Designs for dose-escalation trials

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How should such trials be designed?

Standard designs

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

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There are n cohorts of m subjects each.

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Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, some subjects receive dose i;
no subject receives dose j if $j > i$.

Put $s_{ki} =$ number of subjects who get dose i in cohort k. Then

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

How to assess designs?

I shall treat cohort effects as fixed
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(there is analogous work for random cohort effects).

I shall seek to minimize the average of the pairwise variances,
comparing dose i with dose j for $0 \leq i < j \leq n$.
(Another approach is to concentrate on comparisons with placebo
and seek to minimize the average of the variances for
comparing dose 0 with dose j for $1 \leq j \leq n$.)

Scaled variance

Assume that the expectation of the response of a subject who gets dose i in cohort k is $\tau_i + \beta_k$,
and that responses are uncorrelated with common variance σ^2.

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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
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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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Cohort 4	2	0	0	0	8

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

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Example: $n = 4, m = 8$

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

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

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In 2006–2009 I investigated various patterns of design satisfying these principles.

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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.

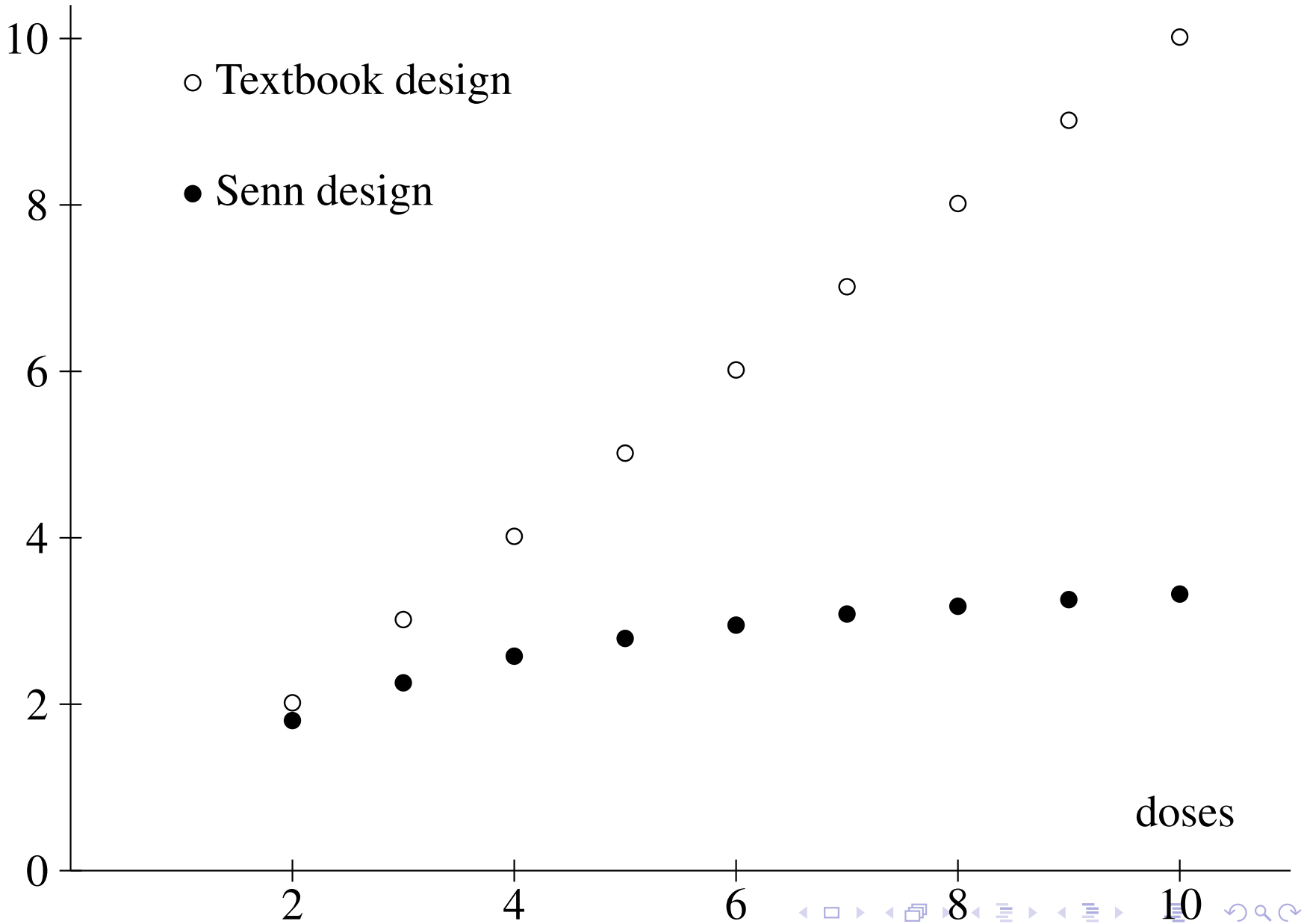
Example of a uniform halving design

Example: $n = 4, m = 8$

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

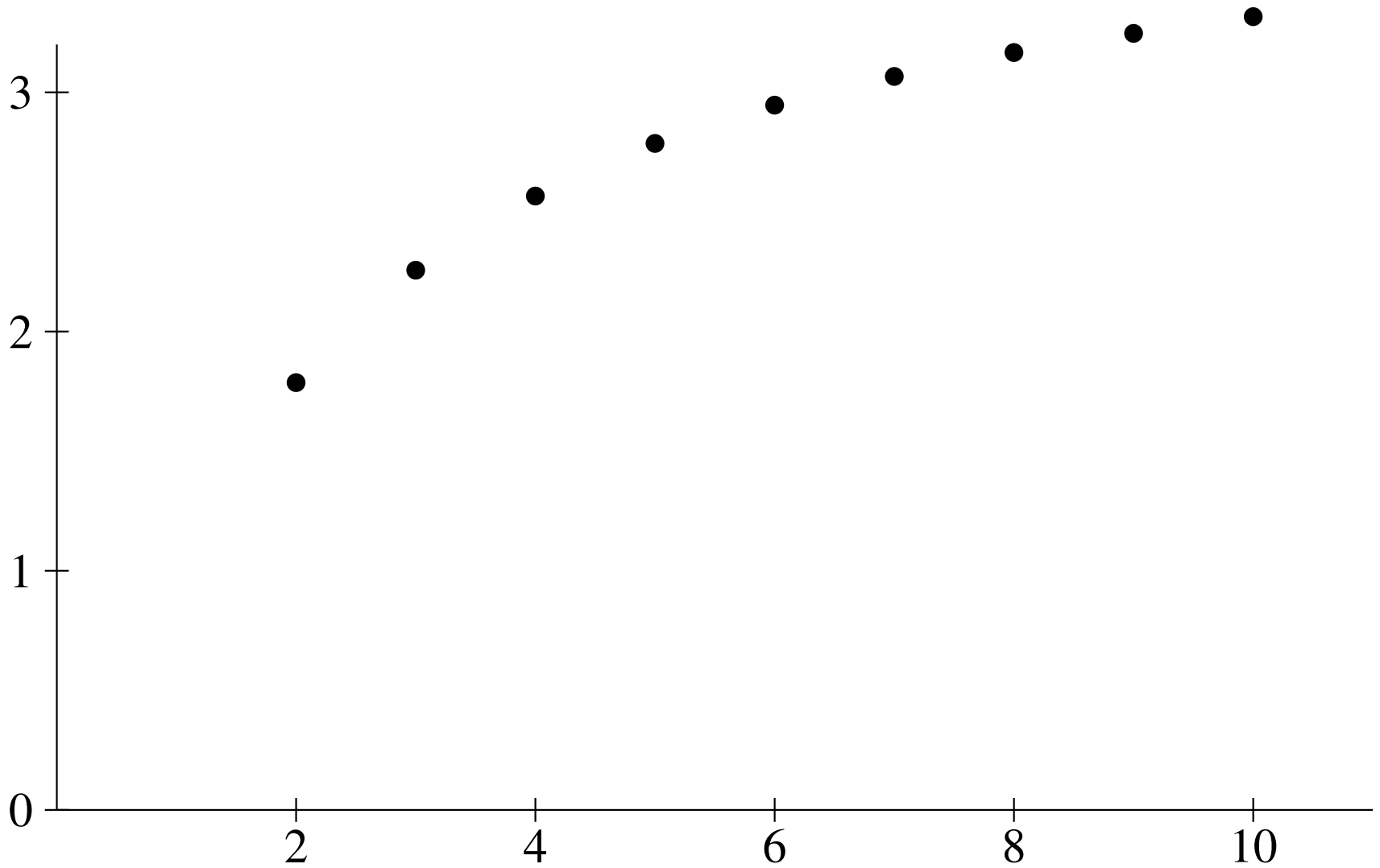
The scaled variances v_{ij} have to be calculated numerically.

