymbol{Y} = 0 + K'\boldsymbol{\epsilon} \sim MVN(0, K'VK).$$

  - Lets use the linear transformed response $K'\boldsymbol{Y}$ and do maximum likelihood; our new (ReML) log-likelihood is

$$L^*(\boldsymbol{\gamma}) = -\frac{1}{2}\log|K'VK| - \frac{1}{2}\boldsymbol{y}'K(K'VK)^{-1}K'\boldsymbol{y}$$

which does not contain $\boldsymbol{\beta}$

– ReML makes inferences about $\boldsymbol{\gamma}$ with $L^*(\boldsymbol{\gamma})$ and does not involve estimating $\boldsymbol{\beta}$ at all

- One example for such K':

$$K' = A' = I - X(X'X)^{-1}X'$$

Then

$$\begin{aligned} A'X &= \{I - X(X'X)^{-1}X'\}X \\ &= X - X(X'X)^{-1}X'X \\ &= 0 \end{aligned}$$

- **Problem**: $A' = I - X(X'X)^{-1}X'$ is not full rank:
  - A' is $N \times N$, $\mathrm{rank}(A) = N - p$
  - This will lead to singular multivariate Gaussian distribution

$$A'\boldsymbol{Y} \sim MVN(0, A'VA)$$

$$\Rightarrow |A'VA| = 0$$

  - Solution:
    * Use $K' = B'$, where $BB' = A'$, $B'B = I_{N-p}$ (decomposition of idempotent and symmetric A)
    * Then B is full rank with $\mathrm{rank}(B) = N - p$, and

$$B'X = B'BB'X = B'A'X = 0$$

- **Note**: It actually does not matter what you use for K, as long as
  - $\mathrm{rank}(K) = N - p$ and
  - $\mathrm{E}(K'\boldsymbol{Y}) = 0$
- More details for ReML derivation in Diggle, Heagerty, Liang and Zeger's book Sec 4.5

- Special case:

  When we have independent data with $V = \sigma^2 I_N$, here we show that ReML estimator with $K' = B'$ will be the unbiased estimator for σ^2:

$$
\begin{aligned}
L^*(\sigma^2) &= -\frac{1}{2}\log|\sigma^2 B'B| - \frac{1}{2}\boldsymbol{y}'B(\sigma^2 B'B)^{-1}B'\boldsymbol{y} \\
&= -\frac{1}{2}\log\sigma^{2(N-p)}|B'B| - \frac{1}{2\sigma^2}\boldsymbol{y}'B(B'B)^{-1}B'\boldsymbol{y} \\
&= -\frac{1}{2}\log\sigma^{2(N-p)}|I| - \frac{1}{2\sigma^2}\boldsymbol{y}'A'\boldsymbol{y}
\end{aligned}
$$

  use the property of $A'\boldsymbol{y} = \boldsymbol{y} - X\hat{\boldsymbol{\beta}}$ and A is symmetric and idempotent, we can solve $\frac{\partial\{L^*(\sigma^2)\}}{\partial\sigma^2} = 0$ to obtain

$$
\hat{\sigma}^2_{ReML} = \frac{(\boldsymbol{y} - X\hat{\boldsymbol{\beta}})'(\boldsymbol{y} - X\hat{\boldsymbol{\beta}})}{N-p}
$$

- Solving for ML/ReML:
  - Closed analytical solutions are only available in very special cases
  - A wide variety of iterative techniques for solving ML/REML equations have been proposed based on various modifications of two basic approaches (not covered here)
    - Newton-Raphson algorithm
    - EM algorithm

- Why ReML is a great idea:
  - Some evidence that ReML is more robust to outliers
  - it is **still maximum likelihood**, just not with the same likelihood
    - all of the **statistical theory** backing up maximum likelihood applies to ReML as well
    - you can obtain LRTs, Wald tests, and Wald CI's for the covariance parameters, just as with ML
  - Now we do not know

    $$\mathrm{E}(Y) = X\boldsymbol{\beta}$$

    without also estimating β, we **do know** that

    $$\mathrm{E}(K'\boldsymbol{Y}) = 0$$

    regardless of what the true value of $\boldsymbol{\beta}$ is (a benefit of ReML)!

    – ReML is more robust to small samples or complicated mean models than is ML

- Note: **ReML still depends on the specified mean model**, because K depends on covariates X
  - REML can only be compared across models with same mean model (eg, LRT)
- In particular, here is the practical implication:
  - suppose you had a particular **mean model** in mind, e.g.:

$$\mathrm{E}(\texttt{arm}_{ij}) = \beta_0 + \beta_1 \texttt{wt}_{ij} + \beta_2 \texttt{age}_{ij} + \beta_3 \texttt{sex}_i$$

  - you want to make sure to estimate the variance / covariance / correlation model correctly
  - you remember that the correlation model depends on the mean model
  - i.e., the target of estimation and inference is a covariance model for **residual variance** in $\boldsymbol{Y}_i$ after removing effects of age, weight, sex
  - so you would like to be thorough about removing effects of weight, age and sex

