From Rothamsted to Northwick Park: designing experiments to avoid bias and reduce variance

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Experiments are important in medicine, agriculture, engineering, "pure" physics, ..., and many, many areas of enquiry.

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We aim to make variance small.

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Better quality experiments enable us to make better quality decisions to make better use of Earth's resources and to save lives.

Bias II: randomization

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write down a systematic plan then permute it by a randomly-chosen permutation.

Lanarkshire milk experiment: early 20th century

Treatments: extra milk rations or not.
These should have been randomized to the children within each school.
The teachers decided to give the extra milk rations to those children who were most undernourished.

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Broadbalk

I worked in the Statistics Department there from 1981 to 1990.

An experiment at Rothamsted that I designed

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If the total $n+m$ is fixed, the value of $\dfrac{1}{nm}$ is smallest when $|m-n|\leq 1$.

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\text{new variance is smaller} \quad &\iff \quad \frac{1}{(n+1)(m-1)} < \frac{1}{nm} \\
&\iff \quad (n+1)(m-1) > nm \\
&\iff \quad nm + m - n - 1 > nm \\
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If $m-n \geq 2$ (or $n-m \geq 2$), we can change the replications to get a design with smaller variance. □

Variance IV: many varieties

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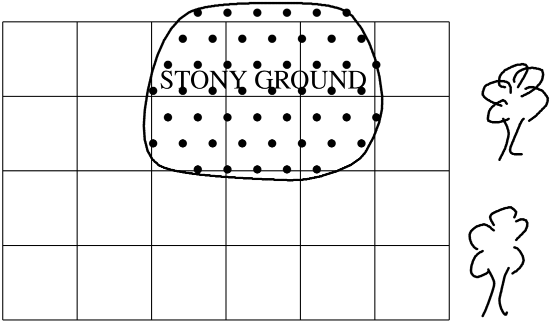
Blocking

We have 6 varieties to compare in this field. How do we avoid bias?



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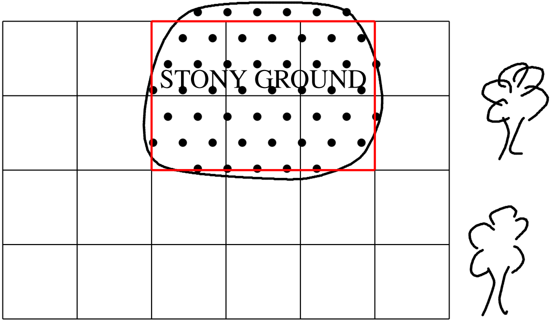

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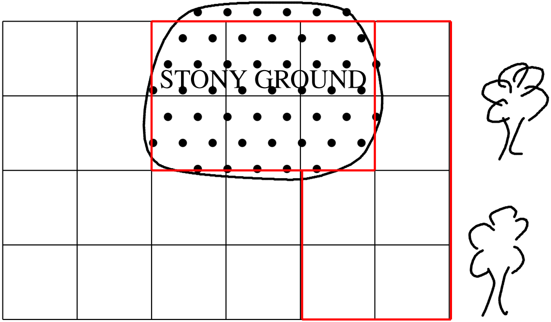

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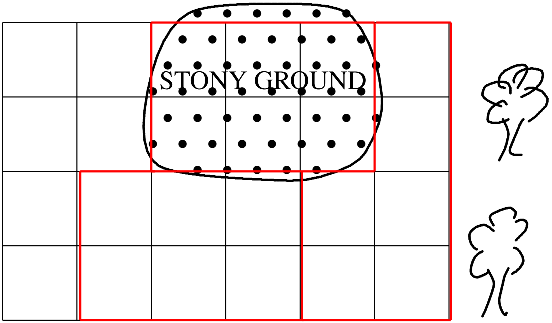

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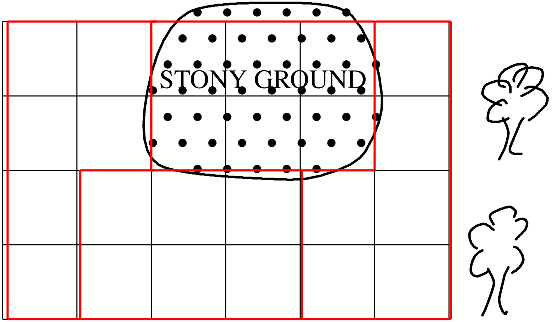