Average scaled pairwise variance



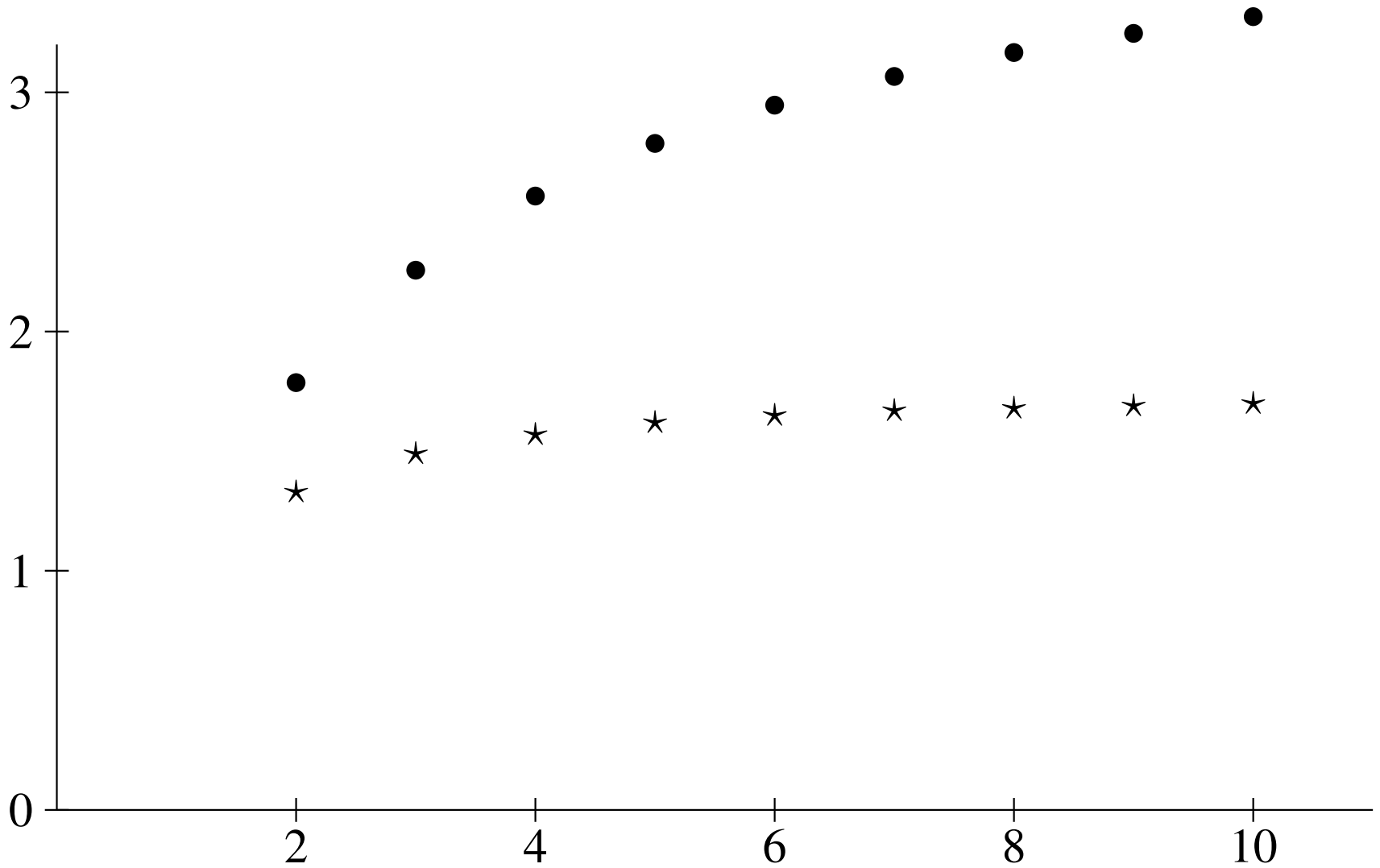
Average scaled pairwise variance: continued

