Designs with Large and Small Units

1. Experimental Units
2. Split Plot Designs
3. Repeated Measures Anova

Study in Dental Medicine

- Can measurement of electric resistance help in detecting tooth decay?
- 40 measurements on teeth with and without inflamed gums, with and without special treatment.
- 2^2 factorial with factor A (inflammation) and factor B (special treatment).

Correct anova table?

Source	df	MS	F
A	1		MS_A/MS_{res}
B	1		MS_B/MS_{res}
AB	1		MS_{AB}/MS_{res}
Residual	36		
Total	39		

Depends on design structure. How many subjects, how many teeth?

8 subjects, one tooth each

One treatment per person, 5 repeated measurements

Stratum	Source	df	F
Person	A	1	$MS_A/MS_{res-person}$
	B	1	$MS_B/MS_{res-person}$
	AB	1	$MS_{AB}/MS_{res-person}$
	Residual	4	
	Total	7	
Measurement	Residual	32	
	Total	39	

5 subjects, 4 teeth each

Each person has 2 inflamed and 2 not inflamed teeth. Each tooth was measured once with special treatment and once without special treatment.

Stratum	Source	df	F
Person	Person	4	
Tooth	A	1	$MS_A / MS_{res-tooth}$
	Residual	14	
	Total	15	
Measurement	B	1	$MS_B / MS_{res-meas}$
	AB	1	$MS_{AB} / MS_{res-meas}$
	Residual	18	
	Total	20	
	Total	39	

Special properties of this design

- Replication on three stages: persons, teeth and measurements.
- One factor varies between teeth, the other between measurements.
- main plot= tooth, sub-plot = measurement

Split-plot design

- A first factor needs to be applied to large plots, called main plots.
- Main plots are split into smaller plots, called subplots. These are assigned to different levels of a second factor.
- Two different levels for comparing factor levels: effects of the first factor must be examined relative to main plot variation, effects of the second factor must be examined relative to subplot variation.

Rice experiment

4 irrigation methods I1-I4 on main plots, 3 fertilizer mixtures x, y, z on sub-plots, 2 complete replicates.

Layout:

Block I				Block II			
z	x	y	z	x	y	z	x
x	z	z	y	z	x	x	y
y	y	x	x	y	z	y	z
I4	I2	I3	I1	I2	I1	I4	I3

Irrigation is confounded with main plots.

Skeleton Anova

Stratum	Source	df		F
Blocks	Blocks		1	
Main plots	Irr	3		$MS_{Irr}/MS_{res-main}$
	Residual	3		
	Total		6	
Sub-plots	Fert	2		$MS_{Fert}/MS_{res-sub}$
	Irr:Fert	6		$MS_{Irr:Fert}/MS_{res-sub}$
	Residual	8		
	Total		16	
	Total		23	

Model

$$Y_{ijk} = \mu + b_i + Irr_j + \epsilon_{ij} + Fert_k + (Irr : Fert)_{jk} + \delta_{ijk}$$

$i = 1, \ldots, I; j = 1, \ldots, J; k = 1, \ldots, n.$

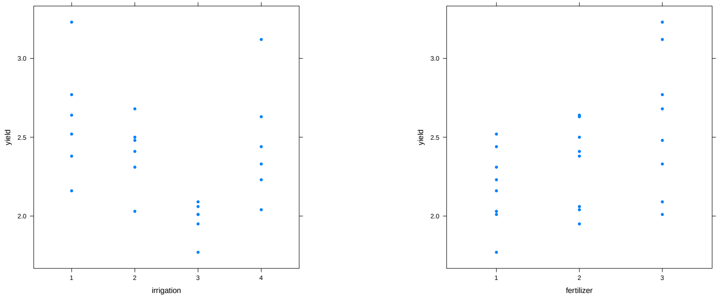
b_i	: ith block effect	$b_i \sim \mathcal{N}(0, \sigma_b^2)$
Irr_j	: jth effect of irrigation	
ϵ_{ij}	: main plot error	$\epsilon_{ij} \sim \mathcal{N}(0, \sigma_e^2)$
$Fert_k$	: kth effect of fertilizer	
$(Irr : Fert)_{ij}$	: jkth interaction	
δ_{ijk}	: sub-plot error	$\delta_{ijk} \sim \mathcal{N}(0, \sigma_d^2)$

Data on crop yield (tonnes/hectare)

	Irrigation			
Block I	I1	I2	I3	I4
Fertilizer x	2.16	2.03	1.77	2.44
y	2.38	2.41	1.95	2.63
z	2.77	2.68	2.01	3.12

	Irrigation			
Block I	I1	I2	I3	I4
Fertilizer x	2.52	2.31	2.01	2.23
y	2.64	2.50	2.06	2.04
z	3.23	2.48	2.09	2.33

