# EXPLORATORY / DESCRIPTIVE ANALYSIS OF LONGITUDINAL DATA Exploration of Correlation Structure

- Recall that the correlation among repeated measures is what makes longitudinal data so powerful
- We will want to incorporate the **correlation structure** into our models for longitudinal data
  - the correlation may be of **direct scientific interest** in the study (more emphasis in earlier text by Diggle et al)
     or
  - knowing the correlation (or being able to model it) will result in increased statistical efficiency in modelling trends in the mean (by optimally weighting the data; given greater emphasis in current text by Fitzmaurice et al)
  - reducing bias in SE and obtaining correct CI and p-value
- Preliminary analyses and (later on) model checking will require tools for exploring the correlation structure:
  - scatterplot and correlation matrix
  - autocorrelation function and correlogram
  - variogram

Consider a general (marginal) (working) model

$$Y_{ij} = \mathbf{x}'_{ij}\mathbf{\beta} + \epsilon_{ij} \tag{1}$$

where  $x_{ij}$  contains important covariate effects, generally including time and any fixed covariates.

- No subject-specific random variable  $b_i$  in model
- Instead  $\epsilon_{ij}$  are correlated within subject i.
- We are interested in studying the correlation structure among the error terms,

$$\operatorname{corr}(\epsilon_{ij}, \epsilon_{ik}), \text{ for } j \neq k$$

where  $\epsilon_{ij}$  and  $\epsilon_{ik}$  are two error terms on the same subject (i) at different points ( $t_{ij}$  and  $t_{ik}$ ) in time

• For exploration purpose, define the (exploratory) residuals

$$r_{ij} = \hat{\epsilon}_{ij} = Y_{ij} - oldsymbol{x}_{ij}' \widehat{oldsymbol{eta}} = \mathsf{resp} - \widehat{\mathsf{pred}}$$

where  $\widehat{\boldsymbol{\beta}}$  is some quick-and-dirty estimator for  $\boldsymbol{\beta}$  (e.g., OLS, ignoring longitudinal structure)

## Generating Residuals from Model (1) and Examining Dispersion

• Example: Protein content of cows milk:

To explore the correlation structure among protein, first remove the time trends for each treatment group, by subtracting mean for each time in each treatment group:

• R program example:

```
> # read data
> data=read.csv("cows.csv")
>
> # Compute residuals, removing effects of diet and time
> dietgrp=levels(data$diet)
> dietgrp
[1] "barley" "lupins" "mixed"
>
> week=levels(as.factor(data$week))
> week
   [1] "1" "2" "3" "4" "5" "6" "7" "8" "9" "10" "11" "12" "13" "14" "15"
[16] "16" "17" "18" "19"
>
> # subtract mean for each combination of diet and week
> data$protrs=data$prot
> for(d in 1:length(dietgrp))
+ for(w in 1:length(week))
```

```
+ {
+ #select observations in this combination
+ index=which(data$diet==dietgrp[d] & as.factor(data$week)==week[w])
+ data$protrs[index]=data$prot[index]-mean(data[index,]$prot)#residual
+ }
```

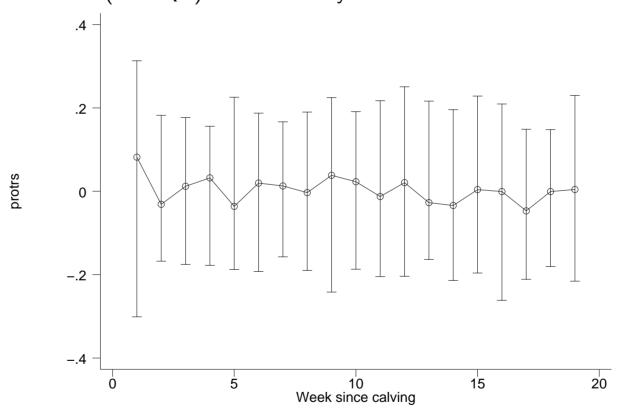
#### • Notes:

- Here the model (1) contains a dummy variable for each time point, each treatment group, and all two-way interaction terms
- A simpler model could probably be used, but it is useful to be flexible during exploratory analyses
- As a preliminary step, we might examine the degree of dispersion (spread) among the residuals as a function of time

```
> ## create summary table for residual by week
> #Mean of residual by week
> mean.resid=aggregate(data$prot.resid, list(data$week), mean)
> #SD of residual by week
> sd.resid=aggregate(data$prot.resid, list(data$week), sd)
> #frequency of residual by week
> freq.resid=aggregate(rep(1,dim(data)[1]), list(data$week), sum)
>
> summ.resid=cbind(mean.resid,sd.resid[,2],freq.resid[,2])
> names(summ.resid)=c("week","mean","SD","freq")
> summ.resid
   week
                             SD freq
                 mean
1
      1 -4.495939e-17 0.3974150
                                  79
2
      2 -6.263005e-17 0.2703849
                                  78
      3 -6.183589e-17 0.2547052
                                  79
      4 -4.496626e-17 0.2508063
                                  79
                                  78
5
      5 3.416627e-17 0.3280103
6
      6 5.058421e-17 0.2905210
                                  79
                                  77
      7 1.845636e-16 0.2348227
8
      8 6.344554e-17 0.3015270
                                  77
                                  77
      9 5.189808e-17 0.2915378
10
     10 0.000000e+00 0.2728563
                                  78
11
     11 4.555439e-17 0.3033748
                                  78
12
     12 -3.373777e-17 0.2805961
                                  79
                                  78
13
    13 -7.401035e-17 0.2839899
14
    14 -3.934427e-17 0.3160343
                                  79
15
     15 -1.505369e-16 0.3147629
                                  59
16
     16 3.553418e-17 0.3334893
                                  50
```

```
17 17 2.896293e-17 0.2817822 46
18 18 0.000000e+00 0.2919066 46
19 19 -2.166338e-17 0.3046098 41
```

• Plot for median (and IQR) of residuals by week:

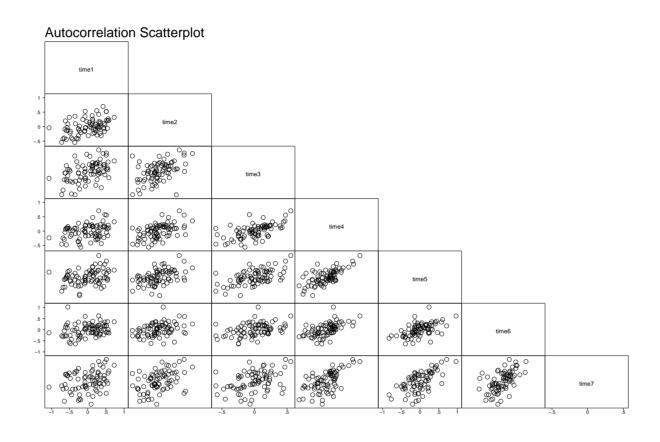


#### **Notes:**

- From the table and plot, appears as if the variance is fairly constant across time (except week 1)
- This somewhat unusual with longitudinal data . . . often we see variance increasing with time
- In most analyses, one would present either a table or a graphic, but not both
- In some data sets where time is more continuous, it might be necessary to group observation times in order to prepare such a table
   If data are grouped, it should only be for purposes of exploratory analysis
- Alternatively, the plot could be replaced with a scatterplot which shows the dispersion
- Also, if time is continuous, a scatterplot smoother might be required to remove time trends (here, we have just used a separate mean for each time point wihtin each treatment group)

# **Autocorrelation Scatterplot Matrix and Correlation Matrix**

- Goal: examine graphically or otherwise the association across time between observations on the same subject
- ullet For each **pair of** observation times, the residuals  $r_{ij}$  can be examined in a **scatterplot matrix**
- Here, we just examine the association among the first 7 time points for Cows data



Each point in this picture represents a pair of observations (protrs residuals) on the same subject in the original data set. E.g., the topmost cell plots week  $2\ vs.$  week 1

## • We note several things:

- the plots along the first diagonal, corresponding to a time lag of one week, show the strongest association
- both association and information weaken as time lags get greater
- Pearson's correlation coefficient would be a good summary measure of association for each plot