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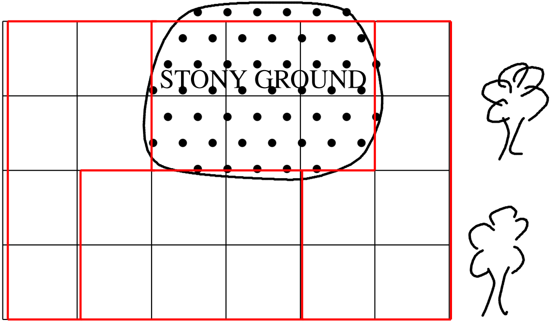
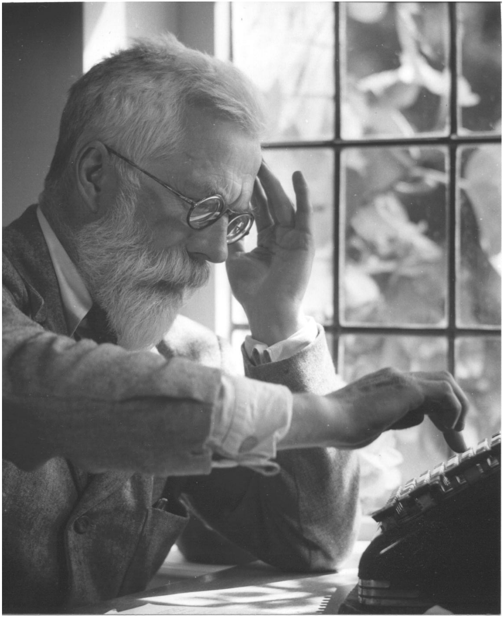


Partition the experimental units into homogeneous blocks
and apply each treatment to one plot in each block.

R. A. Fisher, statistician at Rothamsted 1919–1933



- randomization
- replication
- blocking

1952 portrait by Barrington Brown, reproduced by permission of the Fisher Memorial Trust

Incomplete blocks

What do we do if the blocks are too small for each one to contain all the treatments?

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A design for v treatments in b blocks of size k is balanced if there is some constant λ such that every pair of treatments occur together in precisely λ blocks.

Two designs with $v = 7$, $b = 7$, $k = 3$: columns are blocks

1	2	3	4	5	6	7
2	3	4	5	6	7	1
4	5	6	7	1	2	3

balanced ($\lambda = 1$)

1	2	3	4	5	6	7
2	3	4	5	6	7	1
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non-balanced

Results about balanced incomplete-block designs

v = number of treatments b = number of blocks
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2. *BIBDs do not exist for all values of v, b and k.*
3. *If there is a BIBD, then it gives the minimum average variance of pairwise differences.*

Kirkman's Schoolgirls Problem (1847)

There are 15 schoolgirls in a certain class.
Every day, they go for a walk, and the teacher insists that they walk in groups of size 3.
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Homework

Solve Kirkman's Problem for 15 *schoolgirls.*

From Rothamsted to London

In 1991 I left Rothamsted and joined the University of London.

I have continued to help with the design of experiments in many areas, such as

- human–computer interaction
- biomaterials
- two-phase variety trials
- biodiversity in freshwater systems
- genomics
- a cross-over grazing trial
- the effect of plant spacing on insect populations.

New Delhi, December 2006

Experiments in microarrays

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these are block designs with all blocks of size 2.

So which designs have the smallest average variance of the estimates of pairwise differences?

