Faculty of Health Sciences

Models for longitudinal data

Analysis of repeated measurements, 2018

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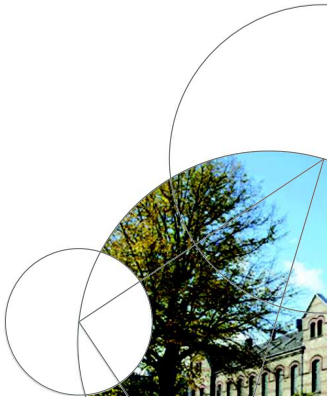


ATT: Exercise classes

FINAL ROOM ALLOCATIONS TO ENSURE A MORE EVEN DISTRIBUTION OF TEACHERS...

- **Ph.D. students and master students together**

SAS-classes:

- Both days in 2-1-02.
- Taught by Lene/Julie and Karl.

R-classes:

- Tuesdays in 2-2-02, fridays in 7-0-08.
- Taught by Brice and Elisabeth.

Contents

More about longitudinal data analysis

- Longitudinal studies
- Models for the mean
- Models for the covariance
- Analysis of summary statistics

Suggested reading: FLW chapters 6 and 7.

Outline

Typical set-up for longitudinal measurements

Want to compare two or more *groups* of subjects.

- E.g. two different treatments, possibly randomized.

Repeated measurements over *time* for each subject.

- calender time / age / duration of treatment
- planned or ad hoc times of measurement.

ATT: statistical results may be biased unless we account for correlation between measurements on the same subject.

How do I model my particular data?

- **Answer:** Several possibilities. *It depends . . .*

Characterizing your longitudinal study

Type of study:

- Randomized or observational?

Time schedule:

- Fixed times or ad hoc observations?

Type of data:

- Continuous, binary, count, ordinal, or categorical?

Sample sizes:

- How many subjects? How many time points?

Data structure:

- Wide or long format?

Study type

Randomized: One homogeneous population is studied.

- Randomization to two (or more) treatment groups
- One or more follow-up measurements + usually a measurement at baseline.

Observational: One or more (sub)populations are studied.

- Beginning at a well defined starting point (e.g. diagnosis).
- A single population followed over time . . .
- **or** comparison of two or more populations, e.g. men and women or different diagnoses.
- Beware of confounding when comparing non-randomized treatments (adjusting for time-varying confounding is very difficult).

Observation schedules

Fixed time points (balanced design):

- Measurements collected at prespecified time points.
- Equidistant: 5, 10, 15, 20 minutes, or every month.
- Non-equidistant: 5, 10, 20, and 60 minutes.

Ad hoc time points (unbalanced design):

- Subejcts were seen e.g. when the doctor decided or when the patient felt the need.
- Beware of bias. What are the time points representative of? Difficult both to analyze data and to interpret the results.

BUT: In practice, designs planned to be balanced often turn out more or less unbalanced....

Case: Calcium supplements

Randomized study: including 112 girls at age 11.

Treatment: calcium supplement or placebo.

Outcome: BMD=bone mineral density, in mg/cm^3

Planned follow-up: every 6 months in two years

- 5 visits in total including baseline.

Does calcium increase bone gain in adolescent women?

Note: `calcium.txt` and `calcium-demo1.sas` on the course webpage.

Time points in the calcium study

`visit`: Number 1, 2, 3, 4, or 5.

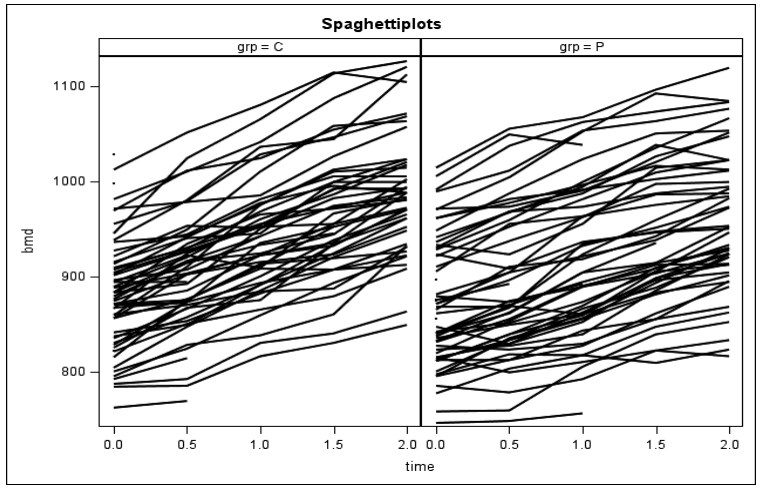
`time`: Scheduled follow-up 0, 1/2, 1, 1 1/2, 2 years.

`obstime`: Actual time of follow-up (individual).

Analysis Variable : obstime

time	N	Mean	Std Dev	Minimum	Maximum
0	112	0	0	0	0
0.5	105	0.52	0.04	0.42	0.72
1	97	0.96	0.06	0.85	1.19
1.5	94	1.50	0.08	1.34	1.78
2	91	1.98	0.08	1.80	2.23

Planned time line (ignore deviations from time schedule)



Repetition: Baseline follow-up studies

Comparison of change over n time points (5 visits)
within g groups (2 treatments) of subjects.