- you therefore choose a more **flexible** mean model for **purposes of estimating the covariance / correlation**

  e.g., you use:

  $$\mathrm{E}(\texttt{arm}_{ij}) = \beta_0 + \beta_1 \texttt{wt}_{ij} + \beta_2 \texttt{age}_{ij} + \beta_3 \texttt{sex}_i + \beta_4 \texttt{age}_{ij} * \texttt{wt}_{ij} + \beta_5 \texttt{age}_{ij}^2$$

  to obtain covariance / correlation parameter estimates $\widehat{\gamma}_{\mathrm{ReML}}$

- you then **fix** the covariance / correlation model and parameter estimates at $\widehat{\gamma}_{\mathrm{ReML}}$ and do more careful modelling of the mean

• Such a protocol is analogous to estimating σ^2 with the "biggest" model in OLS, and then keeping the same $\widehat{\sigma}^2$ for tests, model reduction, and model evaluation

• SAS `proc mixed` have many options for variance-covariance-correlation models using ReML

Fitting Variance-Covariance-Correlation Models
SAS Examples

- **Example:** Nepalese children: arm circumference data
- **Important points:**
  - Inferences on the **covariance model** are for a **given mean model**
  - Different mean models may produce different covariance model estimates, tests and interpretations
  - In general, in the absence of sample size constraints, it is best to use the most / more flexible mean models
- For now, lets use the following mean model:

$$\mathrm{E}(\texttt{arm}_{ij}) = \beta_0 + \beta_1 \texttt{wt}_{ij} + \beta_2 \texttt{age}_{ij} + \beta_3 \texttt{sex}_i + \beta_4 \texttt{wt}_{ij}\texttt{age}_{ij} + \beta_5 \texttt{age}_{ij}^2$$

even though it may be richer than necessary

Exchangeable Correlation Model

- Here is how we would set this up in SAS `proc mixed`

```
data temp;
    set nepal;
    wtage = wt*(age-36);
    age2=(age-36)*(age-36);
    age4=age/4;
run;

proc mixed data=temp dfbw  ;
     title2 "1st run" ;
     class id;
     model arm = wt age sex wtage age2 / s ;
     repeated / subject=id type=cs r;
     run;
```

- Here:
  - the `class` statement identifies categorical variables
  - the `model` statement is where you state the **mean model**

- the `repeated` statement tells SAS that observations with the same value of `id` (which must be given in the class statement) are repeated measures on the same subject
- the `type=cs` option tells SAS to fit a **compound symmetry** correlation model
  - recall: compound symmetry $=$ exchangeable
  - Equivalent to replace `repeated / subject=id type=cs r;` by `random intercept/ subject=id;`
- the `/ s` option says to print the estimated $\boldsymbol{\beta}$ coefficients
- the `/ r` option says to print out the fitted covariance matrix for the first subject (i.e., V_1) (R_i matrix in SAS is our V_i)
- `dfbw` selects an option on how to compute the degrees-of-freedom for $\boldsymbol{\beta}$ inferences

• Some output:

```
                    The Mixed Procedure
```

```
                         Model Information

         Data Set                        WORK.TEMP
         Dependent Variable              arm
         Covariance Structure            Compound Symmetry
         Subject Effect                  id
         Estimation Method               REML
         Residual Variance Method        Profile
         Fixed Effects SE Method         Model-Based
         Degrees of Freedom Method       Between-Within

                      Class Level Information

          Class    Levels    Values

          id          197    1 2 3 4 5 6 7 8 9 10 11 12 13
                             14 15 16 17 18 19 20 21 22 23
<snip>
                             197 198 199 200

                             Dimensions

               Covariance Parameters            2
```

Columns in X	6
Columns in Z	0
Subjects	197
Max Obs Per Subject	5

Number of Observations Read	1000
Number of Observations Used	877
Number of Observations Not Used	123

Estimated R Matrix for id 1

Row	Col1	Col2	Col3	Col4
1	0.4541	0.3308	0.3308	0.3308
2	0.3308	0.4541	0.3308	0.3308
3	0.3308	0.3308	0.4541	0.3308
4	0.3308	0.3308	0.3308	0.4541

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
CS	id	0.3308
Residual		0.1233

Fit Statistics

-2 Res Log Likelihood	1199.0

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	5.1785	0.4368	195	11.86	<.0001
wt	0.7023	0.02324	676	30.23	<.0001
age	0.01703	0.009782	676	1.74	0.0821
sex	0.2847	0.08615	195	3.30	0.0011
wtage	-0.00781	0.000929	676	-8.41	<.0001
age2	0.001207	0.000145	676	8.32	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
wt	1	676	913.61	<.0001
age	1	676	3.03	0.0821
sex	1	195	10.92	0.0011
wtage	1	676	70.67	<.0001
age2	1	676	69.30	<.0001

- Interpretation of $\hat{\beta}_1 = 0.7023$ is the same as in an ordinary linear regression model:
  – difference in mean response for each unit difference in weight (weight slope) among persons with age of 36 (because age is centralized at 36)

- Recall, in exchangeable correlation model:

$$\epsilon_{ij} = U_i + Z_{ij}$$

- The variance parameter estimates are

$$\text{between-subject variance} = \widehat{\text{var}}(U_i) = \hat{\nu}^2 = 0.3308 \quad \text{and}$$

$$\text{within-subject variance} = \widehat{\text{var}}(Z_{ij}) = \hat{\tau}^2 = 0.1233$$