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12 blocks (edges)

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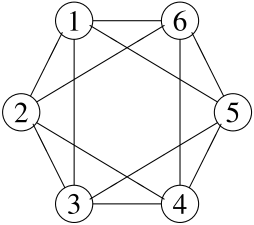

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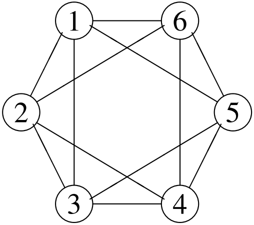

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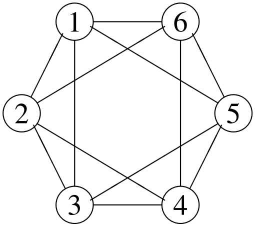

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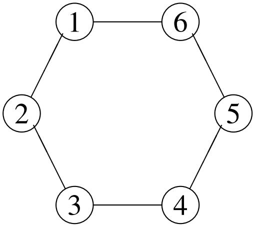

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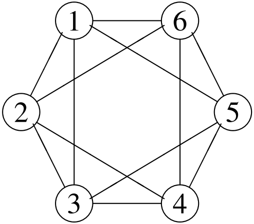

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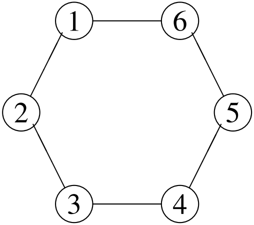

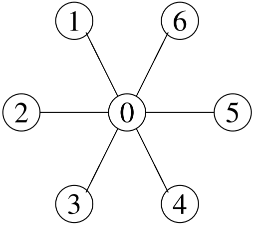

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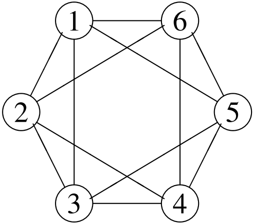

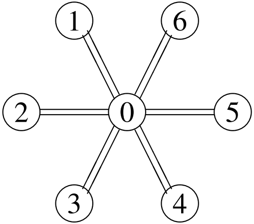

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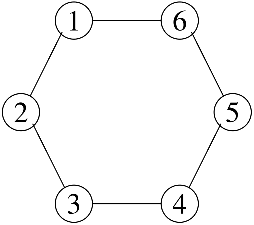
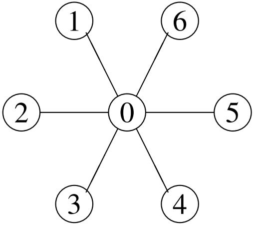
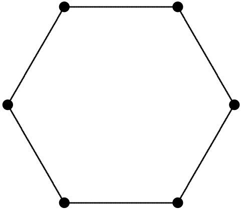


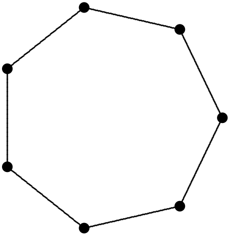


Designs with smallest variance when $k = 2$ and $b = v$

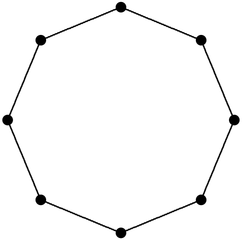
$v = 6$



$v = 7$



$v = 8$



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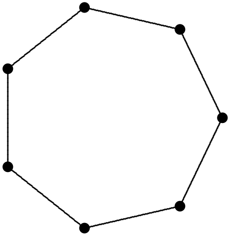

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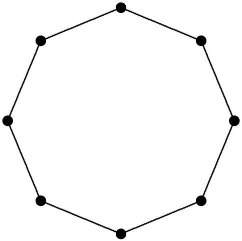
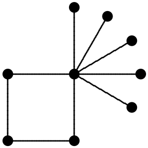


$v = 9$



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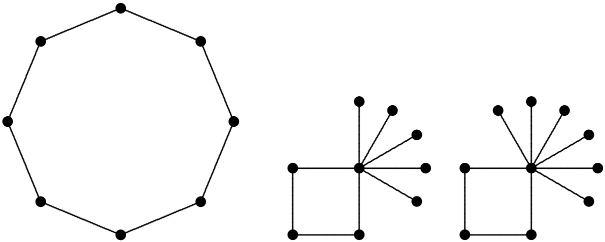

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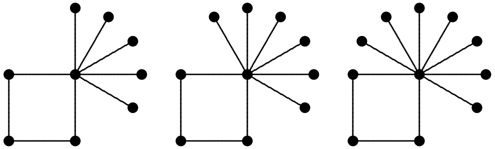
$v = 9$ $\quad$ $v = 10$ $\quad$ $v = 11$



Designs with average replication less than 2.5

Which designs have the smallest variance
when average replication is low,
for arbitrary block size?

Research is still ongoing.

There are many strange results.

