Designs for dose-escalation trials

R. A. Bailey
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How should such trials be designed?

How did I get into this?

My background is in the design and analysis of agricultural experiments.

- Which of these varieties of wheat will give us the most bread per hectare?
- How should we allow for the direction of sowing in sugar-beet trials?
- If we are comparing varieties of sunflower, how can we allow for the fact that taller varieties may shade their Northern neighbours?
- If we control aphids on one plot, should we expect them to spread to nearby plots?
- If we have a factorial experiment, what should we do if levels of one factor must be applied to large areas of land?
- Most experiments take place on the ground, or in a standard layout in a glasshouse: how do we allow for the effects of rows and columns?

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	Randomised 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	

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SB: I will, but we want you too.

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Standard designs

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

0 denotes the placebo.

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There are n cohorts of m subjects each.

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 initially
(then later show analogous work for random cohort effects).

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(then later show 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 $1 \leq j \leq n$: see later.)

Scaled variance

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

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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.

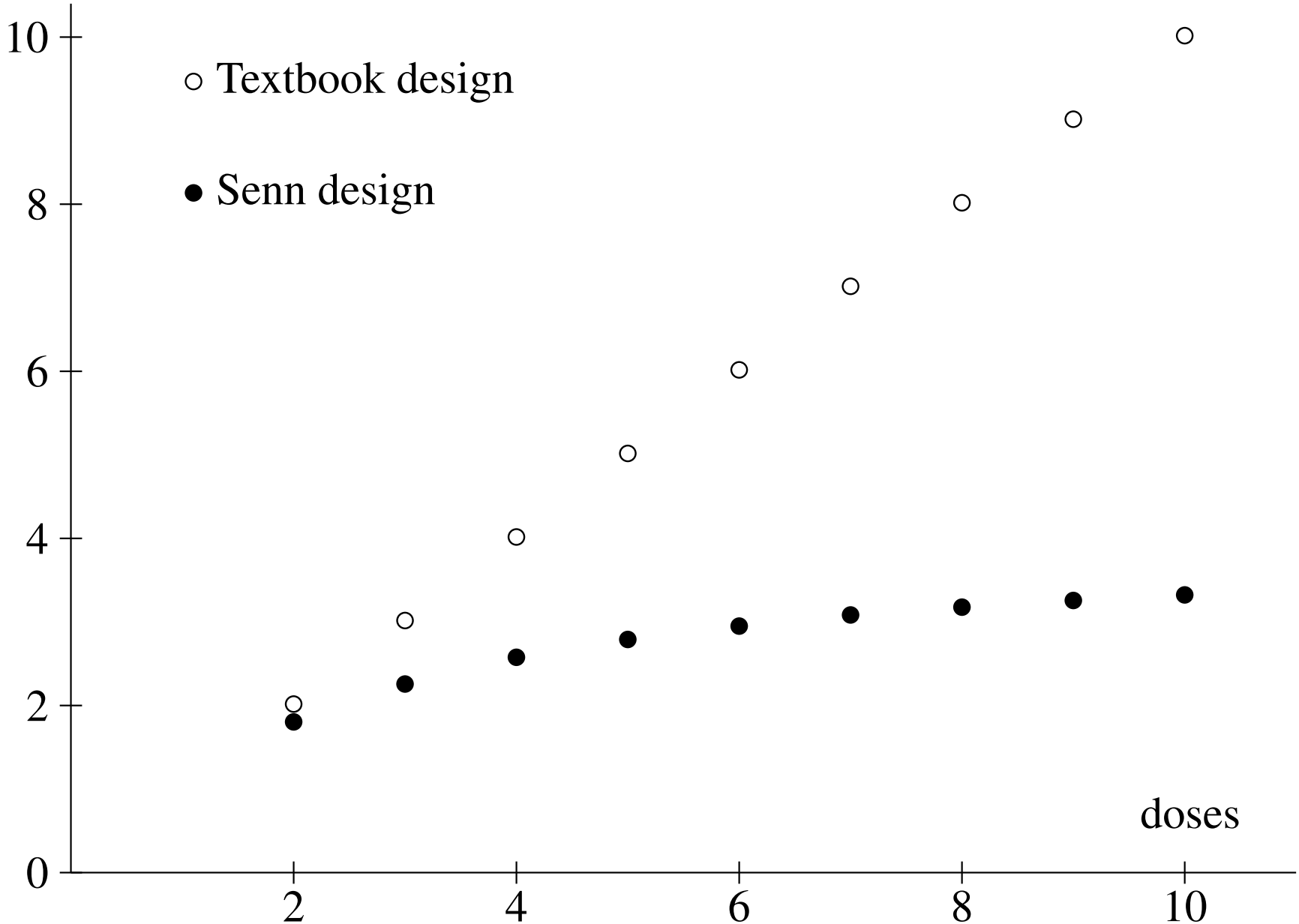
Example of a uniform halving design

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

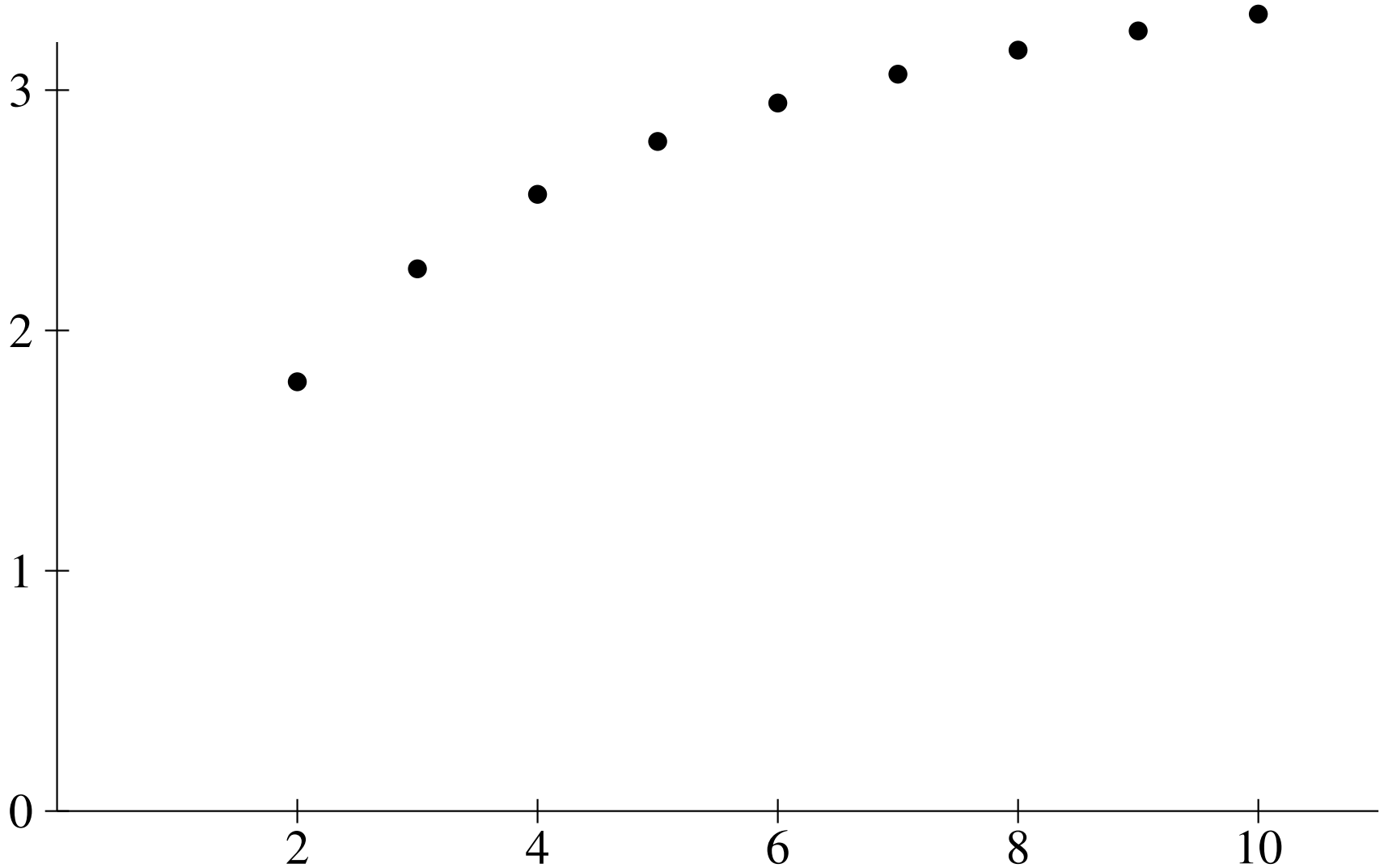
The scaled variances v_{ij} have to be calculated numerically.