- The estimated **total variance** (for ϵ_{ij}) is therefore

$$\text{total variance} = \widehat{\sigma}^2 = \hat{\nu}^2 + \hat{\tau}^2 = .3308 + .1233 = 0.4541$$

and the **within-subject** correlation coefficient is

$$\widehat{\rho} = \frac{.3308}{.3308 + .1233} = 0.728$$

- Printout of R (which is our V_1 here) is helpful for interpretation

- Note: In Stata, we can use `xtmixed` to obtain the same results

  ```
  xtmixed arm wt age sex wtage age2 || id:, nocons
  residual(exc) var reml nolog
  ```

  - `|| id: nocons` specifies the random effect portion. If we omit `nocons` option, Stata will add a random intercept.
  - `residual(exc)` specifies residual correlation structure to be exchangeable
  - `var` option request Stata to report variances rather than standard deviations

- Another way to fit this model is to request a **random intercept**. The two models should be equivalent.
- SAS code:

```
proc mixed data=temp dfbw  ;
     title2 "2nd run" ;
     class id;
     model arm = wt age sex wtage age2 / s ;
     random intercept / subject=id g;
     run;
```

  - the `random intercept` statement requests that there be a random intercept (U_i) at each subject defined by `id`.
  - the `/ g` option requests printout of $\widehat{\text{var}}(U_i)$ (what SAS calls the G matrix)
- Relevant output (all very similar to what was obtained with the `repeated ...type=cs` statement)

```
                    Estimated G Matrix

    Row     Effect       group(id)         Col1

      1     Intercept      1             0.3308

               Covariance Parameter Estimates

             Cov Parm      Subject    Estimate

             Intercept     id           0.3308
             Residual                   0.1233

                      Fit Statistics

          -2 Res Log Likelihood          1199.0
```

- Note: In Stata, we can run the same model using `xtmixed arm wt age sex wtage age2 || id:, residual(ind) var reml nolog`

Exponential Correlation Model in SAS

- `proc mixed` is extremely flexible
- To fit the exponential correlation model, recall that (in this example),

$$\rho_{jk} = \alpha^{|t_j - t_k|}$$

where $t_j, j = 1, \ldots, 5$ indicates **age** in units of four-months.

- The data for the first subject are:

	id	obsno	arm	age	sex
1.	1	1	14.3	41	1
2.	1	2	13.5	45	1
3.	1	3	14.5	49	1
4.	1	4	14.1	53	1
5.	1	5	.	57	1

- We need a variable that captures age in "time units" of four months (age/4)

- Then, SAS needs to know what that **time variable** is in order to fit the exponential correlation model

- Recalling that we created `age4` earlier in a data step, we specify:

```
proc mixed data=temp dfbw  ;
     title2 "3rd run" ;
     class id;
     model arm = wt age sex wtage age2 / s ;
     repeated / subject=id type=sp(pow)(age4) r;
     run;
```

- the option `type=sp(pow)(age4)` says to use the power correlation model with `age4` as the time variable
  - This option does not require time to be in equal units

- An advantage to using SAS `proc mixed` (unlike some options in Stata) is that the time correlation structure allows for unequally-spaced times

- Output

```
                    The Mixed Procedure

                    Model Information

         Data Set                          WORK.TEMP
         Dependent Variable                arm
         Covariance Structure              Spatial Power
<snip>

                 Estimated R Matrix for id 1

     Row        Col1        Col2        Col3        Col4

       1      0.4606      0.3497      0.2655      0.2016
       2      0.3497      0.4606      0.3497      0.2655
       3      0.2655      0.3497      0.4606      0.3497
       4      0.2016      0.2655      0.3497      0.4606


                Covariance Parameter Estimates
```

Cov Parm	Subject	Estimate
SP(POW)	id	0.7592
Residual		0.4606

Fit Statistics

-2 Res Log Likelihood	1279.0

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	4.2463	0.5062	195	8.39	<.0001
wt	0.7136	0.02387	676	29.90	<.0001
age	0.03918	0.01124	676	3.49	0.0005
sex	0.2673	0.07971	195	3.35	0.0010
wtage	-0.01027	0.001102	676	-9.32	<.0001
age2	0.001626	0.000183	676	8.87	<.0001

- Recall, exponential correlation: $\epsilon_{ij} = W_{ij}$, and

$$W_{i1} \sim N(0, \delta^2)$$

$$W_{ij} = \alpha W_{i,j-1} + E_{ij}, \quad j = 2, 3, \ldots$$

where $E_{ij} \sim N\{(0, \delta^2(1-\alpha^2)\}$

- The total variance estimate (of ϵ_{ij}) is

$$\widehat{\mathrm{var}}(W_{ij}) = \widehat{\sigma}^2 = \widehat{\delta}^2 = 0.4606$$

- The within-subject correlation estimate for two observations separated by 4 months is

$$\widehat{\alpha} = 0.7592$$

- Can check that in R matrix $0.3497 = 0.4606 \times 0.7592$

- Note: In Stata, we can run the same model using
`xtmixed arm wt age sex wtage age2 || id:, nocons res(ar 1, t(age)) var reml nolog`
  - However, `t(age)` must be integer here, and thus we cannot use `age4` as time variable.
  - The reported $\hat{\alpha} = .9334534$ in Stata is for two observations separated by 1 month, and $\hat{\alpha}^4 = .7592$ is for 4-month interval.