#### R program example:

```
> # keep week 1-7 and necessary variables only
> subset=data[data$week<=7,c(1,3,5)]
> # into wide format
> wide<-reshape(subset, v.names="protrs", idvar="id", timevar="week", direction="wide")
> # plot for Autocorrelation Scatterplot Matrix
> pairs(wide[,-1])
> # correlation matrix
> cor(wide[,-1],use="pairwise.complete.obs")
         protrs.1 protrs.2 protrs.3 protrs.4 protrs.5 protrs.6 protrs.7
protrs.1 1.0000000 0.4397052 0.4723762 0.3213910 0.3165455 0.2553003 0.2989087
protrs.2 0.4397052 1.0000000 0.4852995 0.5170111 0.4637478 0.3471221 0.4277654
protrs.3 0.4723762 0.4852995 1.0000000 0.6009765 0.5746046 0.3949390 0.3941880
protrs.4 0.3213910 0.5170111 0.6009765 1.0000000 0.6870871 0.5683348 0.6017598
protrs.5 0.3165455 0.4637478 0.5746046 0.6870871 1.0000000 0.5357291 0.6263782
protrs.6 0.2553003 0.3471221 0.3949390 0.5683348 0.5357291 1.0000000 0.5721362
protrs.7 0.2989087 0.4277654 0.3941880 0.6017598 0.6263782 0.5721362 1.0000000
```

#### • Notes:

- As with the scatterplot matrix, we see that association is strongest with a time
   lag of one week, and weakens with greater lags (across diagonals)
- As we read *along* a diagonal, lag is constant. Correlation tends to increase over time; this is not uncommon in longitudinal data analysis

## **Autocorrelation Function and Correlogram**

- For now, let us ignore the differences in correlation along a diagonal, and make the working assumption that the residuals are **weakly stationary**, that is:
  - they have **constant mean** (over time and other factors). in this case:  $E(\epsilon_{ij}) = 0$ . (easily satisfied since we have removed the time and treatment trends)
  - constant variance:

$$var(\epsilon_{ij}) = \sigma^2$$

(have checked this and does not appear unreasonable)

- **correlation** that only depends on the **time lag**,  $|t_{ij} - t_{ik}|$ , between two residuals:

$$\operatorname{corr}(\epsilon_{ij}, \epsilon_{ik}) = \rho(u_{ijk}), \quad u_{ijk} = |t_{ij} - t_{ik}|$$

(here we ignore differences in correlation later versus earlier in the study)

• Autocorrelation function (ACF)  $\rho(u)$  is defined as

$$\rho(u) = \operatorname{corr}(\epsilon_{ij}, \epsilon_{ik}), \quad u = |t_{ij} - t_{ik}|$$

- In this case, it makes sense to pool all of the **pairs of items** along each diagonal in the scatterplot matrix, and then compute the correlation for each pair. This results in in the (empirical) **autocorrelation function**:
- Computation of the empirical autocorrelation function For each time lag  $u=1,2,\ldots$  :
  - 1. Construct a data set of all pairs of observations (residuals) that are separated by lag u:

$$r_{ij} = \hat{\epsilon}_{ij}, r_{ik} = \hat{\epsilon}_{ik}, \text{ where } |t_{ij} - t_{ik}| = u, \quad j < k$$

2. Compute Pearson's sample correlation coefficient between the two observations for each observed lag u:

$$\widehat{\rho}(u) = \widehat{\mathrm{corr}}(r_{ij}, r_{ik})$$

 A plot of the autocorrelation function versus the time lag is called a correlogram.

- Tolerance limits (TL) to complement the autocorrelation function:
  - Null hypothesis  $H_0$ : for a given lag u, the true correlation  $\rho(u)=0$
  - For a 95% TL:  $\Pr(\widehat{\rho}(u) \text{ within } TL_{0.95}(u)|H_0) = 95\%$
  - 95% TL represents the bounds outside of which the empirical (observed)
     correlation will fall only 5% of chance, given null hypothesis of zero correlation is true
  - Correlations outside of the TL are significantly different than zero at the 5% level