Graphical display



Anova Table

```
>mod2=aov(yield~irrigation*fertilizer+Error(block/irr..))
>summary(mod2)
Error: block
          Df    Sum Sq   Mean Sq F value Pr(>F)
Residuals  1 0.0003375 0.0003375

Error: block:irrigation
           Df  Sum Sq Mean Sq F value Pr(>F)
irrigation  3 1.32971 0.44324  2.0424 0.2862
Residuals   3 0.65105 0.21702

Error: Within
                      Df  Sum Sq Mean Sq F value   Pr(>F)
fertilizer             2 0.67530 0.33765 16.6262 0.001414
irrigation:fertilizer  6 0.20110 0.03352  1.6504 0.250110
Residuals              8 0.16247 0.02031
```

Longitudinal data

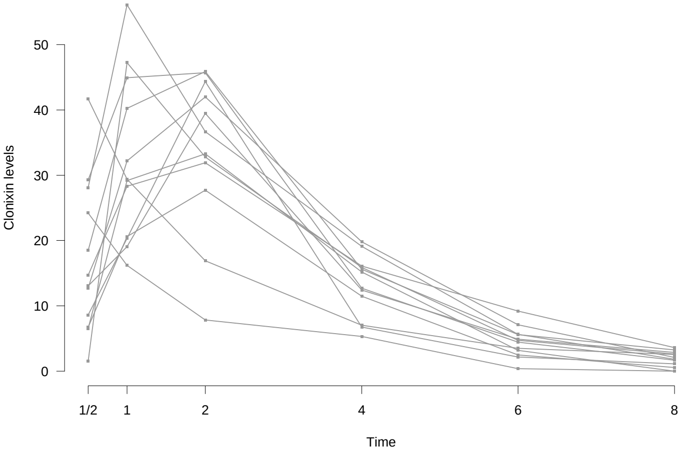
- Subjects are measured more than once
  - Compare values of an outcome variable before and after a treatment
  - Look at changes over time in an outcome variable
- Measurements at the same unit are correlated with each other

Rheumatoid arthritis

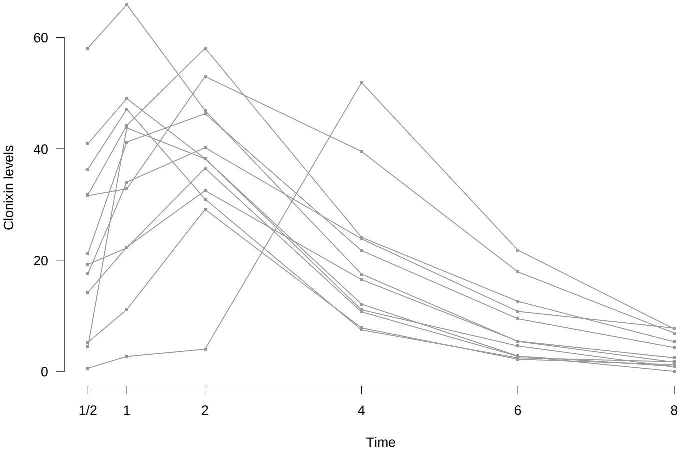
Patients with rheumatoid arthritis and normal controls obtained an anti-inflammatory analgesic. Serum clonixin levels (in mg/ml) were measured 1/2, 1, 2, 4, 6 and 8 hours after administration of a single dose of three 250 mg tablets of clonixin.

	Time (in hours)					
Subject	1/2	1	2	4	6	8
1	12.70	32.20	42.00	19.80	7.09	2.10
2	18.48	40.24	45.87	15.61	5.58	3.25
3	6.70	20.60	27.70	11.49	2.48	0.56
4	24.20	16.20	7.84	5.30	0.38	0.00
⋮	⋮					

Patients with arthritis



Controls



How to analyze the data?

- Separate analysis at each time point
- Summary measure: mean, maximal value, time until maximal value, steepest slope, area under curve (AUC)
- Repeated measures anova, split-plot approach: subjects=main plots, subject× time=subplot.
  - Critical assumption is sphericity: same variance of measurements at each time point and the same correlation between measurements taken at different times.
  - Correction for deviation from sphericity: Greenhouse-Geisser, Huynh-Feldt
- Mixed-effects model

Anova table

Stratum	Source	df		F
Person	Treatment	1		$MS_{treat}/MS_{res-Person}$
	Residual	22		
	Total		23	
Person $\times$ Time	Time	5		$MS_{time}/MS_{res-Person\times time}$
	Treatment $\times$ Time	5		
	Residual	110		
	Total		120	
	Total		143	

R Output

```
>mod1=aov(clonixin~time*group+Error(id),data=rheuma.long)
>summary(mod1)

Error: id
          Df Sum Sq Mean Sq F value  Pr(>F)
group      1  658.4  658.44  3.0483 0.09477 .
Residuals 22 4752.0  216.00
---


Error: Within
                    Df  Sum Sq Mean Sq F value Pr(>F)
time                 5 22152.8  4430.6 42.0703 <2e-16 ***
time:group           5   138.2    27.6  0.2624 0.9326
Residuals          110 11584.5   105.3
```

Other types of split-plot designs

- Repeated splitting: a third factor may be applied to sub-subplots
- Confounding interactions of sub-plot factors in split-plot designs
- Other designs for main plots, e.g. Latin squares
- Strip-plot design