- There are many other correlation functions (as a function of lag u) available in `proc mixed`, for example
  - Gaussian:
$$\rho(u) = \alpha^{u^2} \qquad (0 \le \alpha < 1)$$
  - Linear:
$$\rho(u) = \begin{cases} 1 - \alpha|u|, & \alpha|u| \le 1 \\ 0, & \text{o.w.} \end{cases}$$

  making this a very flexible modeling environment

Unstructured Variance-Covariance Model in SAS

- Suppose that we did not want to make any assumptions about the variance or covariance or correlation of the repeated observations on an individual
- Then, we might fit an **unstructured** variance-covariance model
- To do this, we need a **finite number** of unique time points and relatively **good balance** among them, because:
  - variance of each time point will be estimated separately
  - correlation between each pair of two time points will be estimated separately

- We can illustrate this with the Nepal data, using the order of the observations as the time variable (Why wouldn't age work?)
- Note: With missing data in the middle of a series, this creates a problem because, if observation 3 is missing, then observation 4 becomes 3 and observation 5 becomes 4. So, missing data should be minimal
- Here is the SAS code, which **assumes the data are already sorted by time**:

```
proc mixed data=temp dfbw  ;
     title2 "4th run" ;
     class id;
     model arm = wt age sex wtage age2 / s ;
     repeated / subject=id type=un r rcorr;
     run;
```

  - The option `type=un` says to use an unstructured v-c-c model
  - the `r` and `rcorr` options request the first subject's estimated V_1 matrix in variance-covariance and in correlation form

- And some output

```
                         The Mixed Procedure

                          Model Information

         Data Set                         WORK.TEMP
         Dependent Variable               arm
         Covariance Structure             Unstructured
<snip>
                             Dimensions

              Covariance Parameters            15
              Columns in X                      6
 <snip>
                    Estimated R Matrix for id 1

           Row        Col1        Col2        Col3        Col4

             1      0.4920      0.3387      0.3104      0.3347
             2      0.3387      0.4622      0.3182      0.3538
             3      0.3104      0.3182      0.3958      0.3223
             4      0.3347      0.3538      0.3223      0.4115
```

Estimated R Correlation Matrix for id 1

Row	Col1	Col2	Col3	Col4
1	1.0000	0.7104	0.7033	0.7440
2	0.7104	1.0000	0.7439	0.8113
3	0.7033	0.7439	1.0000	0.7985
4	0.7440	0.8113	0.7985	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	0.4920
UN(2,1)	id	0.3387
UN(2,2)	id	0.4622
UN(3,1)	id	0.3104
UN(3,2)	id	0.3182

```
                     UN(3,3)      id            0.3958

                     UN(4,1)      id            0.3347
                     UN(4,2)      id            0.3538
                     UN(4,3)      id            0.3223
                     UN(4,4)      id            0.4115

                     UN(5,1)      id            0.3631
                     UN(5,2)      id            0.3837
                     UN(5,3)      id            0.3324
                     UN(5,4)      id            0.3892
                     UN(5,5)      id            0.5837

                             Fit Statistics

                  -2 Res Log Likelihood          1152.5
<snip>
```

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	5.0128	0.4494	195	11.15	<.0001
wt	0.7234	0.02319	195	31.20	<.0001
age	0.01535	0.009957	195	1.54	0.1249
sex	0.2802	0.08557	195	3.27	0.0013
wtage	-0.00795	0.000954	195	-8.33	<.0001
age2	0.001216	0.000150	195	8.11	<.0001

- Note: In Stata, we can use following code to fit unstructured model

```
. xtmixed arm wt age sex wtage age2 || id:, nocons res(uns, t(obs))
    var reml
```

Expanded Covariance Pattern Models

Exponential plus Measurement Error Variance-Covariance Model

- We have examined some simple **covariance pattern** models. **Hybrid covariance pattern** models can be obtained by combining or expanding upon these

- The **exponential plus measurement error** variance-covariance model is given by:

$$\epsilon_{ij} = W_{ij} + Z_{ij}$$

  where:

  - W_{ij}'s follow an **exponential correlation** model with autocorrelation parameter α

$$W_{ij} = \alpha W_{i,j-1} + E_{ij} \ ,$$

$$\mathrm{var}(W_{ij}) = \delta^2$$

– Z_{ij}s are all independent of each other and of the W_{ij}'s and

$$\mathrm{var}(Z_{ij}) = \tau^2$$

- In this model:
  - W_{ij}'s represent smooth, unobserved time-varying processes contributing to the response variable (Y_{ij}).
    – Smooth in the sense that W_{ij} and W_{ik} very close together in time are nearly perfectly correlated.
  - Z_{ij} is random noise (**measurement error**) specific to each observation (time point)
- This gives rise to the total variance (for ϵ_{ij}):

$$\mathrm{var}(\epsilon_{ij}) = \sigma^2 = \delta^2 + \tau^2$$

and correlation model

$$
\begin{aligned}
\mathrm{corr}(\epsilon_{ij}, \epsilon_{ik}) &= \frac{\mathrm{cov}(W_{ij} + Z_{ij}, W_{ik} + Z_{ik})}{\mathrm{var}(\epsilon_{ij})} \\
&= \frac{\mathrm{cov}(W_{ij}, W_{ik})}{\mathrm{var}(\epsilon_{ij})} \\
&= \frac{\mathrm{corr}(W_{ij}, W_{ik})\mathrm{var}(W_{ij})}{\mathrm{var}(\epsilon_{ij})} \\
&= \alpha^{|t_{ij} - t_{ik}|} \frac{\delta^2}{\delta^2 + \tau^2}
\end{aligned}
$$