- Senn design



Average scaled pairwise variance: continued

• Senn design ⋆ uniform halving design



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the highest dose has all of its subjects in the final cohort.

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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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no subject receives dose j if $j > i$.

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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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	1	1
					1
				1	1
Cohort 5	1	1	1	2	3

Average scaled pairwise variance: continued (again)

standard designs

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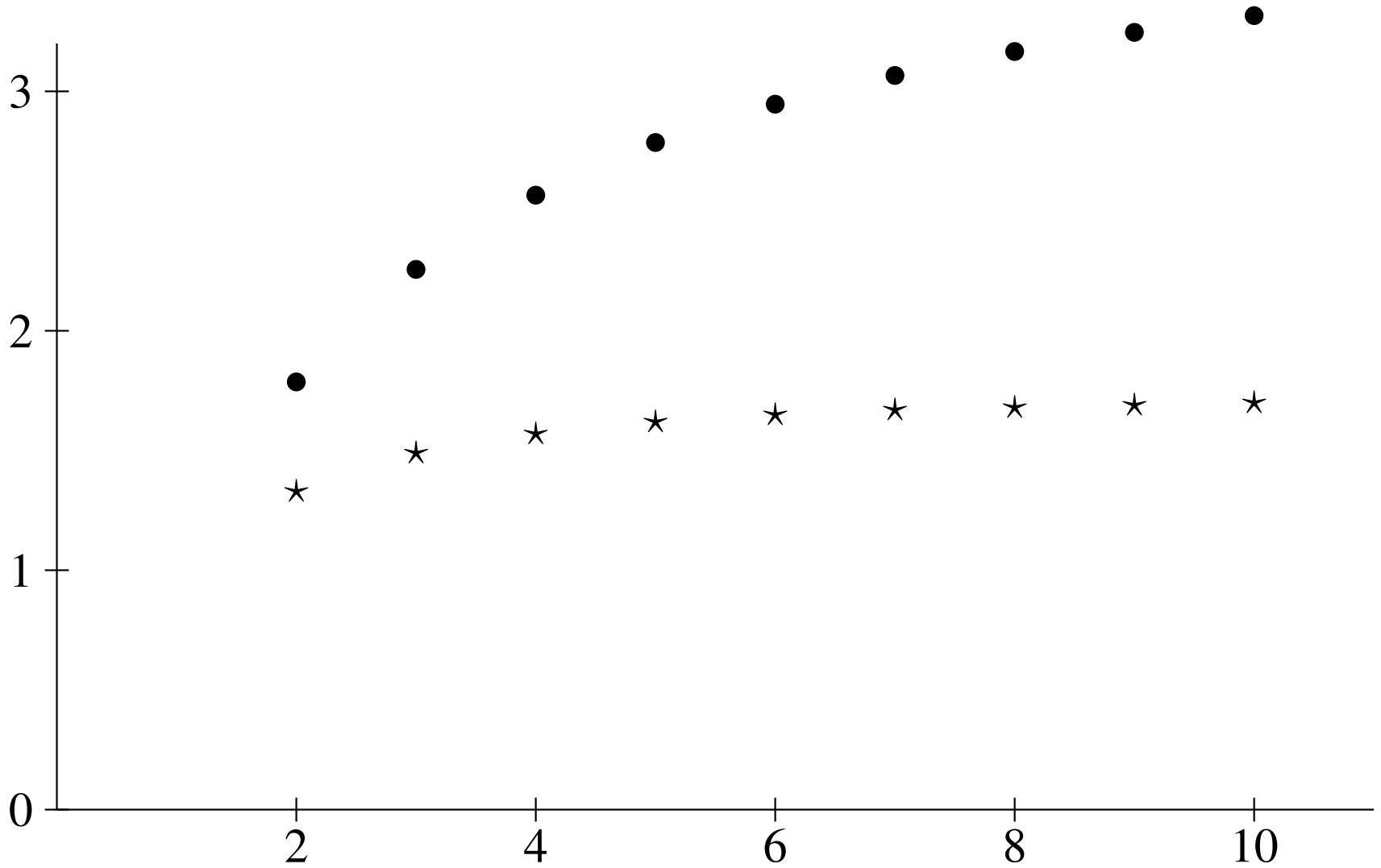