- Similar to two-way ANOVA, only with correlated data.
  - **Covariates:** time and group (both categorical).
- Use a constrained linear mixed model (cLMM) to make baseline adjustment, if treatments are randomized.
- An unstructured covariance pattern is assumed.

Model assumptions:

- Multivariate normal distribution, but the analysis is robust w. decent sample size + not too large deviation from normality.
- Same covariance in all groups (may be relaxed).

Results

Mean gain in BMD (mg/cm^3) since baseline with calcium supplement or placebo

years	Calcium group	Placebo group	Difference
1/2	27 (20;33)	20 (14;27)	6 (0;13)
1	56 (47;65)	45 (35;54)	12 (2;21)
1 1/2	83 (72;94)	71 (60;82)	12 (1;23)
2	106 (94;118)	87 (75;99)	19 (6;31)

- We see a significantly higher gain in BMD with calcium at last follow-up (P=0.0032)
- Estimated mean at baseline 875 mg/cm^3 (95% CI 863 to 887)

Drawbacks of the 'usual' model

- It can only handle balanced designs.
- Not good with many groups or time points, results may be unstable due to having too many model parameters.
- Do not make use of a priori known data patterns, e.g.
  - correlation decreasing with time.
  - monotone / linear growth.

Hence has reduced efficiency (power) compared to more specific models.

Outline

Models for the mean

Changes over time usually appear gradually and often following a distinct pattern.

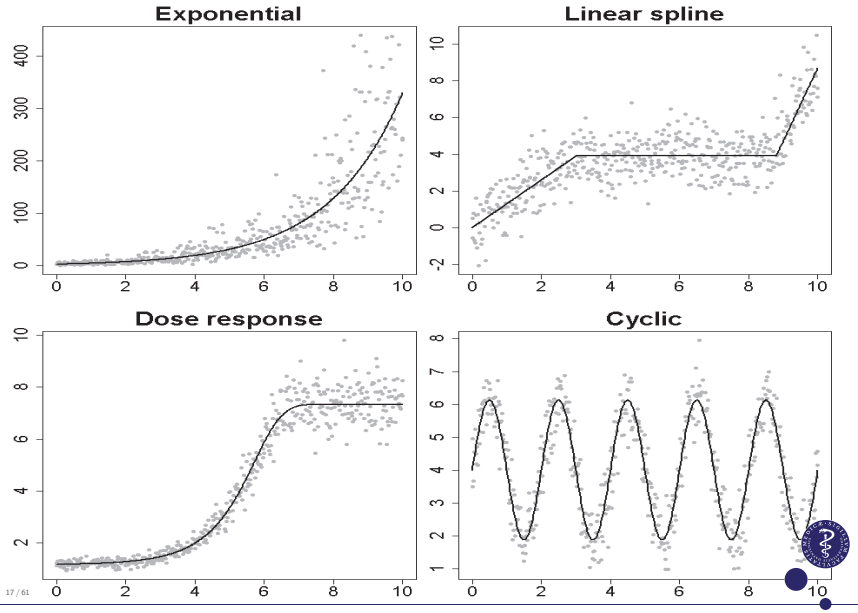
- We gain power by incorporating this in our models.
- We only need to report few parameters such as growth rates.

Model the mean as a **continuous function of time**, e.g.

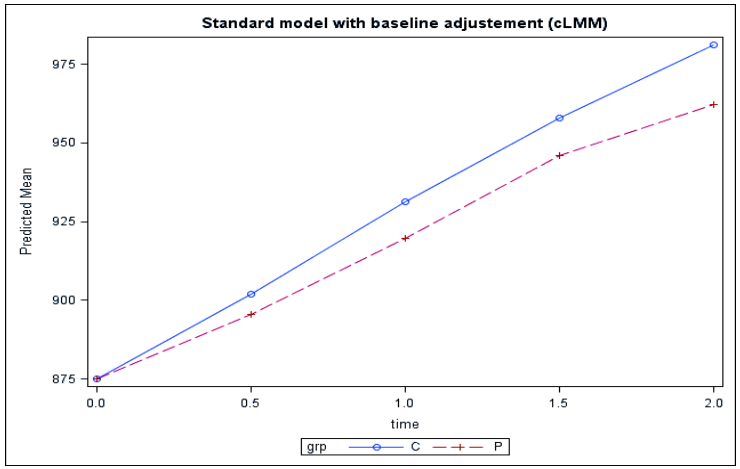
- Linear
- Exponential (log-linear)
- Piecewise linear (linear spline)
- Nonlinear (cyclic, dose-response curve, etc)
- Nonparametric (loess, smoothing spline, etc)

(many possibilities, not all treated in this course).

Examples of mean curves



Calcium: cLMM estimated means



- Looks as mean BMD increases linearly with time.

Calcium: linear model

Assuming constant growth rates in each treatment group:

$$Y_{ij} = \alpha + \beta \cdot t_j + \gamma \cdot I\{\text{calcium}\} \cdot t_j + \varepsilon_{ij}$$

where $t_1 = 0$, $t_2 = 0.5$, $t_3 = 1$, $t_4 = 1.5$, and $t_5 = 2$ years.