- **At home:** check correlation, write the variance-covariance matrix

  Note how the measurement error puts extra τ^2 on the diagonal of V_i

- **Note:** Even as time lag tends to zero 0, $\mathrm{corr}(\epsilon_{ij}, \epsilon_{ik})$ will not tend to 1

- The extra noise Z_{ij} due to measurement error is sometimes called a “nugget” or a “local” error because it is “local” in time
- To fit this model in SAS, we would specify `proc mixed` just as for the exponential correlation model, with the following change:

```
repeated / subject=id type=sp(pow)(age4) local r;
```

  – where `local` requests the measurement error (nugget) term

Exchangeable plus Exponential Variance-Covariance Model

- This model is given by

$$\epsilon_{ij} = U_i + W_{ij}$$

  where:

  - U_i is constant for all observations on a subject, $\mathrm{var}(U_i) = \nu^2$
  - W_{ij}s follow an exponential correlation model with autocorrelation parameter α and $\mathrm{var}(W_{ij}) = \delta^2$, i.e.,

$$W_{ij} = \alpha W_{i,j-1} + E_{ij}$$

  - U_i independent of W_{ij}'s

- U_i represents time-invariant factors specific to subject i that affect the outcome Y_{ij}

- **At home:** Compute the correlation $\mathrm{corr}(\epsilon_{ij}, \epsilon_{ik})$ for this model

  Note how the exchangeable model puts extra ν^2 in every cell of V_i

- How is this model different from the "exponential plus measurement error" correlation model?

- This model is fitted in SAS by casting U_i as a **random intercept**

- Returning to the Nepal example, the `proc mixed` code is

```
proc mixed data=temp dfbw covtest ;
     title2 "5th run" ;
     class id;
     model arm = wt age sex wtage age2 / s ;
     random intercept / subject=id g;
     repeated / subject=id type=sp(pow)(age4) r;
     run;
```

  – `random` statement specified variables to be included as predictors with coefficients that vary from subject to subject.

– The most common such variable is the **intercept**

– May also include random slope (coming later)

– `repeated` statement specifies the v-c-c model for the residual process not accounted for by the random terms

- Result

```
                          Model Information

        Data Set                        WORK.TEMP
        Dependent Variable              arm
        Covariance Structures           Variance Components,
                                        Spatial Power
        Subject Effects                 id, id
        Estimation Method               REML
        Residual Variance Method        Profile
        Fixed Effects SE Method         Model-Based
        Degrees of Freedom Method       Between-Within
<snip>
                             Dimensions
```

Covariance Parameters	3
Columns in X	6
Columns in Z Per Subject	1
Subjects	197
Max Obs Per Subject	5

Number of Observations Read	1000
Number of Observations Used	877
Number of Observations Not Used	123

Estimated R Matrix for id 1

Row	Col1	Col2	Col3	Col4
1	0.1316	0.01743	0.002309	0.000306
2	0.01743	0.1316	0.01743	0.002309
3	0.002309	0.01743	0.1316	0.01743
4	0.000306	0.002309	0.01743	0.1316

Estimated G Matrix

Row	Effect	group(id)	Col1
1	Intercept	1	0.3243

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr Z
Intercept	id	0.3243	0.03979	8.15	<.0001
SP(POW)	id	0.1324	0.06196	2.14	0.0326
Residual		0.1316	0.009083	14.49	<.0001

Fit Statistics

-2 Res Log Likelihood	1193.9

```
                     Solution for Fixed Effects

                                  Standard
Effect          Estimate         Error       DF     t Value     Pr > |t|

Intercept         5.0550        0.4486      195       11.27       <.0001
wt                0.7069       0.02347      676       30.12       <.0001
age              0.01905       0.01006      676        1.89       0.0587
sex               0.2825       0.08634      195        3.27       0.0013
wtage           -0.00809      0.000958      676       -8.44       <.0001
age2            0.001258      0.000151      676        8.36       <.0001
```

- The estimated random effects variance is

$$\widehat{\mathrm{var}}(U_i) = \widehat{\nu}^2 = 0.3243$$

- The estimated autoregressive variance is

$$\widehat{\mathrm{var}}(W_{ij}) = \widehat{\delta}^2 = 0.1316$$

- The within-subject correlation for two observations separated by 4 months is

$$\widehat{\text{corr}}(W_{ij}, W_{i,j-1}) = \widehat{\alpha} = 0.1324$$

- The total variance estimate is therefore

$$\widehat{\sigma}^2 = \widehat{\text{var}}(\epsilon_{ij}) = \widehat{\text{var}}(U_i) + \widehat{\text{var}}(W_{ij}) = 0.3243 + 0.1316 = 0.4559$$

- This will also allow us to **test for positive autocorrelation** in the exponential part of the model, having removed the correlation due to subject-to-subject variability (U_i)
  – Next we will see how such tests are constructed