Northwick Park: the TeGenero trial

First-in-Man trial of a monoclonal antibody on healthy volunteers, March 2006: 4 cohorts of 8 volunteers each.

Cohort	TGN1412		Placebo
	Dose mg/kg body-weight	Number of Subjects	Number of Subjects
1	0.1	6	2
2	0.5	6	2
3	2.0	6	2
4	5.0	6	2

What happened to Cohort 1 on 13 March 2006

Healthy Volunteer	Randomized to	Time of intravenous administration	Time of transfer to critical care
A	TGN1412 8.4mg	0800	2400
B	Placebo	0810	
C	TGN1412 6.8mg	0820	2350
D	TGN1412 8.8mg	0830	0030
E	TGN1412 8.2mg	0840	2040
F	TGN1412 7.2mg	0850	0050
G	TGN1412 8.2mg	0900	0100
H	Placebo	0910	

The Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies: Membership

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Sheila Bird, Principal Scientist/Statistician, MRC Biostatistics Unit
Barbara Bogacka, Reader in Probability and Statistics, QMUL
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Recommendations include

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Planned analysis of the TeGenero trial

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	6	2
2	2	6	2
3	3	6	2
4	4	6	2

If all responses are uncorrelated with variance σ^2 then
Variance (dose $i -$ placebo) in cohort i is $\left(\frac{1}{6}+\frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2$

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- Different types of people can volunteer at different times.

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There have been many trials, in many topics, where, with hindsight, cohort effects swamp treatment effects.

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The Experimental Medicines Group of the Association of the British Pharmaceutical Industry (ABPI) says that trials should always be designed on the assumption that there will be cohort effects.

Analysis of the TeGenero trial with cohort effects

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$$\text{Variance (dose } i - \text{ placebo) in cohort } i = \left(\frac{1}{6} + \frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2.$$

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$$\text{So variance (dose } i - \text{ dose } j) = \left(\frac{2}{3} + \frac{2}{3}\right)\sigma^2 = \frac{4}{3}\sigma^2.$$

Senn's proposed design

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	4	4
2	2	4	4
3	3	4	4
4	4	4	4

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The TeGenero design is inadmissible because everything can be estimated, from the same resources, with smaller variance, by another design.

Dose-escalation trials: standard designs

There are n doses, with dose $1 <$ dose $2 < \cdots <$ dose n.

0 denotes the placebo.

There are n cohorts of m subjects each.

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In Cohort i, some subjects receive dose i;
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Put $s_{ki} =$ number of subjects who get dose i in cohort k. Then

$$s_{ki} > 0 \quad \text{if} \quad i = k$$
$$s_{ki} = 0 \quad \text{if} \quad i > k.$$

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so define the scaled variance v_{ij} to be

$$\frac{\text{Variance (dose } i - \text{ dose } j) \times \text{number of observations}}{2(n+1)\sigma^2}.$$

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Aim:

- only doses 0 and k in cohort k
- equal replication overall.

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Example: $n = 4$, $m = 10$

Dose	0	1	2	3	4
Cohort 1	2	8	0	0	0
Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
Cohort 4	2	0	0	0	8

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$$v_{0i} = \frac{n+1}{2} \qquad v_{ij} = n+1$$

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Example: $n = 4$, $m = 8$

Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
Cohort 2	4	0	4	0	0
Cohort 3	4	0	0	4	0
Cohort 4	4	0	0	0	4

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Cohort 4	4	0	0	0	4

$$v_{0i} = \frac{2n}{n+1} \qquad v_{ij} = \frac{4n}{n+1}$$

Lessons from experience with block designs: I

The design is effectively a block design, with the cohorts as blocks.

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Principle

In each cohort, no treatment should be allocated to more than half of the subjects.

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Aim:

- make pairwise variances lower than in other designs, whether or not there are cohort effects.

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In Cohort 1: $\frac{m}{2}$ subjects get dose 1; $\frac{m}{2}$ subjects get placebo.

In Cohort k: $\frac{m}{2}$ subjects get dose k; remaining subjects are allocated as equally as possible to treatments 0 to $k-1$, with larger values given to make the 'replication so far' as equal as possible.