- α is the baseline mean for the study population.
- β is the growth rate with placebo.
- γ is the difference in growth rates between calcium treatment and placebo, i.e. the treatment effect.
- ($\beta + \gamma$ is the growth rate with calcium treatment).

Error terms $\varepsilon_i = (\varepsilon_{i1}, \ldots, \varepsilon_{i5})$ are assumed multivariate normal with zero mean and an unstructured covariance matrix.

Calcium: linear model for the mean in SAS

To fit the linear model, we need the **continuous variable** `time` which contains the scheduled times of visit in years since baseline.

```
proc mixed data=calcium method=ml plots=all;
class grp (ref='P') girl visit;
model bmd = time grp*time / ddfm=kr solution cl;
repeated visit / type=un subject=girl r rcorr;
run;
```

Note:

- We omit the main effect of `grp` (no difference at baseline).
- Use the **categorical variable** `visit` to specify the unstructured covariance pattern (`type=un`).
- Use `plots=all` for making diagnostic plots.
- The argument `method=ml` is explained in a few slides ...

Calcium: linear model for the mean in R

To fit the linear model, we need the **continuous variable** `time` which contains the scheduled times of visit in years since baseline.

```
fit <- gls(bmd~time grp*time,
           method='ML',
           data=calcium,
           correlation=corSymm(form=~visit|girl),
           weights=varIdent(form=~1|visit),
           na.action=na.exclude,
           control=glsControl(opt='optim'))
```

Note:

- We omit the main effect of `grp` (no difference at baseline).
- Use the **numerical variable** `visit` to specify the unstructured covariance pattern.
- The argument `method='ML'` is explained in a few slides . . .

Calcium: Estimates and other select output

Fit Statistics

-2 Log Likelihood	-2430.4 <------ Used for testing the linear model
AIC (Smaller is Better)	-2394.4
AICC (Smaller is Better)	-2393.0
BIC (Smaller is Better)	-2345.5

Solution for Fixed Effects

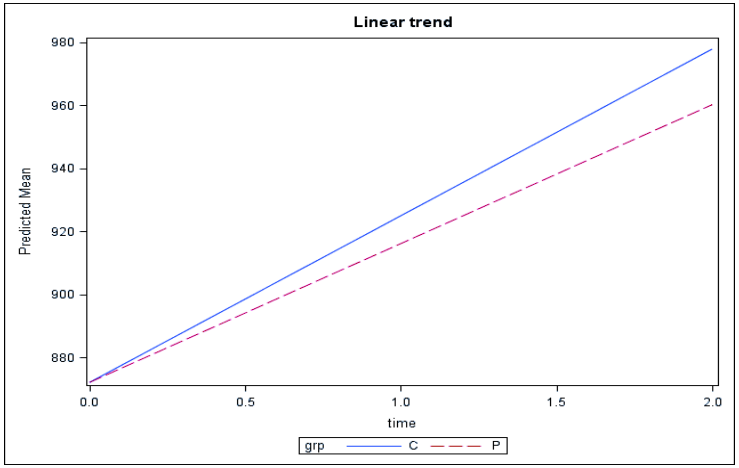
Effect	grp	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		872.0	5.712	111	152.66	<.0001	0.05	860.7	883.4
time		44.10	2.185	98.3	20.18	<.0001	0.05	39.76	48.43
time*grp	C	8.828	3.141	98.9	2.81	0.0060	0.05	2.596	15.06
time*grp	P	0	.	.	.	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
time	1	99.1	969.59	<.0001
time*grp	1	98.9	7.90	0.0060

Extra increase in BMD with calcium of 8.8 mg/cm^3 per year, (95%CI: 2.6 to 15.1, P=0.006).

Calcium: Estimated means over time



BUT: Is linear evolution at all plausible?

Comparison of models for the mean*

Do a likelihood ratio test to compare the linear model to the model with unrestricted response profiles (i.e. with time as a factor).

- Better fitting models have large values of likelihood and therefore small values of deviance: `-2 log Likelihood`.
- **ATT:** We need the `method=ml`-option to get the right values.
- Compute the difference in deviances (called `-2 log Q`) and compare to a χ^2-distribution with `df`$= \Delta$ no. params.
- Only *nested* models can be compared this way.

Calcium study: Test of linear growth hypothesis

$$\begin{aligned} -2\log Q &= 2444.1 - 2430.4 = 13.7 \\ &\sim \chi^2(9-3) = \chi^2(6) \Rightarrow P = 0.0332 \end{aligned}$$

Technical note on likelihood-types*

When testing a submodel for the mean, the deviances of the compared models must be computed using

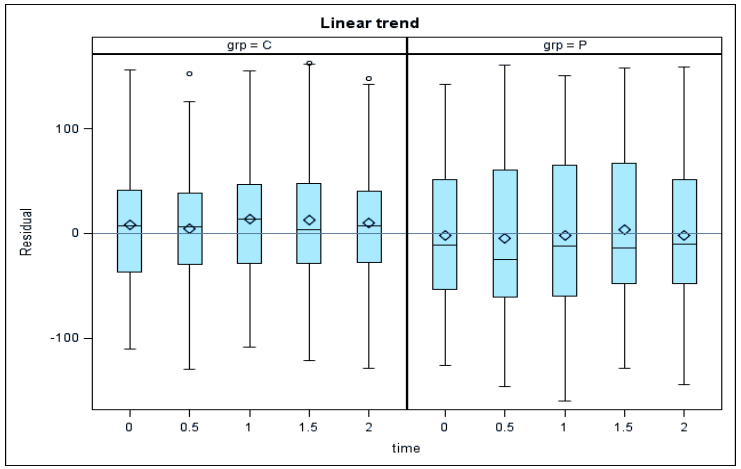
- the full (or conventional) likelihood `method=ML`
- not residual likelihood (`method=REML`) which is default and should be used in any other case.