- Note: In Stata, we can use following code to fit this hybrid model

```
xtmixed arm wt age sex wtage age2 || id:, res(ar 1, t(age))
    var reml nolog
```

- **Final note on such hybrid v-c-c models:** Empirical features of correlation in longitudinal data are reflected in these models:
  - correlation decreases with time lag separating observations: captured by the exponential correlation part of the model
  - even observations close together in time do not have correlation one: captured by the measurement error term Z_{ij}
  - even observations far apart in time are positively correlated: captured by including a random intercept term U_i for each subject

ReML Likelihood-based Tests and CIs for Covariance Parameters

- **Example:** Nepalese children: Suppose we wanted to compare the "exponential plus exchangeable" model to the "exchangeable only" covariance model

  I.e., in the "exponential plus exchangeable" model, we wish to test

$$H_0 : \alpha = 0 \quad \text{vs.} \quad H_A : \alpha \neq 0$$

- We generally make such comparisons under one of the more flexible mean models

  Here, we continue with the following mean model:

$$\mathrm{E}(\texttt{arm}_{ij}) = \beta_0 + \beta_1 \texttt{wt}_{ij} + \beta_2 \texttt{age}_{ij} + \beta_3 \texttt{sex}_i + \beta_4 \texttt{wt}_{ij} \texttt{age}_{ij} + \beta_5 \texttt{age}_{ij}^2$$

- In the foregoing example, we saw the SAS `proc mixed` code for "exchangeable plus exponential" model.
- For simple exchangeable only model, we would remove the line:

  ```
  repeated / subject=id type=sp(pow)(age4) r;
  ```

  and rerun the model

- Best statistical test: Likelihood ratio test (LRT) for nested models (actually, ReLRT for residual likelihood ratio test)
  - Recall, in LRT: $-2\{ln(L_{reduce}) - ln(L)\} \sim \chi^2_{DF}$
    - where L is likelihood of with all the parameters unrestricted
    - L_{reduce} is likelihood of reduced model
    - DF $=$ number of parameters lost in reduced model

- In this example,
  - Exponential plus exchangeable:

```
                    Fit Statistics

       -2 Res Log Likelihood          1193.9
```

    $-2ln(L)$ under random intercept, plus exponential correlation model is 1193.9
  - Exchangeable model (from earlier):

```
       -2 Res Log Likelihood          1199.0
```

    $-2ln(L_{reduce})$ under random intercept only model is 1199.0

- Difference on 1 DF (1 parameter less in exchangeable model): $\chi^2 = 5.1$, which gives

$$P\text{-value} = \Pr(\chi^2_1 \geq 5.1) \approx 0.02$$

- Conclusion: The exponential autocorrelation α among the residuals ϵ_{ij} on the same subject is significantly greater than zero, even after accounting for a subject-level random intercept

- **Careful!** When using any software package, make sure that the log-likelihood is multiplied by 2! Otherwise, you must multiply the difference by 2 to get the χ^2 value

- **Another caution:** Do not use LRTs to compare mean models when using ReML to estimate the model.
  - If must use LRT (and not $\mathcal{F}$-tests) to compare mean models: Estimate model with ML

- Alternative test: Wald Test
  - When the model is estimated, the score equations are solved:

$$\frac{\partial L^*(\boldsymbol{\beta}, \boldsymbol{\gamma})}{\partial(\boldsymbol{\beta}, \boldsymbol{\gamma})} = 0 \quad \text{yields} \quad (\widehat{\boldsymbol{\beta}}, \widehat{\boldsymbol{\gamma}})$$

  - A by-product is the **observed information**:

$$\mathcal{I}_O = -\frac{\partial^2 L^*(\boldsymbol{\beta}, \boldsymbol{\gamma})}{\partial(\boldsymbol{\beta}, \boldsymbol{\gamma})\partial(\boldsymbol{\beta}, \boldsymbol{\gamma})}|_{(\widehat{\boldsymbol{\beta}}, \widehat{\boldsymbol{\gamma}})}$$

  - The inverse of $\mathcal{I}_o$ is an estimate of $\mathrm{var}(\widehat{\boldsymbol{\beta}}, \widehat{\boldsymbol{\gamma}})$, which can be used to get standard errors for components of the variance parameter $\boldsymbol{\gamma}$
  - Tests based on these standard errors are called Wald tests
  - These are obtained with the `covtest` option in `proc mixed`

- **Example:** In the "exponential plus exchangeable" model, we may want to test whether $\alpha = 0$:
  - We fit the model and obtain $\widehat{\alpha}$
  - Then

$$\widehat{\mathrm{se}}(\widehat{\alpha}) = \sqrt{(\mathcal{I}_o^{-1})_{\alpha,\alpha}}$$

  - Then a Z-test can be constructed:

$$Z = \frac{\widehat{\alpha}}{\widehat{\mathrm{se}}(\widehat{\alpha})}$$

and squared to obtain χ^2

- This produces:

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr Z
Intercept	id	0.3243	0.03979	8.15	<.0001
SP(POW)	id	0.1324	0.06196	2.14	0.0326
Residual		0.1316	0.009083	14.49	<.0001

- Note that $\chi^2 = 2.14^2 = 4.58$
  – not that much different to 5.1 in LRT

- This can also be used for **approximate** confidence intervals for covariance parameters:

  A 95% CI for α is

$$\widehat{\alpha} \pm 1.96 \times \widehat{\mathrm{se}}(\widehat{\alpha})$$

which is

$$.1324 \pm 1.96 * .06196 = [0.011, 0.254]$$

- **Note**:
  - These tests are **approximate**. They require adequate sample sizes
  - SAS PROC MIXED uses observed information $\mathcal{I}_O$
  - Other packages may use **expected information**:

$$\mathcal{I}_E = -\mathrm{E}\left\{\frac{\partial^2 L^*(\boldsymbol{\beta}, \boldsymbol{\gamma})}{\partial(\boldsymbol{\beta}, \boldsymbol{\gamma})\partial(\boldsymbol{\beta}, \boldsymbol{\gamma})}\right\}\Big|_{(\widehat{\boldsymbol{\beta}}, \widehat{\boldsymbol{\gamma}})},$$

  - Usually LRTs are more powerful than Wald tests, but more work to produce

Problem: Some Covariance Parameter Tests are Naturally One-sided

- **Example:** Exchangeable correlation model

$$\mathrm{corr}(\epsilon_{ij}, \epsilon_{ik}) = \rho$$

which can be motivated by the random effects model

$$\epsilon_{ij} = U_i + Z_{ij}$$

Obviously $\mathrm{var}(U_i) = \nu^2 \geq 0$ and so

$$\rho = \frac{\mathrm{var}(U_i)}{\mathrm{var}(U_i) + \mathrm{var}(Z_{ij})} \geq 0$$

- Note: More generally, you could allow $\rho < 0$ (but not due to RE model)

- Under the **random effects model**, a significance test for the exchangeable correlation ρ would be for a **one-sided** alternative:

$$H_0 : \rho = 0 \quad \text{vs.} \quad H_A : \rho > 0$$

or

$$H_0 : \nu^2 = 0 \quad \text{vs.} \quad H_A : \nu^2 > 0$$

- **Example:** Exponential plus exchangeable:

$$\epsilon_{ij} = U_i + W_{ij}$$

where

$$W_{ij} = \alpha W_{i,j-1} + Z_{ij}$$

(if time lags are all in 1-unit intervals)

Here, if time is **continuous**, $\mathrm{corr}\{W_i(t), W_i(t+u)\} = \alpha^u$ we cannot have $\alpha < 0$, so we would again want to test

$$H_0 : \alpha = 0 \quad \text{vs.} \qquad H_A : \alpha > 0$$

- **Problem:** LRT chi-square tests are set up for two-sided alternatives:

$$H_0 : \alpha = 0 \quad \text{vs.} \quad H_A : \alpha \neq 0$$

  - The null hypothesis value of the parameter is on the **boundary** of the parameter space (see Self and Liang, 1987)
  - The theoretical distribution of the LRT chi-square statistic X^2 comes from the square of a Z
  - Negative Z would correspond to $\widehat{\alpha} < 0$, positive Z to $\widehat{\alpha} > 0$

- As we cannot have $\widehat{\alpha} < 0$, under the null hypothesis, X^2 will only be greater than some critical value **half as often** as we expect

- **Solution**: you can (and should!) **divide your** P-values **by 2** for one-sided covariance parameter hypothesis tests

- In the LRT for the exponential correlation α, we would then have

$$P\text{-value} = \frac{1}{2}\Pr\left(\chi^2 \geq 5.1\right) \approx \frac{1}{2}0.02 = 0.01$$

- Note: This does not change computation of Wald-based confidence intervals (bad CI!).

Selecting and Evaluating Covariance Models

- How does one choose among a set of candidate covariance models? How does one evaluate whether they fit the data well?
- If using maximum likelihood or restricted maximum likelihood estimation:
  - Perform LRTs for comparing **nested** models

    Example: Nepal data comparing the exponential plus exchangeable to the exchangeable only models
  - Akaike's Information Criterion (AIC), Bayesian information criterion (BIC) (or other information criteria).

    – Will not discuss here. With either AIC or BIC, if two models, non-nested, have the same number of parameters, can just compare the likelihood values

- Examine empirical ACF (auto-correlation function) to help select candidate models
  - must assume that $\mathrm{var}(\epsilon_{ij})$ is approximately constant and that $\mathrm{corr}(\epsilon_{ij}, \epsilon_{ij})$ depends only on the lag $|t_{ij} - t_{ik}|$, at least approximately
- A more powerful technique is to use empirical and fitted model variograms.