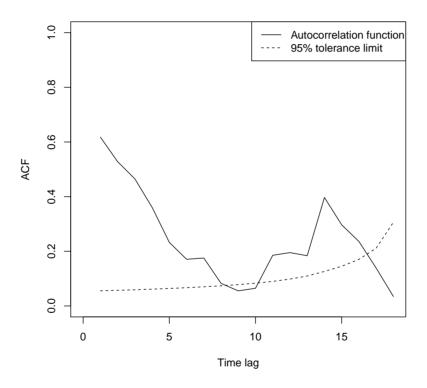
#### • Calculation of **Tolerance limits**:

- The simplest rule of thumb: A correlation coefficient r has standard error  $\frac{1-r^2}{\sqrt{N}}$ , where N is the number of independent pairs of observations in the calculation.
- Under  $H_0$  of no correlation, a correlation coefficient has standard error  $\frac{1}{\sqrt{N}}$ .
- 95% Tolerance limits  $=\frac{\pm 1.96}{\sqrt{N_u}}$ , where  $N_u$  is the number of pairs of observations at lag u.

R program for autocorrelation function and correlogram:

```
> # extract all pairs within each subject
> data.pairs=list()
> for(i in 1:79)
+ subject.i=data[data$id==i,]
+ data.pairs.i=gtools::combinations(dim(subject.i)[1], 2,repeats=FALSE)#index of all possible pairs
+ data.pairs.add=data.frame(id=rep(i,dim(data.pairs.i)[1]),
+ week1=subject.i$week[data.pairs.i[,1]],week2=subject.i$week[data.pairs.i[,2]],
+ protrs1=subject.i$protrs[data.pairs.i[,1]],protrs2=subject.i$protrs[data.pairs.i[,2]]
+ )# all pairs within subject i
+ data.pairs=rbind(data.pairs,data.pairs.add)
+ }
> data.pairs$lag=abs(data.pairs$week2-data.pairs$week1)
> # Autocorrelation function and tolerance limit
> ACF=TL=rep(NA,18)
> for(lag in 1:18)
+ {
+ subset=data.pairs[which(data.pairs$lag==lag),4:5]
+ ACF[lag]=cor(subset)[1,2]
+ TL[lag]=1.96/sqrt(dim(subset)[1])
+ }
> summ.acf=cbind(lag=1:18,ACF,TL)
> summ.acf
                 ACF
                             TL
 [1,] 1 0.61775471 0.05548157
```

```
[2,]
        2 0.52777616 0.05727665
 [3,]
        3 0.46503729 0.05933947
 [4,]
       4 0.36084984 0.06161207
 [5,]
       5 0.23253822 0.06413316
 [6,]
        6 0.17091309 0.06691330
 [7,]
       7 0.17543312 0.07013431
 [8,]
       8 0.08273442 0.07381787
        9 0.05528019 0.07815032
 [9,]
[10,]
      10 0.06486405 0.08342314
[11,]
      11 0.18548433 0.08993097
[12,]
      12 0.19528698 0.09836958
[13,]
      13 0.18387957 0.10956733
[14,]
      14 0.39705065 0.12625470
[15,]
      15 0.29701636 0.14528487
[16,]
      16 0.23604609 0.17059610
     17 0.13893101 0.21135224
[17,]
[18,]
      18 0.03480314 0.30610057
>
> # correlogram
> plot(1:18,ACF,"1",xlab="Time lag",xlim=c(0,18),ylim=c(0,1))
> lines(1:18,TL,lty=2)
> legend("topright",c("Autocorrelation function","95% tolerance limit"),lty=1:2)
```



- Interpretation of the correlogram:
  - As observations on the same subject are separated by greater lags (i.e., by greater amounts of time), two observations on the same individual are less alike, at least up to a lag of 10 weeks
  - There appears to be greater correlation around 14 week lag
    - \* some of this is probably noise
    - \* could represent unexplained factors operating on a 14-week cycle (e.g., delivery of fresh grain)