Average scaled pairwise variance



Average scaled pairwise variance: continued

- Senn design



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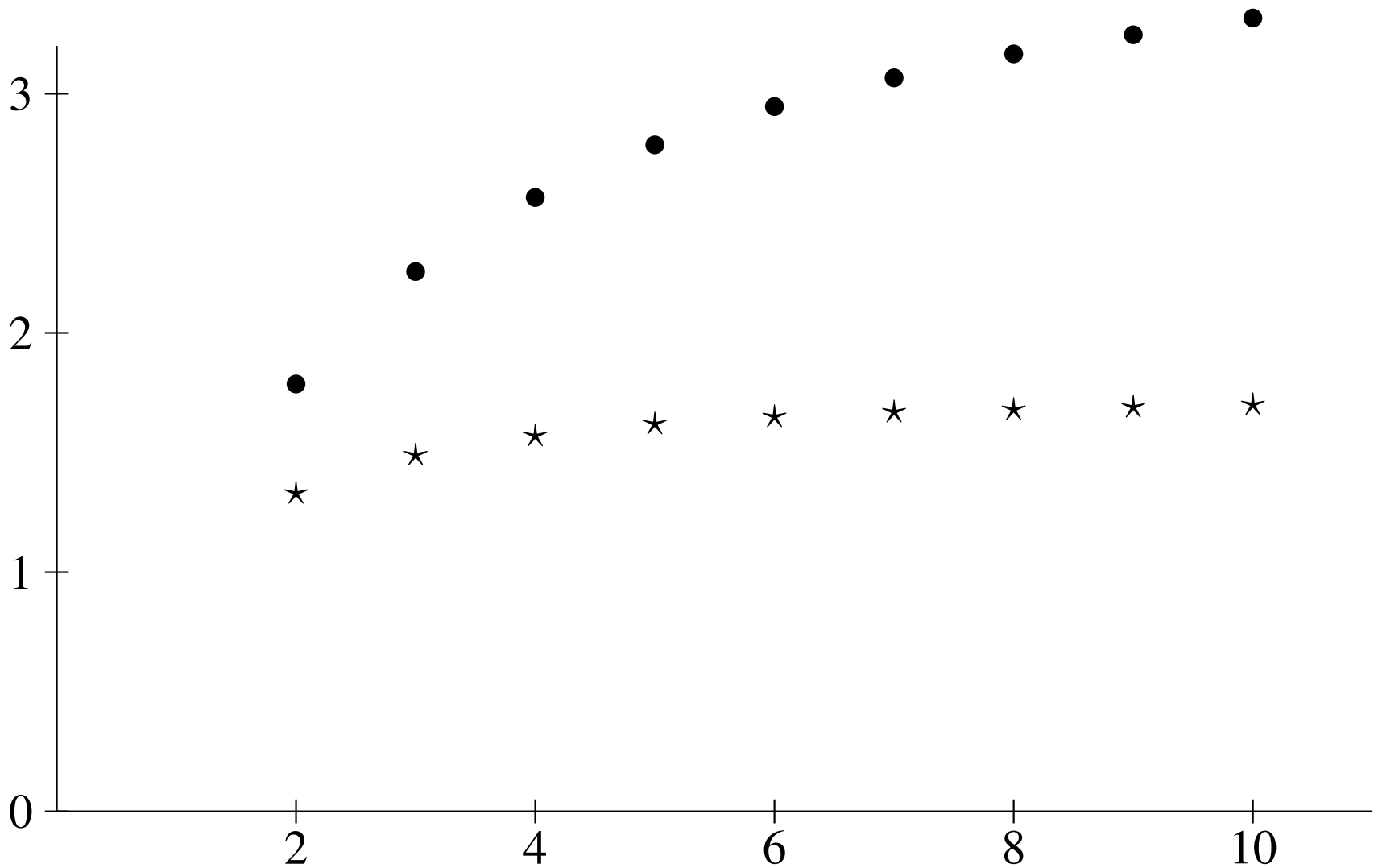

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In ordinary block designs, treatment differences are well estimated
if and only if block differences are well estimated,
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Principle

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

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There are $n+1$ cohorts of m subjects each.