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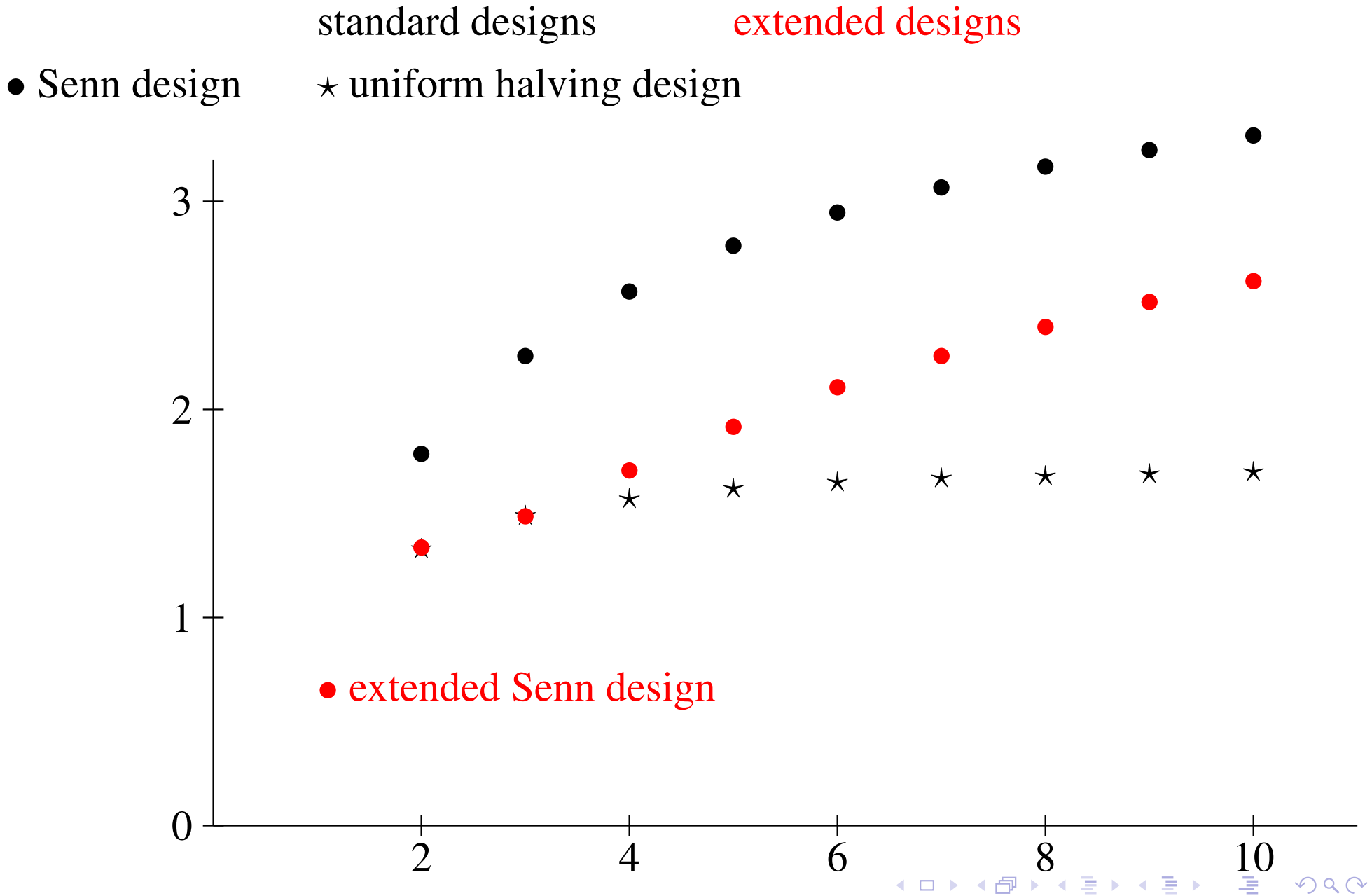
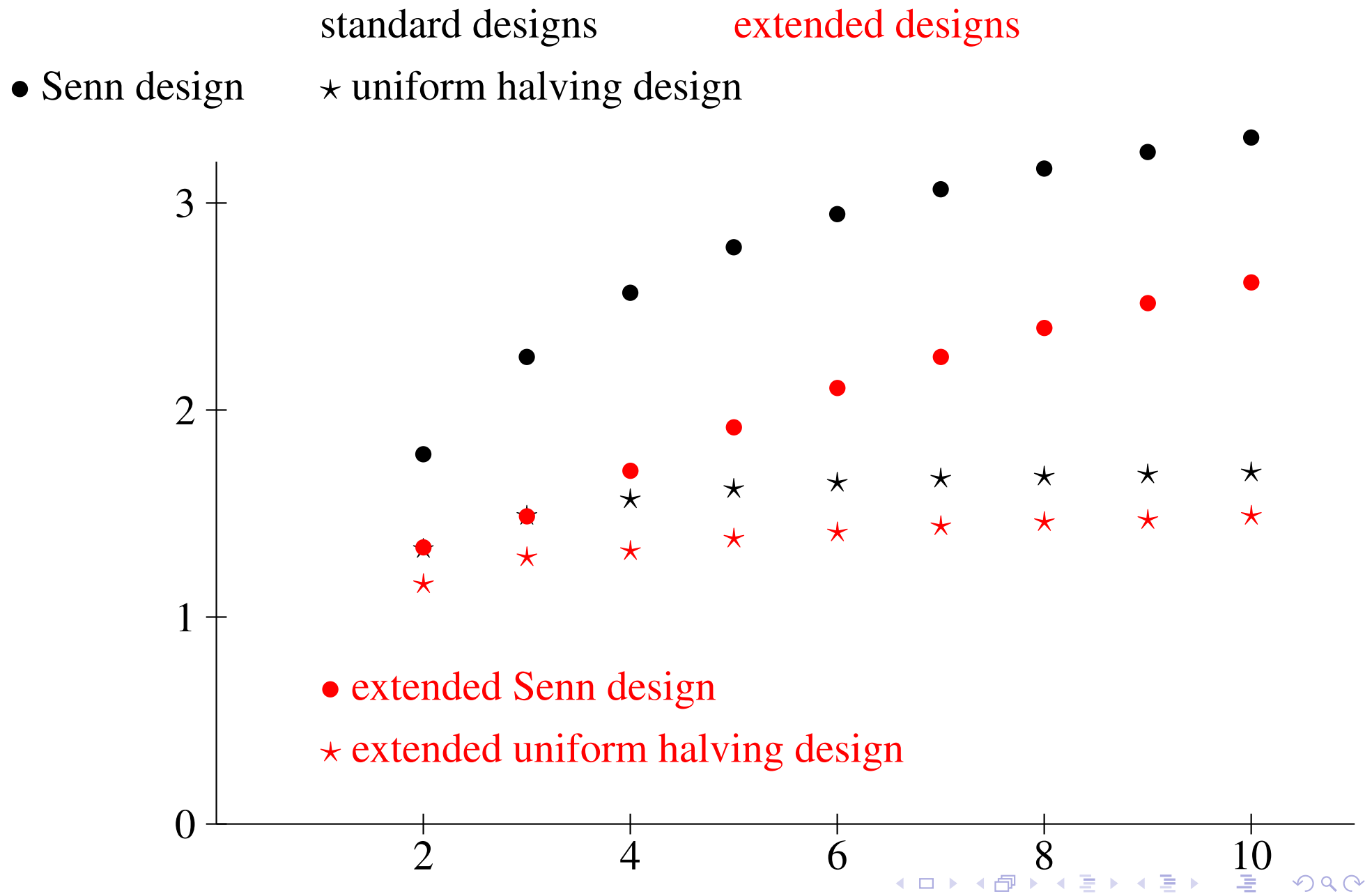