#### Variogram

- The sample autocorrelation function is useful when
  - time points are evenly-spaced, and
  - there are sufficient numbers of pairs  $(Y_{ij}, Y_{ik})$  at each lag u
- When this is not the case (eg, CD4+ data)
  - need to group time points (eg, round to years)
  - variogram provides an alternative tool for exploring correlation structure
- The variogram function  $\gamma(u)$  is defined as

$$\gamma(u) = \frac{1}{2} E\left[ \left\{ \epsilon(t) - \epsilon(t - u) \right\}^2 \right],$$

where u is a positive lag, and t is any time

- given u,  $\gamma(u)$  is constant for any t
- The variogram is also applicable to "weakly stationary" processes (like ACF)

Recall, under Weak stationarity: Pick any u.
 For any t, the mean is constant:

$$E\{\epsilon(t)\} = E\{\epsilon(t-u)\} (= 0 \text{ in this case})$$

variance is constant:  $var\{\epsilon(t)\} = var\{\epsilon(t-u)\} = \sigma^2$ 

within-subject correlation only depends on time lag u:

$$\operatorname{corr}\{\epsilon(t), \epsilon(t-u)\} = \rho(u)$$

ullet Under weak stationarity, relationship between variogram  $\gamma(u)$  and ACF  $\rho(u)$  is

$$\gamma(u) = \frac{1}{2} \operatorname{E} \left[ \{ \epsilon(t) - \epsilon(t - u) \}^2 \right]$$

$$= \frac{1}{2} \left[ 2\sigma^2 - 2\sigma^2 \operatorname{corr} \{ \epsilon(t), \epsilon(t - u) \} \right]$$

$$= \sigma^2 \{ 1 - \rho(u) \}$$

• To satisfy the constant mean assumption, **variograms should be computed on** *residuals*, removing any effects of time and other important covariates

## **Computation of Sample Variogram**

• Starting with the residuals  $r_{ij} = \hat{\epsilon}_{ij}$  and the times  $t_{ij}$ , compute for all possible pairs within same subject:

$$v_{ijk} = \frac{1}{2}(r_{ik} - r_{ij})^2$$

and

$$u_{ijk} = t_{ik} - t_{ij}$$

for j < k

- Fit a model of  $v_{ijk}$  (dependent variable) on  $u_{ijk}$  (independent variable) Model examples:
  - ANOVA model with one parameter for each value of u (if number of possible u is small, eg, Cows data)
  - Smooth model fit (using, e.g., lowess) of v on u (eg, CD4+ data)

• Note: To estimate  $var\{\epsilon(t)\} = \sigma^2$ , use the same way that we obtained  $\hat{\sigma}_t^2$  (half the average of between-subject squared differences)

$$\widehat{\sigma}^2 = \frac{1}{2} \text{average} \{ (r_{ij} - r_{i'k})^2 \}$$

over  $i=1,\dots,m-1, \ i'=i+1,\dots,m, j=1,\dots,n_i, k=1,\dots,n_{i'}$ , That is,

$$\widehat{\sigma}^2 = \frac{\sum_{i=1}^{m-1} \sum_{i'=i+1}^{m} \sum_{j=1}^{n_i} \sum_{k=1}^{n_{i'}} \{ (r_{ij} - r_{i'k})^2 \}}{2 \sum_{i=1}^{m-1} \sum_{i'=i+1}^{m} \sum_{j=1}^{n_i} \sum_{k=1}^{n_{i'}} 1}$$

**Example:** Protein content of cows' milk:

 (ANOVA model) There are 19 time points → 18 different lags. We can fit a discrete-lag variogram model for each of the 18 different lags:

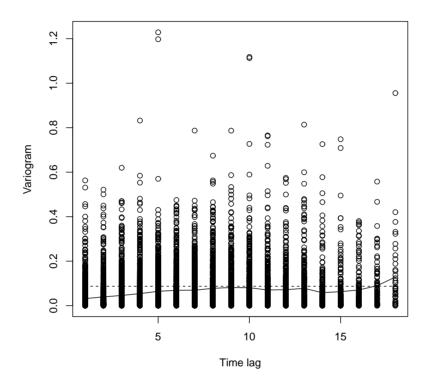
$$v_{ijk} = \alpha_{u_{ijk}} + e_{ijk}$$

and estimated variogram  $\hat{\gamma}(u) = \hat{\alpha}_u$  is predicted value at each time lag u.