But don't forget: Most hypothesis about the mean can be tested using just the default F-tests (optimal, `method=ml` not needed).

```
proc mixed data=calcium;
class grp girl visit treat;
model bmd = time grp*time treat*visit/ ddfm=kr solution;
repeated visit / type=un subject=girl;
run;
```

Effect	NumDF	DenDF	F Value	Pr > F
time	0	.	.	.
time*grp	0	.	.	.
visit*treat	6	126	2.29	0.0392

Residuals for linear trend model



- Deviations from linearity are not that pronounced.

Outline

The unstructured covariance pattern

So far we have made no assumptions about the covariance.

Advantages

- We make no wrong assumptions about the covariance of our observations. No need to think more about them.
- We gain insight in the actual structure of the covariance by looking at the estimates.

Drawbacks

- We use quite a lot of parameters to describe the covariance structure. Thus our analysis becomes less powerful.
- No good with small data sets; The results may be unstable.
- It can only be used in case of balanced data, i.e. all subjects have to be measured at identical times.

Estimated covariance (proc mixed output)

Using the cLMM model for the mean (we are sure this is correct).

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	3942.77	4185.68	4163.02	4238.18	3946.77
2	4185.68	4724.53	4709.06	4807.88	4518.94
3	4163.02	4709.06	4961.24	5042.13	4726.14
4	4238.18	4807.88	5042.13	5326.11	4980.45
5	3946.77	4518.94	4726.14	4980.45	4894.13

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9698	0.9413	0.9249	0.8985
2	0.9698	1.0000	0.9727	0.9585	0.9398
3	0.9413	0.9727	1.0000	0.9809	0.9591
4	0.9249	0.9585	0.9809	1.0000	0.9755
5	0.8985	0.9398	0.9591	0.9755	1.0000

Impact of covariance on statistical results

Impact of variance:

- Means at time points with higher variance are less certain.
- Estimated means have higher standard errors.
- These points will be less influential when a regression line is fitted over time.

Impact of correlation

- Changes between points that are highly correlated will be more certain.
- Estimated mean changes have lower standard errors.
- These pairs of points will be more influential when a regression line is fitted over time.

Extreme correlations ($\approx \pm 1$) may lead to weird results.

Models for the covariance

Most often covariance display distinct features.

E.g. decreasing correlation with increasing time span between observations as in the calcium data.

- We gain power by incorporating these features in our model.

Possibilities:

- Unstructured covariance (lecture 1)
- Covariance pattern models (lecture 2)
- Variance components / random effects (lecture 3)

A huge selection is available in PROC MIXED by means of the `type`-argument. R likewise a wide selection but specification is more technical.

Stationary covariance patterns

Large selection of models for equidistant observations.

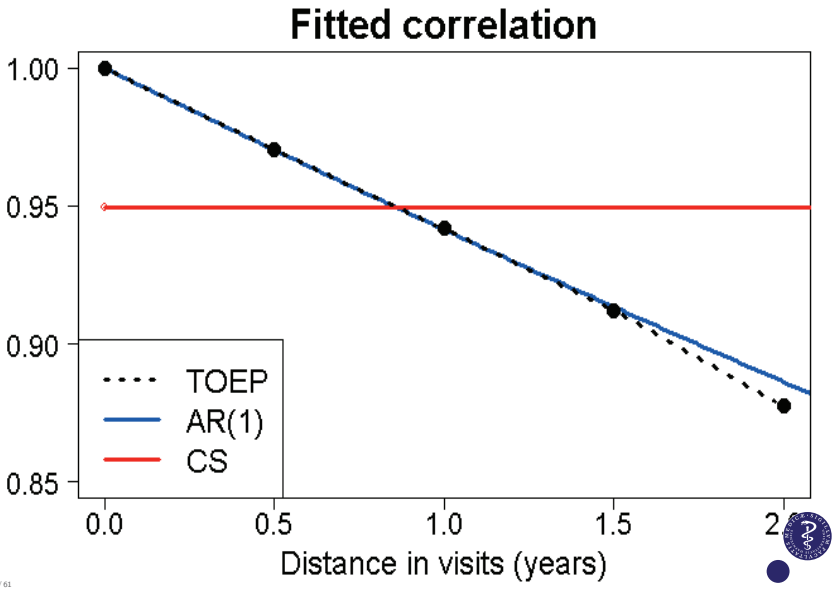
Assumption: variances and correlations are stationary:

- The variance is constant over time.
- Correlation depend only on the time-distance between the observations not the specific times of measurements.