Example of a uniform halving design

Example: $n = 4$, $m = 8$

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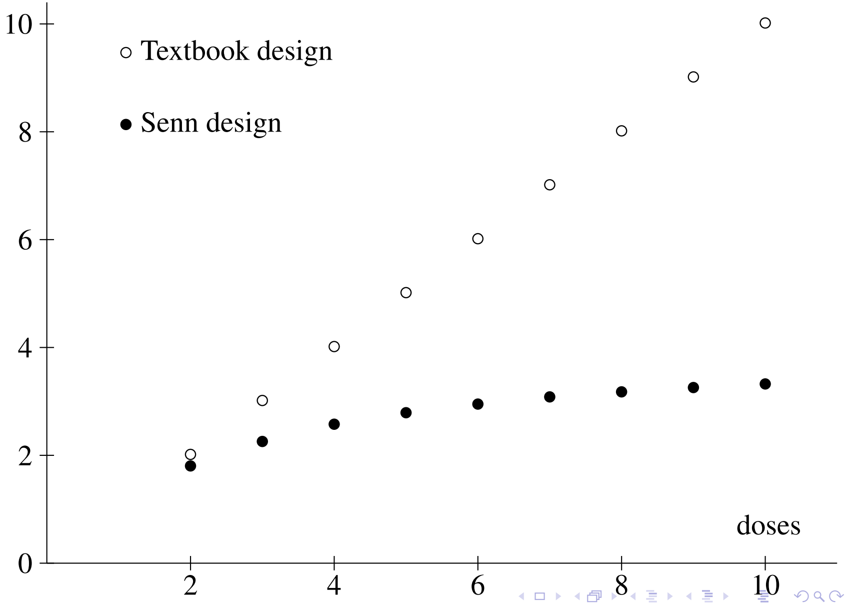
Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4

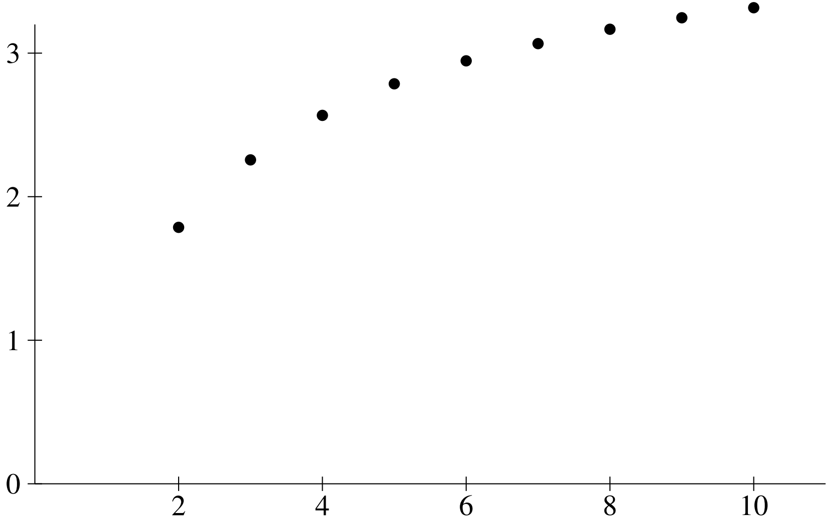
The scaled variances v_{ij} have to be calculated numerically.