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In Cohort i, for $2 \leq i \leq n$, some subjects receive dose i;
no subject receives dose j if $j > i$.

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

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Maintain overall equal replication in the final cohort.

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Cohort 5	2	2	2	2	2

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

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In the final cohort,
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Cohort 3	4	0	0	4	0
Cohort 4	4	0	0	0	4
Cohort 5	0	2	2	2	2

Extended Senn design

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

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

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

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

Extension of the uniform halving design

About half the subjects in the final cohort are equally split between all treatments,
the remainder being allocated to make the overall replications as equal as possible, with any inequalities favouring the higher doses.

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

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Cohort 3	1	1	2	4	0
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					1

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					1
				1	1

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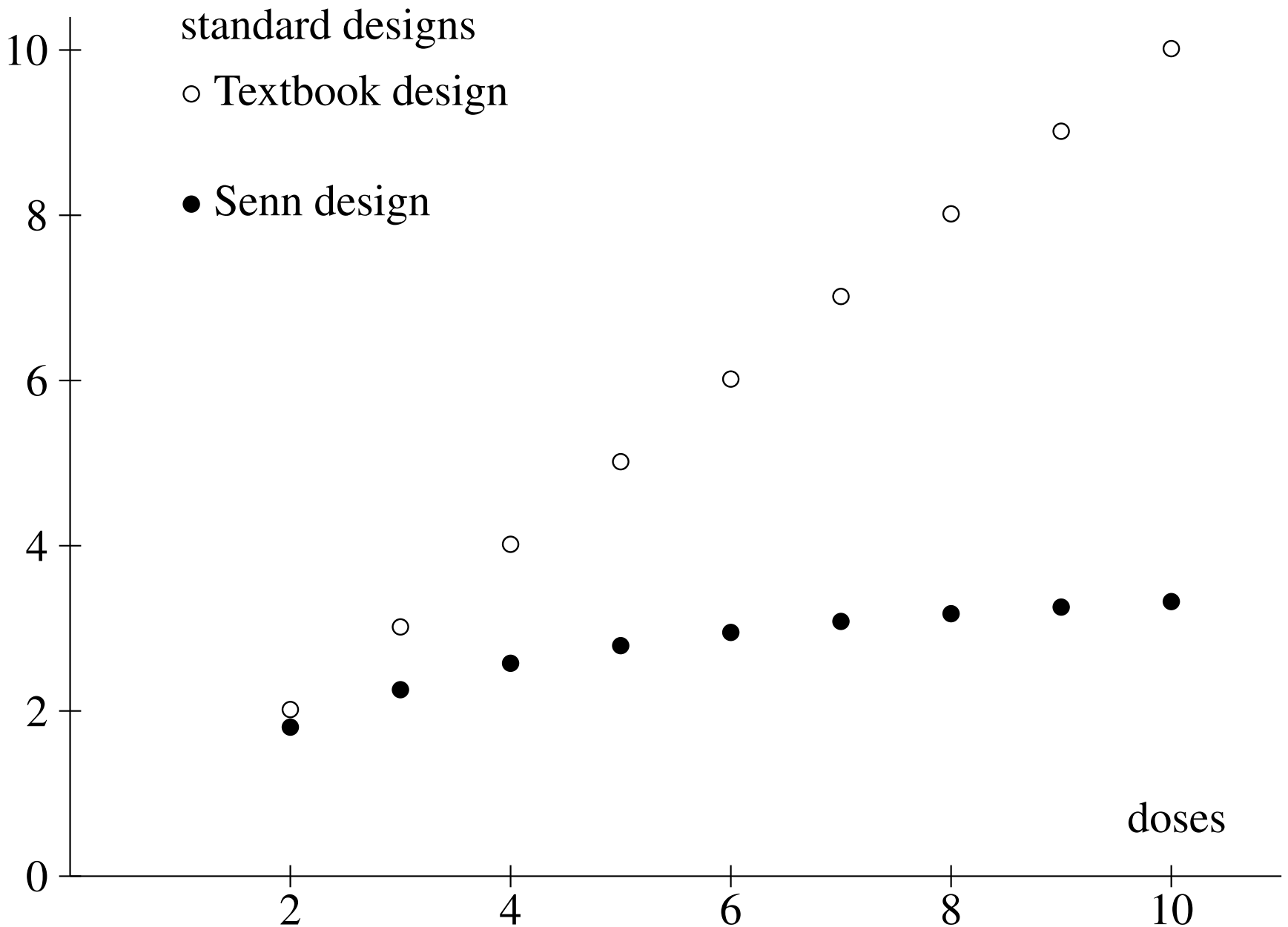
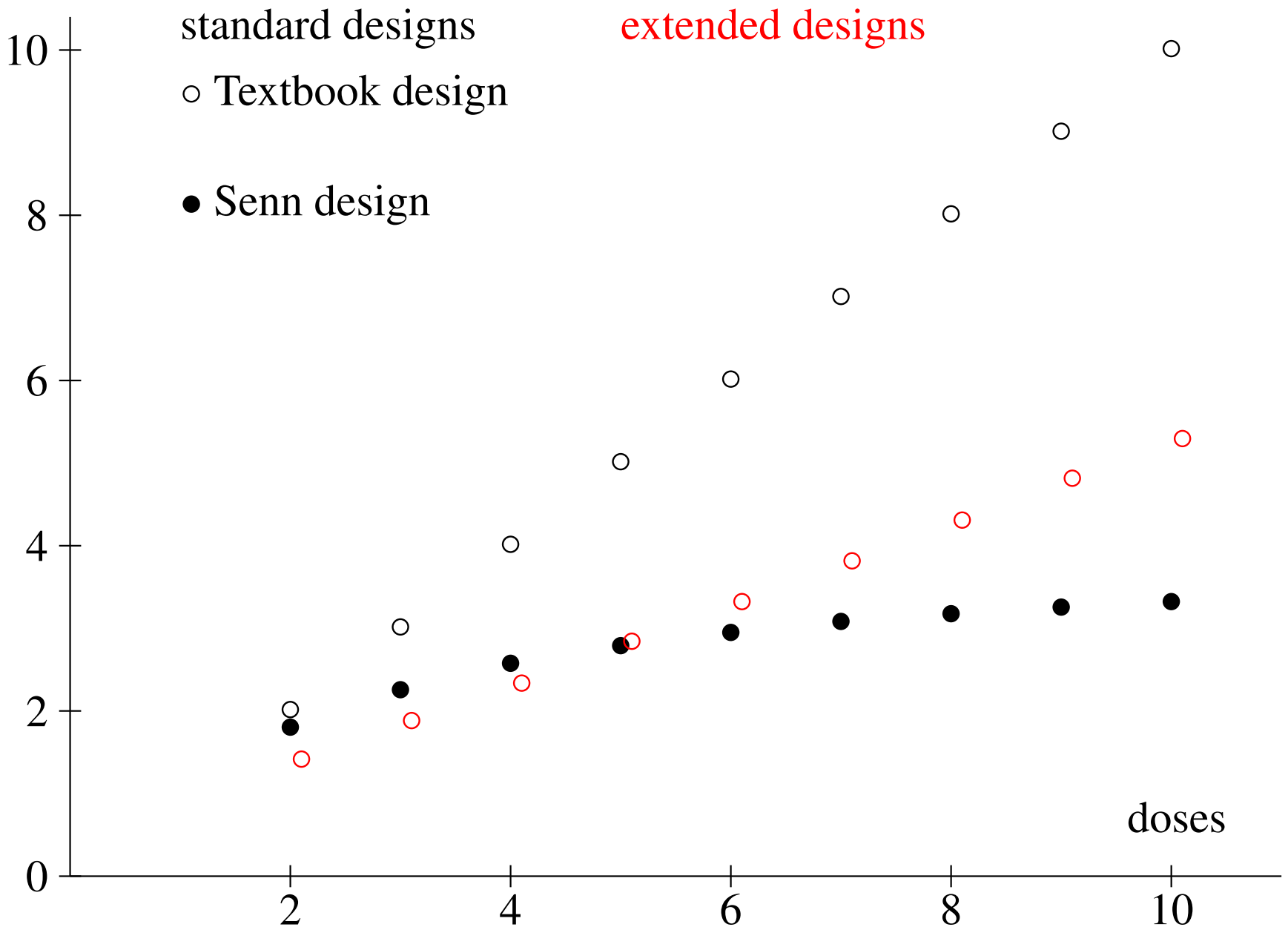
Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4
	1	1	1	1	1
					1
				1	1
Cohort 5	1	1	1	2	3