Examples: *compound symmetry*, *autoregressive*, *autoregressive moving average*, and the *Toeplitz* models.

`proc mixed type`	$\mathrm{Cov}(Y_{ij}, Y_{ik})$	parameters
`CS`	$\sigma^2[I\{j=k\} + \rho \cdot I\{j \neq k\}]$	2
`AR(1)`	$\sigma^2 \rho^{\lvert k-j \rvert}$	2
`ARMA(1,1)`	$\sigma^2[I\{j=k\} + \gamma \cdot \rho^{\lvert k-j \rvert - 1} I\{j \neq k\}]$	3
`TOEP`	$\sigma^2[I\{j=k\} + \rho_{\lvert k-j \rvert} \cdot I\{j \neq k\}]$	n

Fit of stationary correlations



Example: Compound symmetry (`type=cs`)

Also called exchangeable covariance (more on this in lecture 3)

- The variance σ^2 is the same at all time points.
- The correlation ρ is the same between all time points.

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	4660	4425	4425	4425	4425
2	4425	4660	4425	4425	4425
3	4425	4425	4660	4425	4425
4	4425	4425	4425	4660	4425
5	4425	4425	4425	4425	4660

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9496	0.9496	0.9496	0.9496
2	0.9496	1.0000	0.9496	0.9496	0.9496
3	0.9496	0.9496	1.0000	0.9496	0.9496
4	0.9496	0.9496	0.9496	1.0000	0.9496
5	0.9496	0.9496	0.9496	0.9496	1.0000

Calcium data: $\hat{\sigma}^2 = 4660$ and $\hat{\rho} = 0.9496$.

Example: Autoregressive pattern (`type=ar(1)`)

The so-called autoregressive covariance structure has

- Constant variance σ^2 over time.
- Correlation decreasing exponentially with the distance between the observations, $\mathrm{Cor}(Y_{ij}, Y_{ik}) = \rho^{|k-j|}$

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	4401	4272	4148	4026	3909
2	4272	4401	4272	4148	4026
3	4148	4272	4401	4272	4148
4	4026	4148	4272	4401	4272
5	3909	4026	4148	4272	4401

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9708	0.9424	0.9148	0.8881
2	0.9708	1.0000	0.9708	0.9424	0.9148
3	0.9424	0.9708	1.0000	0.9708	0.9424
4	0.9148	0.9424	0.9708	1.0000	0.9708
5	0.8881	0.9148	0.9424	0.9708	1.0000

Calcium data: $\hat{\sigma}^2 = 4401$ and $\hat{\rho} = 0.9708$.

Heterogeneous covariance patterns

The assumption that the variance does not change with time can be dropped when assuming a heterogeneous covariance pattern.

- No restrictions on the variances $\sigma_1^2, \ldots, \sigma_n^2$
- Correlations are still assumed stationary; They depend only on the time-distance between observations ...
- ... **equidistant** observations, that is.

Examples: the *heterogeneous compound symmetry*, *heterogeneous autoregressive*, and the *heterogeneous Toeplitz* covariance structures.

proc mixed type	$\mathrm{Cov}(Y_{ij}, Y_{ik})$	parameters
CSH	$\sigma_j\sigma_k[I\{j=k\} + \rho \cdot I\{j \neq k\}]$	$n+1$
ARH(1)	$\sigma_j\sigma_k\rho^{\lvert k-j\rvert}$	$n+1$
TOEPH	$\sigma_j\sigma_k[I\{j=k\} + \rho_{\lvert k-j\rvert} \cdot I\{j \neq k\}]$	$2n-1$

Example: Heterogeneous AR (`type=arh(1)`)

Correlations are similiar to AR(1), but variances differ.

- Correlation decreasing exponentially with the distance between the observations, $\mathrm{Cor}(Y_{ij}, Y_{ik}) = \rho^{|k-j|}$
- Variances $\sigma_1^2, \ldots, \sigma_5^2$ are specific to each time point.

Estimated R Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	4013	4265	4215	4221	3939
2	4265	4774	4719	4725	4409
3	4215	4719	4912	4919	4590
4	4221	4725	4919	5188	4841
5	3939	4409	4590	4841	4758

Estimated R Correlation Matrix for girl 101

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.9744	0.9494	0.9251	0.9014
2	0.9744	1.0000	0.9744	0.9494	0.9251
3	0.9494	0.9744	1.0000	0.9744	0.9494
4	0.9251	0.9494	0.9744	1.0000	0.9744
5	0.9014	0.9251	0.9494	0.9744	1.0000

Calcium data: $\hat{\sigma}_1^2 = 4013, \ldots, \hat{\sigma}_5^2 = 4758$, and $\hat{\rho} = 0.9744$.