• R program example:

```
> data.pairs$v=(data.pairs$protrs1-data.pairs$protrs2)^2/2
>
> # ANOVA model
> model.anova=lm(v~as.factor(lag)-1,data=data.pairs)
> pred.anova=predict(model.anova,newdata=data.frame(lag=as.factor(1:18)))
> # variance
> numerator=0
> denominator=0
> for(i in 1:78)# sum up all possible pairs
+ {
+ subset.i=data[data$id==i,]
+ subset.i2=data[data$id>i,]
+ for(j in 1:dim(subset.i)[1])
+ numerator=numerator+sum((subset.i$protrs[j]-subset.i2$protrs)^2)
+ denominator=denominator+dim(subset.i)[1]*dim(subset.i2)[1]
+ }
```

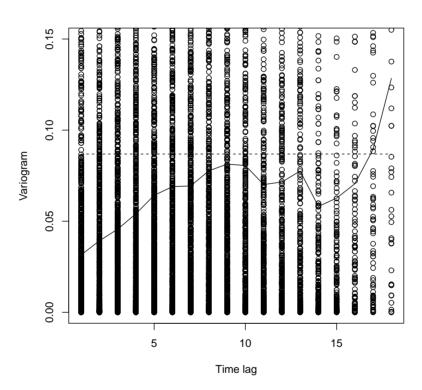
```
> sigma2=numerator/denominator/2
> sigma2
[1] 0.08687206
>
> # Variogram
> plot(data.pairs$lag,data.pairs$v,xlab="Time lag",ylab="Variogram")
> lines(1:18,pred.anova)
> lines(1:18,rep(sigma2,18),lty=2)
```



# Note:

- The horizontal line is  $\widehat{\sigma}^2=0.087$
- The points are the values of  $(v_{ijk},u_{ijk})$ . Some of the  $v_{ijk}$ 's are very large, obscuring detail (this is normal)

- ullet We can avoid plotting the large  $v_{ijk}$ 's
  - > # plot small v only
  - > plot(data.pairs\$lag,data.pairs\$v,ylim=c(0,0.15),xlab="Time lag",ylab="Variogram")
  - > lines(1:18,pred.anova)
  - > lines(1:18,rep(sigma2,18),lty=2)



• (Smooth fit) Instead of fitting a separate mean for each of the 18 lags, we can fit a smooth lowess function through the lags:

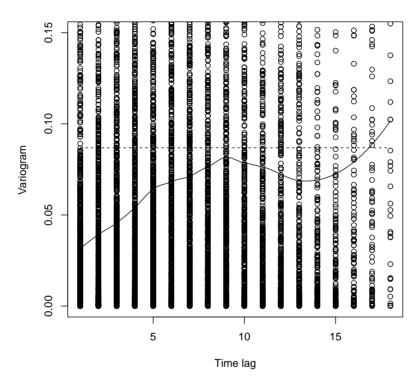
$$v_{ijk} = \mu(u_{ijk}) + e_{ijk},$$

where  $\mu()$  is a smooth function of time lag u obtained by lowess.

• R program:

```
# Lowess
model.lowess=loess(v~lag,data=data.pairs,span = 0.4)
pred.lowess=predict(model.lowess,newdata=data.frame(lag=(1:180)/10))

# Variogram
plot(data.pairs$lag,data.pairs$v,ylim=c(0,0.15),xlab="Time lag",ylab="Variogram")
lines((1:180)/10,pred.lowess)
lines(1:18,rep(sigma2,18),lty=2)
```



#### **Interpretation of Variogram**

ullet Recall that the variogram  $\gamma(u)$  is related to the autocorrelation function  $\rho(u)$  by

$$\gamma(u) = \sigma^2 \{1 - \rho(u)\}$$

which can be re-written as

$$\rho(u) = 1 - \gamma(u)/\sigma^2$$

- Therefore:
  - When  $\widehat{\gamma}(u)$  is close to 0, autocorrelation is close to 1
  - When  $\widehat{\gamma}(u)$  is increasing, autocorrelation is decreasing
  - When  $\widehat{\gamma}(u)$  is close to  $\widehat{\sigma}^2$ , autocorrelation is close to 0
  - A gap between  $\widehat{\gamma}(u)$  and  $\widehat{\sigma}^2$  for large u indicates positive autocorrelation even at largest lag