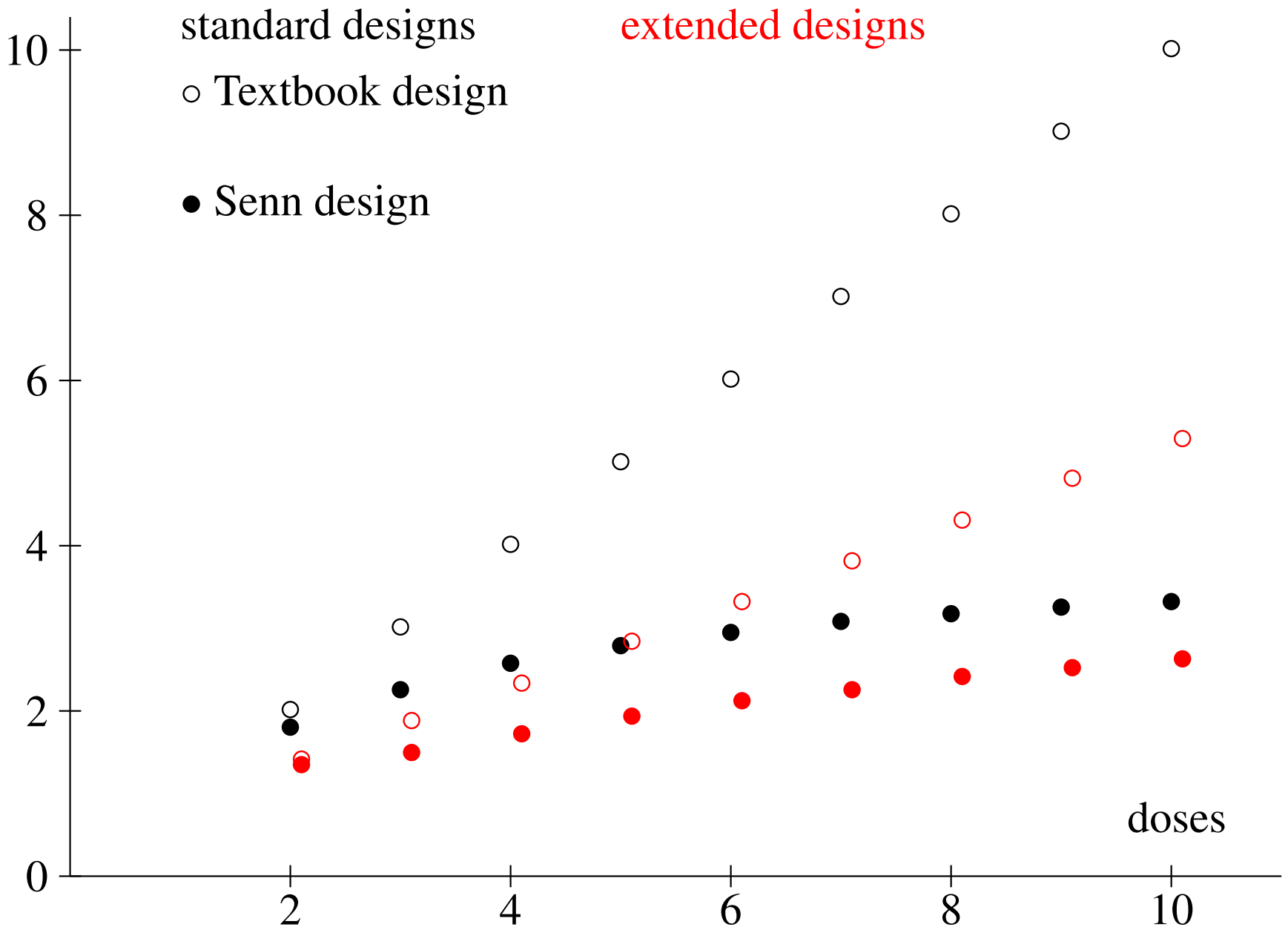
Average scaled pairwise variance (again)