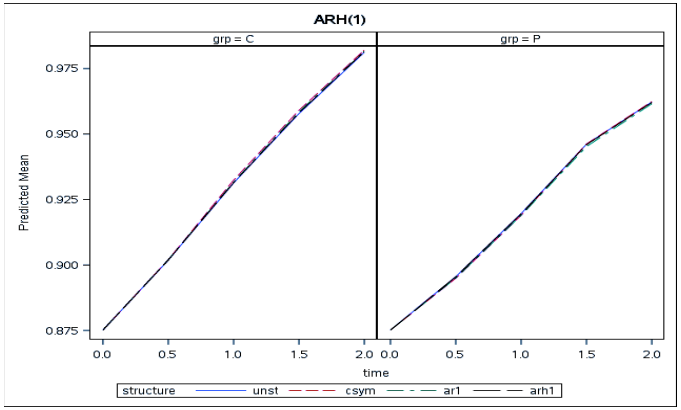
Comparison of covariance structures

Likelihood ratio tests* comparing more restrictive models to the unstructured covariance.

Model	-2 log L	par.	$-2\log Q$	Δdf	P-value
UN	-2352.6	15			
ARH(1)	-2343.4	6	9.2	9	0.42
AR(1)	-2324.8	2	27.8	13	0.0096
CS	-2195.1	2	157.5	13	< 0.0001

* For comparison of covariance patterns either of the likelihood-types (`ml` or `reml`) are ok, just don't compare one to the other.

Estimated means (cLMM)



The estimated response profiles are *almost* identical for all our choices of covariance patterns (due to few missing observations).

Tests of treatment effect

BUT: Confidence intervals and tests depend on the covariance.

Tests of treatment effect* at last follow-up

Covariance pattern	Estimate (95% CI)	P-value
Compound symmetry	19.6 (11.0-28.3)	< 0.0001
Autoregressive	20.1 (7.8-32.4)	0.0014
Heterogeneous autoregr.	19.4 (7.3-31.5)	0.0018
Unstructured	19.0 (6.5-31.4)	0.034

$\star$ Additional gain in BMD with calcium compared to placebo in cLMM.

Warning about compound symmetry

Historically the CS-model has been the standard for modeling longitudinal and other repeated measurments data.

- It is equivalent to the linear mixed model with a random effect of subject (explained in lecture 3).

BUT:

- Correlation tends to decrease with time.
- If this is the case CS overestimates the correlation between baseline and final follow-up.
- This leads to underestimation of the standard error for the change between baseline and final follow-up.
- The p-value for the treatment effect becomes too small and the confidence interval becomes too narrow.

Modeling strategy

How to choose a model according to *Fitzmaurice et al. (2011)*:

1. Put up a plausible (i.e. flexible) model for the mean
2. Fit the data so far ignoring correlation (GLM).
3. Check the residuals for assessing the adequacy of the model for the mean and in order to get an impression of the error covariance.
4. Pick a reasonable model for the covariance (if possible test against the unstructured model)*.
5. Re-check the model fit.
6. Do the analysis.

⋆ But we risk choosing a too restrictive model if power of the test is low.

Outline

Nonequidistant time points

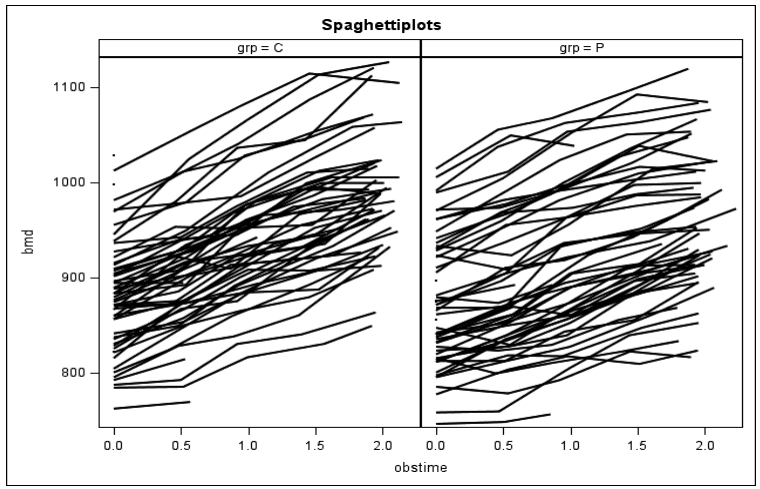
In the calcium study the girls are seen **approximately** twice a year.

- Perhaps we get better estimates of the slopes when replacing planned time of visit with the actual individual times?
- But we loose the option of an unstructured covariance.

Other covariance patterns can still be fitted, e.g.

- the compound symmetry pattern,
- the autoregressive pattern,
- the random regression model (lecture 3).

BMD vs actual time of visit



Non-equidistant observations

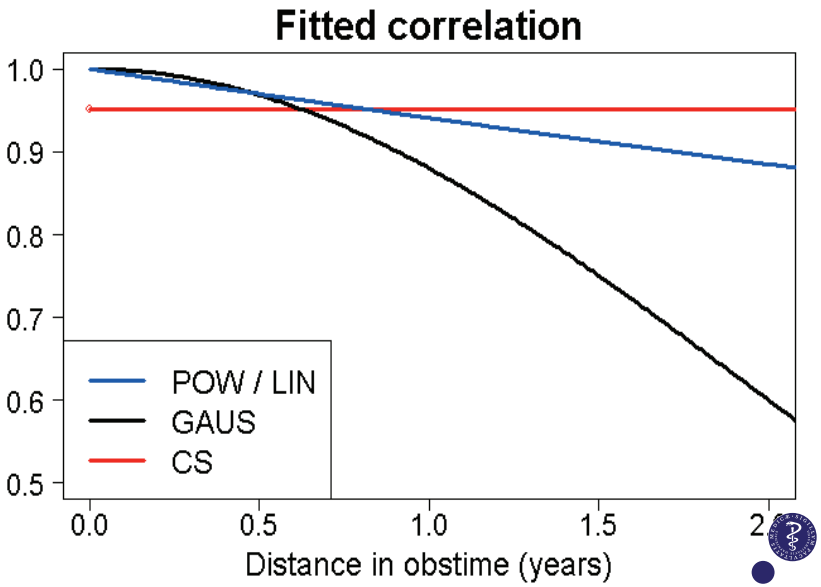
Only a **limited** number of covariance patterns are available in case time points are individual or non-equidistant. All are stationary:

- The variance is constant over time.
- The correlation depend only on the time-distance between the observations.

The `obstime`-variable must be a numerical variable in `SAS`

`proc mixed` type	$\mathrm{Cov}(Y_{ij}, Y_{ik})$	parameters
`CS`	$\sigma^2[I\{j=k\} + \rho \cdot I\{j \neq k\}]$	2
`SP(POW)(obstime)`	$\sigma^2 \rho^{\lvert t_{ij} - t_{ik} \rvert}$	2
`SP(GAU)(obstime)`	$\sigma^2 e^{-\lvert t_{ij} - t_{ik} \rvert^2 / \gamma^2}$	2
`SP(LIN)(obstime)`	$\sigma^2(1 - \rho \lvert t_k - t_j \rvert) \cdot I\{\rho \lvert t_k - t_j \rvert \leq 1\}]$	2

Calcium study: Fit of stationary correlations



Continuous time correlation in SAS

Fit the model with:

- Linear effect of time
- Autoregressive covariance pattern.

```
proc mixed data=calcium plots=all;
class girl grp visit;
model bmd = obstime grp*obstime / ddfm=kr solution cl
                                  outpm=fitctstime;
repeated visit / type=sp(pow)(obstime) subject=girl;
run;
```

ATT: Risk of misspecification due to the more restrictive model.
It's important to check the residuals in the `fitctstime`-dataset.

Continuous time correlation in R

Fit the model with:

- Linear effect of time
- Autoregressive covariance pattern.

```
fit <- gls(bmd~obstime grp*obstime,
           data=calcium,
           correlation=corExp(form=~obstime|girl),
           na.action=na.exclude,
           control=glsControl(opt='optim'))
```

ATT: Risk of misspecification due to the more restrictive model.
It's important to check `residuals(fit, type='pearson')`.

Select output

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
SP(POW)	girl	0.9408
Residual		4371.81

Solution for Fixed Effects

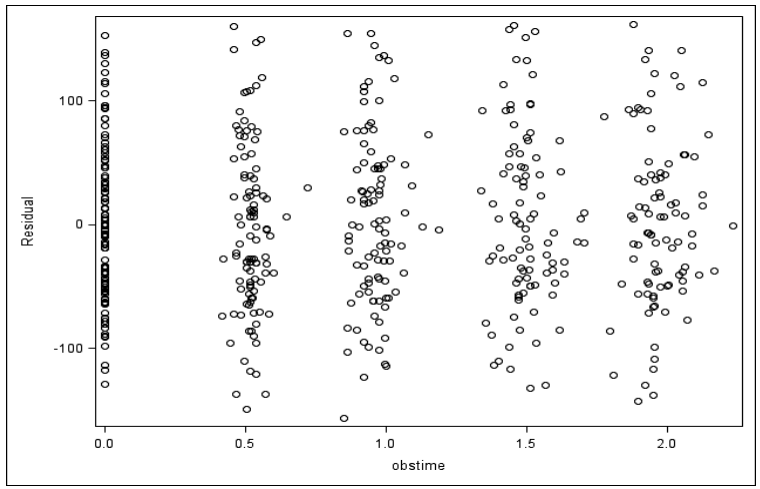
Effect	grp	Estimate	StdError	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		875.23	6.2476	123	140.09	<.0001	0.05	862.86	887.59
obstime		43.7425	2.2460	439	19.48	<.0001	0.05	39.3283	48.1568
obstime*grp	C	10.0152	3.1698	455	3.16	0.0017	0.05	3.7859	16.2444
obstime*grp	P	0	.	.	.	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
obstime	1	423	900.02	<.0001
obstime*grp	1	455	9.98	0.0017

We find an extra increase in BMD of 10.0 mg/cm^3 per year with calcium supplement, 95% CI: 3.8 to 16.2, P=0.0017.

Plot of residuals vs time of observation



Variance looks quite homogeneous.

Estimates and tests of treatment effect

Differences in slopes for different covariance structures:

Covariance pattern	Estimate (95% CI)	P-value
Compound symmetry	9.2 (5.3;13.8)	< 0.0001
Autoregressive	10.0 (3.8;16.2)	0.0017
Linear	10.0 (3.7;16.4)	0.0021
Gaussian	16.5 (5.7;27.3)	0.0028

- Estimates and tests depend on the covariance!