  – not covered here, interested students can read Diggle, Heagerty, Liang and Zeger's book

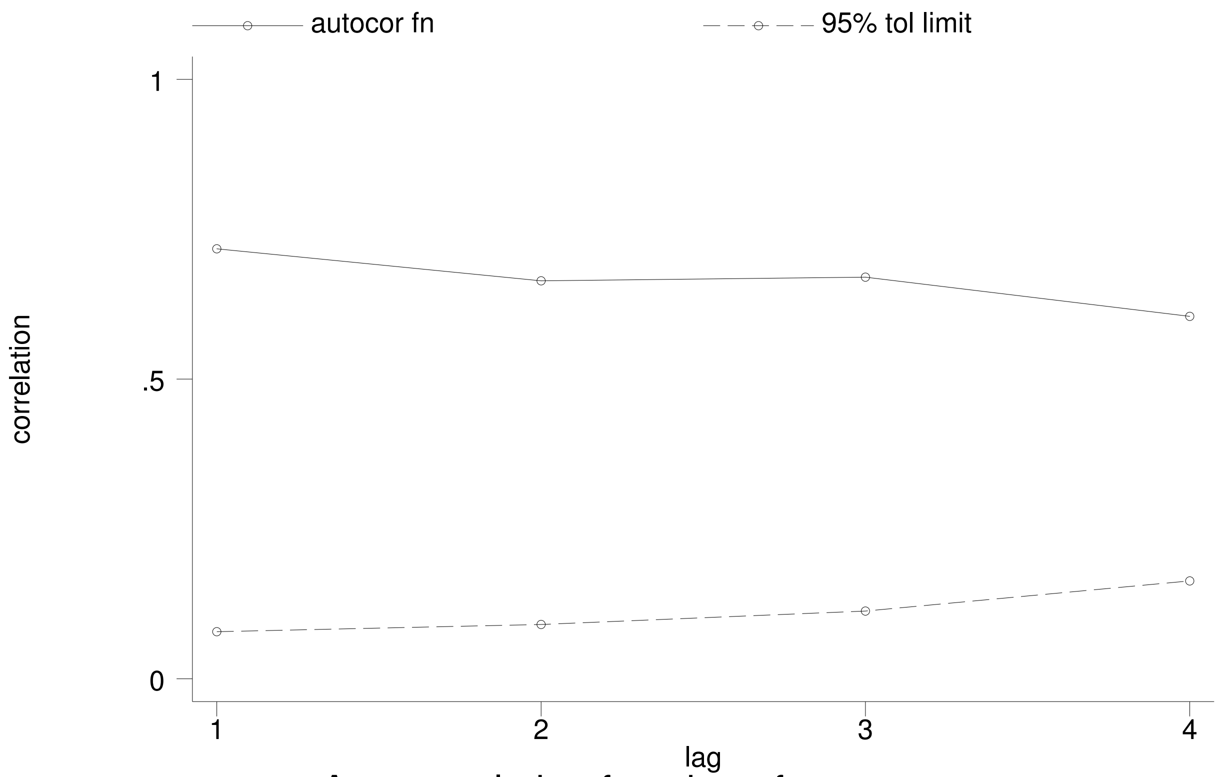
Examining and Interpreting ACF

- Considering the acf:
  - If acf declines strongly with lag, then: "exponential" component
  - If acf does not appear to $\to 0$ as lag $\to \infty$, then: "exchangeable" component
  - If acf does not appear to $\to 1$ as lag $\to 0$, then: "measurement error" component
- **Example:** Nepal data: Generate ACF in an **exploratory mode**, using OLS to generate residuals:

```
# read data
data=read.csv("nepal.csv")
data$obs=rep(1:5,200)

## Compute residuals, removing effects by OLS
data$wtage=data$wt*(data$age-36)
data$age2=(data$age-36)^2
fit<-lm(arm~wt+age+sex+wtage+age2,data)
```

```
data$armrs=rep(NA,dim(data)[1])
data$armrs[!(is.na(data$arm) | is.na(data$wt) |
    is.na(data$age) | is.na(data$sex))]=residuals(fit)

## Autocorrelation function and correlogram

# extract all pairs within each subject
data$id=as.factor(data$id)
id.list=levels(data$id)
data.pairs=list()
for(i in 1:length(id.list))
{
    subject.i=data[data$id==id.list[i],]
    data.pairs.i=gtools::combinations(dim(subject.i)[1], 2,repeats=FALSE)
        #index of all possible pairs

    data.pairs.add=data.frame(id=rep(i,dim(data.pairs.i)[1]),
        obs1=subject.i$obs[data.pairs.i[,1]],obs2=subject.i$obs[data.pairs.i[,2]],
        armrs1=subject.i$armrs[data.pairs.i[,1]],
        armrs2=subject.i$armrs[data.pairs.i[,2]])
        # all pairs within subject i
```

```
    data.pairs=rbind(data.pairs,data.pairs.add)
}
data.pairs$lag=abs(data.pairs$obs2-data.pairs$obs1)

# remove missing observations
# otherwise N in TL calculation will include missing observations
data.pairs=data.pairs[!(is.na(data.pairs$armrs1) | is.na(data.pairs$armrs2)),]

# Autocorrelation function and tolerance limit
lag.list=1:4
ACF=TL=rep(NA,length(lag.list))
for(lag in 1:length(lag.list))
{
    subset=data.pairs[which(data.pairs$lag==lag.list[lag]),4:5]
    ACF[lag]=cor(subset,use="pairwise.complete.obs")[1,2]
    TL[lag]=1.96/sqrt(dim(subset)[1])
}

# correlogram
plot(lag.list,ACF,"l",xlab="Time lag",xlim=c(1,4),ylim=c(0,1))
lines(lag.list,TL,lty=2)
legend("topright",c("Autocorrelation function","95% tolerance limit"),lty=1:2)
```



Autocorrelation function of armres

From this:

– clearly, there is an "exchangeable" component in the model

– "exponential" component might not be that important (even though it was significant in the test)