## **Summary**

- Three features of variance and correlation often seen in longitudinal data:
  - variance of observations increases with time ("fanning out")
  - correlation decreases with time lag separating observations
  - correlation increases (for a given lag) with mean time of two observations
- These principle deviations from standard OLS assumptions:
   We need to account for correlation and heteroscadisticity in analytical approaches to longitudinal data

#### Why we care about correlation and where does it come from?

- Empirical observations about correlation in many longitudinal studies:
  - correlations are positive
  - correlations decrease with time lag separating them
  - correlations do not appear to approach zero even for large time lags
  - correlations do not appear to approach one even for very small lags
  - correlations at a given lag increase as the study progresses

- Correlation among repeated measures on the **same individual** reflects underlying (unobserved) processes that are **not** accounted for in the (mean) model
  - all observations on the same subject share the same underlying processes
  - hence, observations on the same subject are more alike than observations on different subjects, yielding positive correlation between observations on the same subject
  - e.g., milk protein content partly reflects a characteristic (trait) of each individual cow
- Therefore, correlation reflects the **strength of contribution** of underlying processes to observed phenomena
  - Eg, higher correlation of weights within nepalese girls: reflects stronger contribution from underlying factor (eg, gene, diet)
- Also, the strength of correlation may vary with time lag separating observations
  - degree to which underlying time-varying processes contribute to observed phenomena
  - observations closer together on a given person are more correlated than are observations further apart in time
  - e.g., protein content may reflect amount and quality of grain eaten; two

observations close together in time (on same individual) are similar because they are taken under similar circumstances of nourishment

- Three contributing sources to observed patterns of correlation:
  - between-individual heterogeneity: some subjects are simply, on average, higher than others → positive correlation, even at long lags
  - within-individual biological variability: underlying biological processes change through time in smooth / continuous fashion  $\rightarrow$  measurements close in time are more correlated than those far apart in time
  - measurement error: most measures in public health and bio-medical science are subject to error → even observations close together in time are not perfectly correlated

- Statistical reasons to study correlation:
  - e.g., suppose  $Y_1$  is a measure before treatment and  $Y_2$  a measure after treatment,  ${\rm var}(Y_1)={\rm var}(Y_2)=\sigma^2$
  - interest is on

$$\Delta = \mu_2 - \mu_1 = \mathrm{E}(Y_2) - \mathrm{E}(Y_1) = \mathsf{treatment}$$
 difference

- Estimated by difference of sample means  $\hat{\Delta}=\bar{y}_2-\bar{y}_1$
- if data are **independent** (i.e., one set of subjects before treatment and a different set after treatment):

$$\operatorname{var}(\hat{\Delta}) = \operatorname{var}(\bar{Y}_2) + \operatorname{var}(\bar{Y}_1)$$
$$= \frac{2}{n}\sigma^2$$

where n is the number of subjects at each time point

 if data are correlated (i.e., as single set of individuals measured longitudinally both before and after treatment):

$$\operatorname{var}(\hat{\Delta}) = \operatorname{var}(\bar{Y}_2) + \operatorname{var}(\bar{Y}_1) - 2\operatorname{cov}(\bar{Y}_2, \bar{Y}_1)$$

$$= \frac{2}{n}\sigma^2 - 2\operatorname{cov}(\frac{\sum_i Y_{i1}}{n}, \frac{\sum_i Y_{i2}}{n})$$

$$= \frac{2}{n}\sigma^2 - \frac{2}{n}\sigma^2\operatorname{corr}(Y_{i1}, Y_{i2})$$

$$= \frac{2}{n}\sigma^2(1-\rho)$$

where  $corr(Y_{i1}, Y_{i'2}) = 0$  for two different subjects, within-subject correlation  $\rho = corr(Y_{i1}, Y_{i2})$ 

- The latter is smaller if  $\rho > 0$  !
- When studying contrasts within individuals, positive correlation helps
- More generally: Correlated observations provide more precise estimates of rates of change than would be obtained from independent observations from different individuals.