Scheduled vs observed times

Estimated slopes (SE) from the two AR-models:

Group	Scheduled time	Actual time
P	43.23 (2.23)	43.74 (2.25)
C	53.37 (2.29)	53.76 (2.29)
Difference	10.15 (3.16)	10.02 (3.17)
P-value	0.0014	0.0017

Hardly any difference in results!

- Slightly steeper slope estimates (P and C) with actual times (last three visits were on average slightly ahead of schedule).
- Estimated difference in slopes is almost the same.
- As are the standard errors and p-values.

Concluding remarks

Results depend on choice of covariance pattern

- Obvious bias for unrealistic models (independence, CS).
- More similar results for the more complex models.

Not much impact of using exact times of measurement instead of planned times (visit) - WHY?

- There are sophisticated statistical arguments implying that rounding to the nearest scheduled time do not cause bias.
- Assuming that visits are on average on time.
- Variance / standard error may increase if visit times vary a lot.

BUT: We gain in modeling flexibility by rounding the times.

Choosing an apropriate model is a compromise between practical feasibility, realistic model assumptions, and interpretable results.

Outline

Many time points and few subjects

In this situation choosing a reliable model for the covariance is just about impossible.

- Unstructured covariance has too many parameters.
- Compound symmetry underestimates correlation between observations close in time and overestimates correlation between observations far apart in time.
- We have no crystal ball for choosing a simple yet correct covariance pattern.
- Robust standard errors (lecture 5) are anti-conservative.

So what can we do?

Reduction to independent data

By analyzing carefully chosen characteristics for each individual we can resolve to simple analyses which have no repeated measurements issues.

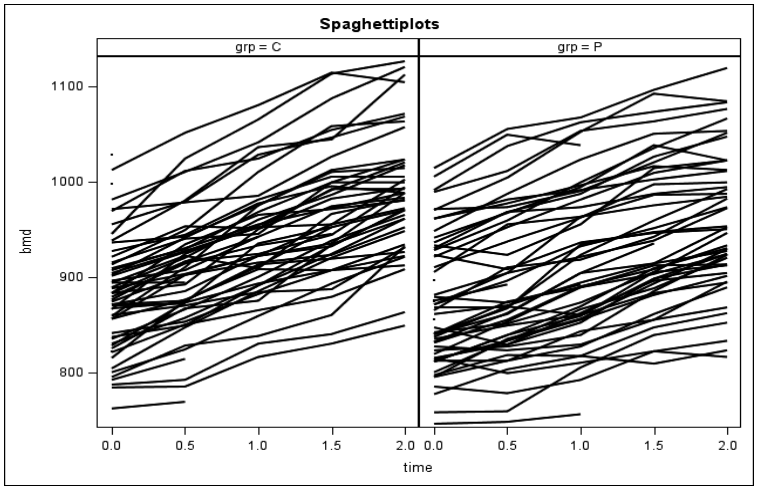
- Maybe not optimal, but feasible – and easy!

Examples of useful summary statistics:

- The changes from baseline to endpoint
- The slopes for individual time effects
- The area under the curve (AUC)
- The time to peak or peak value

Note: Comparing measurements for each time point in turn is *not* recommended without adjustment for multiple testing.

Case: Calcium supplements

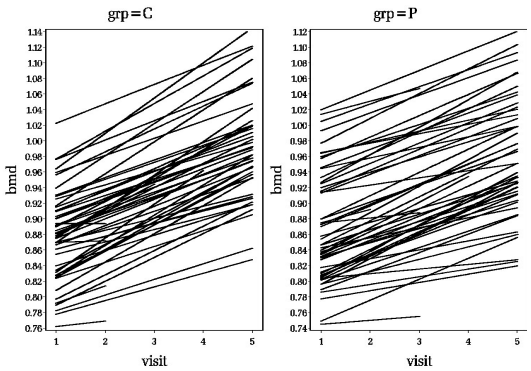


The overall time course looks reasonably linear, but maybe the girls have individual growth rates?

Individual regression

Fit an ordinary linear regression for **each girl**:

$$Y_{ij} = a_i + b_i t_j + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2)$$



Are the slopes of the Calcium group systematically bigger?

Analysis of summary statistics

Comparison of individual intercepts and slopes:

- Use the two-sample t-test for independent data.

Group	Level at baseline (mg/cm^3)	Slope (mg/cm^3 per year)
P	869.7 (851.5;888.0)	41.1 (36.1;46.2)
C	881.7 (865.0;898.5)	49.7 (43.8;55.6)
Dif	12.0 (-12.5;36.5)	8.54 (0.9;16.2)
P-value	0.33	0.029

- Intercepts are similar, since the study is randomized.
- **Note:** smaller slope estimates (P and C) compared to the mixed model analyses. - **WHY?**
- Significantly higher slopes with calcium.

Limitations of summary statistics

No baseline adjustment, hence less power.

Some of the girls in the calcium study dropped out:

- We get less accurate slope-estimates from girls with few observations.
- No slope at all if drop out was right after baseline.
- And maybe those with low BMD are more likely to drop out; Parents think the girl needs supplement and won't risk placebo. This could bias the results.
- **See lecture 6 on missing data!**

Can we make better use of the full data? Next lecture . . .