Crossover designs and Latin Squares

- Persons as blocks
- More than one block factor
- Carry-over effect

Crossover designs

Each person gets several treatments.
block = person, experimental unit = person$\times$time

Example: Wine-tasting

	Judge							
Tasting	1	2	3	4	5	6	7	8
1	2	4	4	2	1	2	4	4
2	1	3	1	4	4	4	2	3
3	3	2	2	3	3	1	1	1
4	4	1	3	1	2	3	3	2

Randomisation: Tasting order of wines

Question: Is this a good design?

Row-Column-Design

- Each judge tastes each wine equally often ($1\times$),
  person$=$block
- Each wine gets equally often tasted first, second, third, fourth ($2\times$).
  position in tasting order$=$block

$\Longrightarrow$ 2 systems of blocks
persons (columns), position (rows)

A Latin square of order n is an arrangement of n symbols in a $n \times n$ square array in such a way that each symbol occurs once in each row and once in each column.

A	B	C	D
B	D	A	C
C	A	D	B
D	C	B	A

A	B	C	D	E	F
B	C	D	E	F	A
C	D	E	F	A	B
D	E	F	A	B	C
E	F	A	B	C	D
F	A	B	C	D	E

Construction of Latin Squares

Cyclic method:

- Write the letters in the top row in any order.
- In the second row, shift the letters one place to the right.
- Continue like this . . .

Interpretation:
n^2 plots

- 2 system of blocks, 1 factor
- 1 system of blocks, 2 factors
- 3 factors

Take a Latin square of order *n* and superimpose upon it a second square with treatments denoted by greek letters. The two squares are orthogonal if each Latin letter occurs with each greek letter exactly once. The resulting design is a Graeco-Latin Square.

Aα	Bβ	Cγ	Dδ	Eϵ
Bγ	Cδ	Dϵ	Eα	Aβ
Cϵ	Dα	Eβ	Aγ	Bδ
Dβ	Eγ	Aδ	Bϵ	Cα
Eδ	Aϵ	Bα	Cβ	Dγ

Construction Row-Column-Design

Take two Latin squares of size 4.

		Judge							
		1	2	3	4	5	6	7	8
	1	A	B	C	D	A	B	C	D
Tasting	2	B	C	D	A	C	D	A	B
	3	C	D	A	B	B	A	D	C
	4	D	A	B	C	D	C	B	A

Randomly permute the rows and columns

Permutation 3241

			Judge							
			1	2	3	4	5	6	7	8
	3	1	C	D	A	B	B	A	D	C
Tasting	2	2	B	C	D	A	C	D	A	B
	4	3	D	A	B	C	D	C	B	A
	1	4	A	B	C	D	A	B	C	D

Permutation 52134687

		Judge							
		5	2	1	3	4	6	8	7
		1	2	3	4	5	6	7	8
	1	B	D	C	A	B	A	C	D
Tasting	2	C	C	B	D	A	D	B	A
	3	D	A	D	B	C	C	A	B
	4	A	B	A	C	D	B	D	C

Model for a Crossover Design

$$Y_{ij} = \mu + p_i + z_j + T_{k(ij)} + \epsilon_{ij}$$

p_i and z_j are person and position effect (both random).
A unit (i, j) gets exactly one treatment (wine) $k(ij)$.
$T_{k(ij)}$ is the effect of wine $k(ij)$.

Anova Table

Sum of squares partition:

$$SS_{tot} = SS_{persons} + SS_{position} + SS_{treat} + SS_{res}$$

Source	df	MS	F
Persons	7		
Tasting	3		
Wine	3	MS_{Wine}	MS_{Wine}/MS_{res}
Residual	18	MS_{res}	
Total	31		

Properties of Crossovers

+ more efficient than parallel designs, lower costs
- no treatment should leave a subject in a very different state at the end of the period (cure, death)
- drop-out more likely
- experimental situation $\neq$ real situation
  sequence one treatment
- carry-over effect: treatment effect lasts into subsequent time-period

  $\boxed{A}$ $\boxed{B}$

  $\uparrow$

  effect of B + lasting effect of A

Pain Medication

36 subjects with chronic pain take three different drugs on demand
response: hours without pain

T_1	T_2	T_3	T_1	T_3	T_2	T_2	T_1	T_3
6	8	7	6	6	5	2	8	7
4	4	3	7	3	3	0	8	11
13	0	8	6	0	2	3	14	13
5	5	4	8	11	10	3	11	12
8	12	5	12	13	11	0	6	6
4	4	3	4	13	5	2	11	8

T_2	T_3	T_1	T_3	T_1	T_2	T_3	T_2	T_1
8	7	12	6	14	4	12	11	7
4	3	6	4	4	6	1	7	9
2	12	10	4	13	0	5	12	8
2	0	9	0	9	3	2	3	14
3	5	11	1	6	8	4	5	6
1	10	11	8	12	5	6	6	5

Anova Table

Source	SS	df	MS	F	P-Wert
Persons	503.6	35	14.4		
Time-period	192.1	2	96.0		
Medication	268.7	2	134.3	14.4	$6.1\cdot 10^{-6}$
Residual	632.6	68	9.3		
Total	1596.9	107			

Treatment comparison:
se $= \sqrt{2MS_{res}/36} = 0.72$
qtukey(0.95,3,68)$/\sqrt{2} = 2.396 \Longrightarrow$ HSD$=$1.725

$T_1 - T_2 = 3.84 \quad T_1 - T_3 = 2.34 \quad T_2 - T_3 = -1.50$

Carry-over Effect

Carry-over effect = Interaction treatment $\times$ time-period

	time-period 1	time-period 2
group 1	T_1	T_2
group 2	T_2	T_1

Approaches:

- wash-out period
- include interaction term in the model
- design for carry-over effects:

A B B		A B B A
	or	
B A A		B A A B