Average scaled pairwise variance: continued (again)



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
Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
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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
Cohort 1	4	4	0	0	0
Cohort 2	2	2	4	0	0
Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4
Cohort 5	1	1	1	2	3

	1	2	3	4
0	0.222	0.285	0.348	0.370
1		0.285	0.348	0.370
2			0.330	0.378
3				0.375

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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

average 1.00

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Both types can be described by the following simple rule:

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; the remaining subjects should be used to make the replication so far as equal as possible by compensating for previous under-replication.

Advantages of the halving designs

- Variance is reduced by a factor of two or more.

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- If cohort effects are small and random, the variance is very little more than for the textbook design (not shown here).
- Blinding is more effective than in textbook designs.

More recent work: I integer optimization

Dose	0	1	...	n
Cohort 1	s_{10}	s_{11}	...	0
...				
Cohort k	s_{k0}	s_{k1}	...	s_{kn}
...				

s_{ki} is an integer and $\sum_{i=0}^{n} s_{ki} = m$

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Linda Haines and Allan Clark have used complete enumeration (for small values of n and m) and exchange algorithms (for larger values) to find the optimal allocation for various combinations of values of n and m.
They consider various optimality criteria, including A-optimality, which is the criterion that I am using.

An example of an optimized design

For 4 doses, 4 cohorts and 8 volunteers per cohort,
Haines and Clark found that this design is A-optimal.

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

More recent work: II continuous designs, using best so far

Dose	0	1	...	n
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...				
Cohort k	w_{k0}	w_{k1}	...	w_{kn}
...				

$$0 \leq w_{ki} \text{ and } \sum_{i=0}^{n} w_{ki} = 1$$

More recent work: II continuous designs, using best so far

Dose	0	1	...	n
Cohort 1	w_{10}	w_{11}	...	0
...				
Cohort k	w_{k0}	w_{k1}	...	w_{kn}
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Given the number m of volunteers per cohort,

set s_{ki} to be an integer close to mw_{ki} such that $\sum_{i=0}^{n} s_{ki} = m$.

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Different ways of doing this give almost identical variances.

An example of an optimized best-so-far continuous design

Dose	0	1	2	3	4
Cohort 1	0.500	0.500	0	0	0
Cohort 2	0.270	0.270	0.460	0	0
Cohort 3	0.170	0.170	0.219	0.441	0
Cohort 4	0.118	0.118	0.138	0.196	0.430
Cohort 5	0.135	0.135	0.163	0.219	0.348

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If there are 8 volunteers per cohort, this gives the following design for 2 doses in 2 cohorts, 3 doses in 3 cohorts, and 4 doses in 4 or 5 cohorts.

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

More recent work: III continuous designs, using constant ratios

Heiko Großmann and I are optimizing the proportions w_{ki}, but cut down the search by imposing the condition

$$\frac{w_{ki}}{w_{kj}} \quad \text{does not depend on } k \text{ if } j \geq k \text{ and } i \geq k$$

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(in some cases, we can prove that the optimal designs must satisfy this).

Examples of optimized designs

Dose	0	1	2
Cohort 1	0.50	0.50	0
Cohort 2	0.27	0.27	0.46

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Dose	0	1	2
Cohort 1	0.50	0.50	0
Cohort 2	0.29	0.29	0.42
Cohort 3	0.29	0.29	0.42

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