Average scaled pairwise variance



Average scaled pairwise variance: continued

- Senn design



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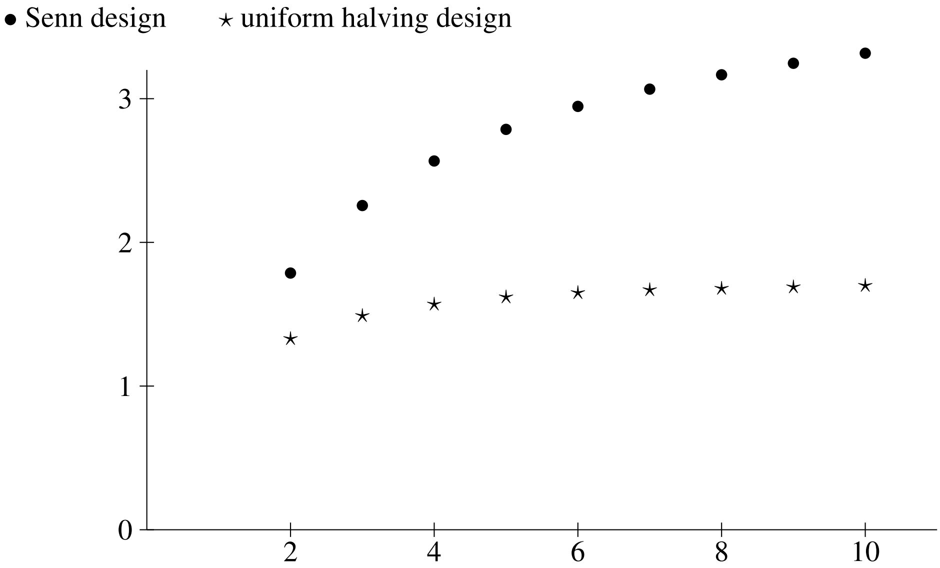

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In the standard designs, the highest dose has all of its subjects in the final cohort.

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In the standard designs, the highest dose has all of its subjects in the final cohort.

In ordinary block designs, you would never limit any treatment to just one block.

Principle

There should be one more cohort than there are doses, so that every dose can occur in at least two cohorts.

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In Cohort $n+1$, any dose, or placebo, may be used.

Extended Senn design

In the final cohort,
compensate for the previous over-replication of placebo.

$$s_{n+1,i} = \begin{cases} 0 & \text{if } i = 0 \\ \dfrac{m}{n} & \text{otherwise} \end{cases}$$

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Example: $n = 4$, $m = 8$

Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
Cohort 2	4	0	4	0	0
Cohort 3	4	0	0	4	0
Cohort 4	4	0	0	0	4
Cohort 5	0	2	2	2	2

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Cohort 5	0	2	2	2	2

$$v_{0i} = \frac{2(n^2+4)}{n(n+4)} \qquad v_{ij} = \frac{4n}{n+4}$$

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About half the subjects in the final cohort are equally split between all treatments,
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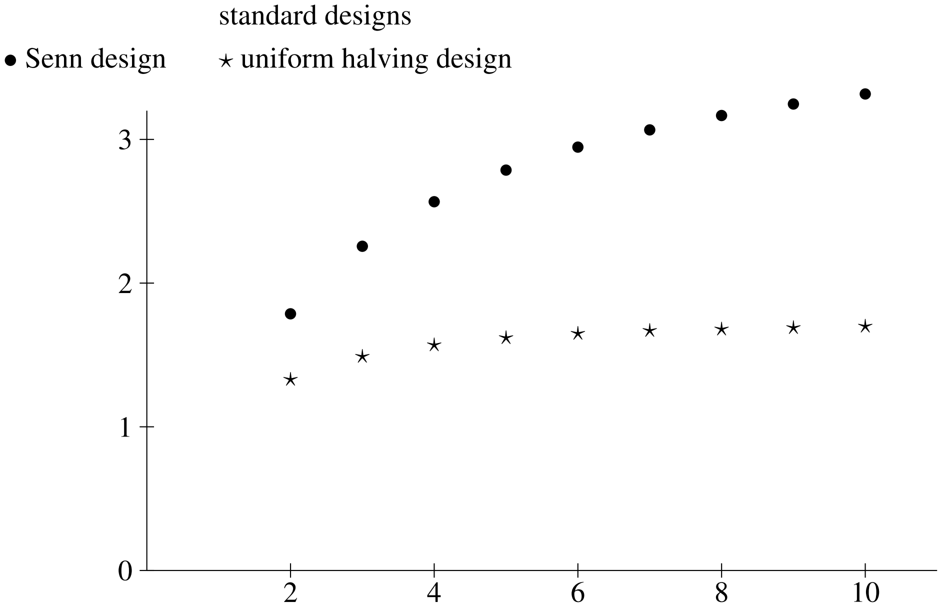
					1
				1	1
Cohort 5	1	1	1	2	3

Average scaled pairwise variance: continued (again)



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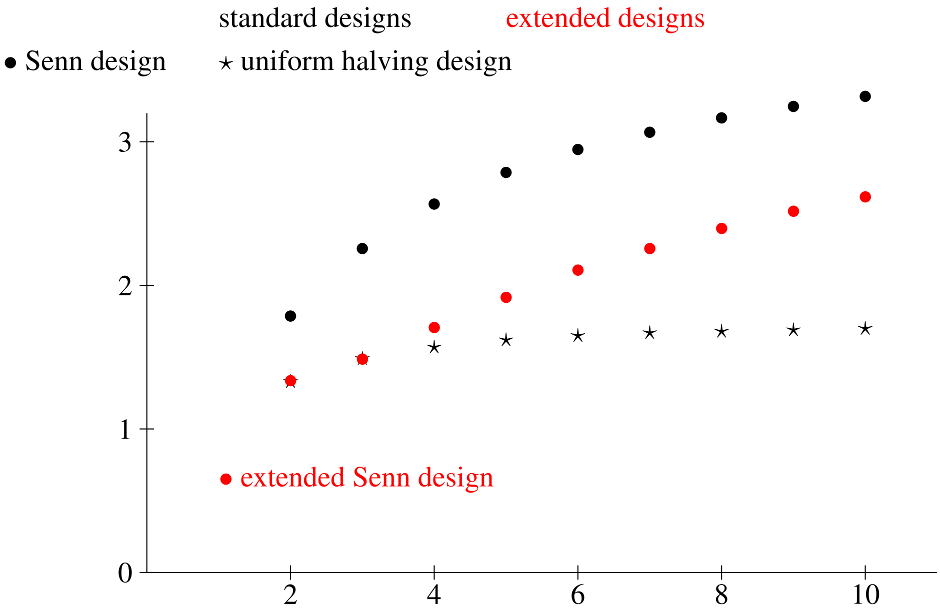

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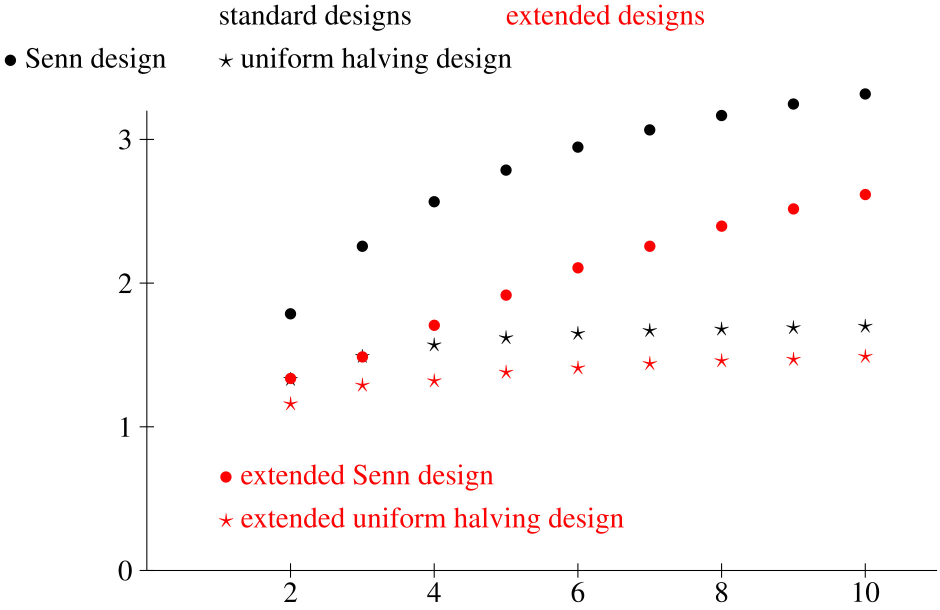

Two designs for 4 doses using 40 subjects

Numbers of subjects

Std TB

Dose	0	1	2	3	4
Cohort 1	2	8	0	0	0
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Cohort 3	2	0	0	8	0
Cohort 4	2	0	0	0	8

Actual pairwise variances/σ^2

	1	2	3	4
0	0.625	0.625	0.625	0.625
1		1.250	1.250	1.250
2			1.250	1.250
3				1.250

Ext UH

Dose	0	1	2	3	4
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Principle

In each cohort,
half of the subjects should be distributed (approximately) equally among all the treatments that have been used in any previous cohort;
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- Don't be afraid to transfer design principles from one area of science to another.