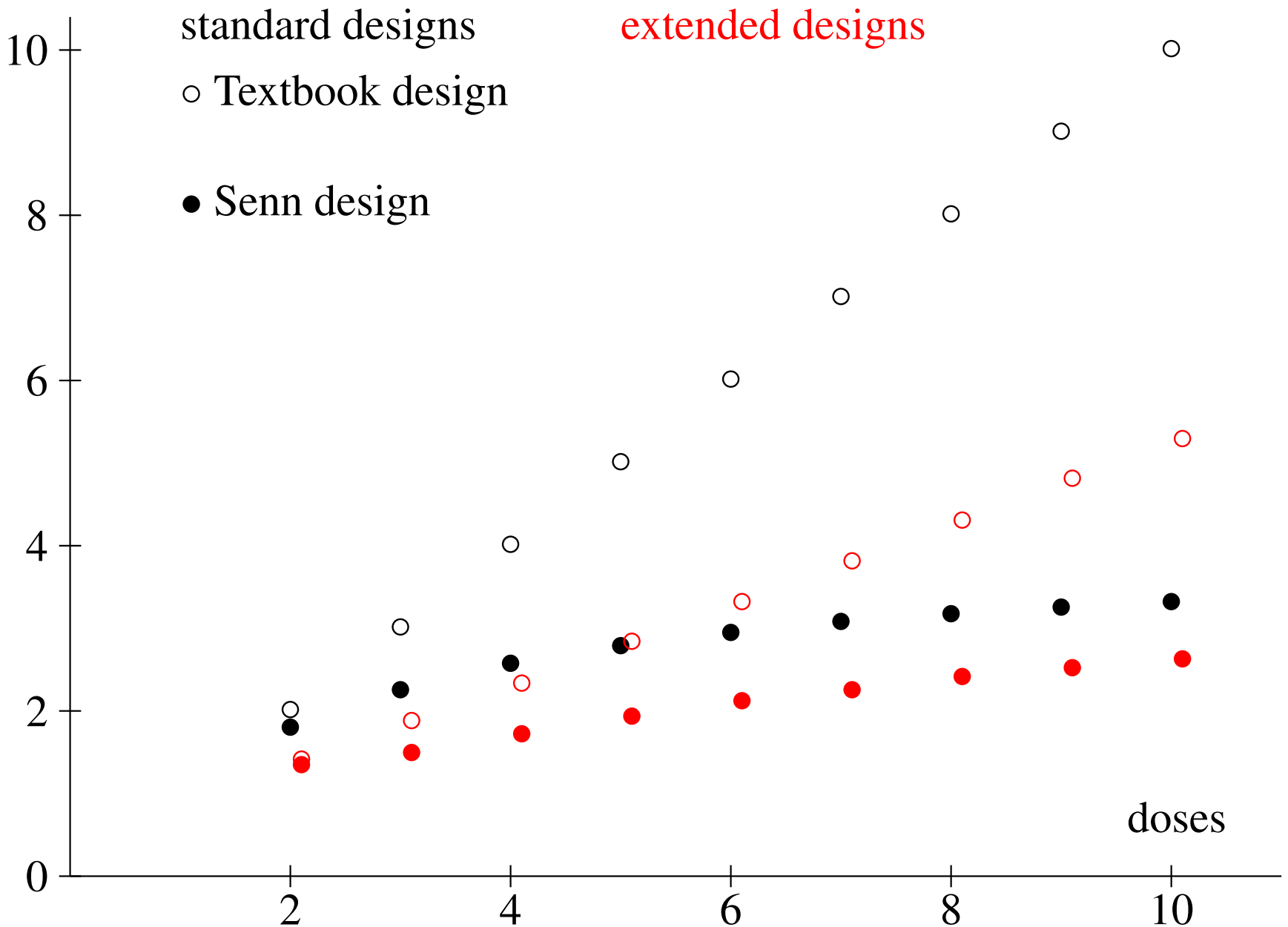
Average scaled pairwise variance (again)



Average scaled pairwise variance (again)



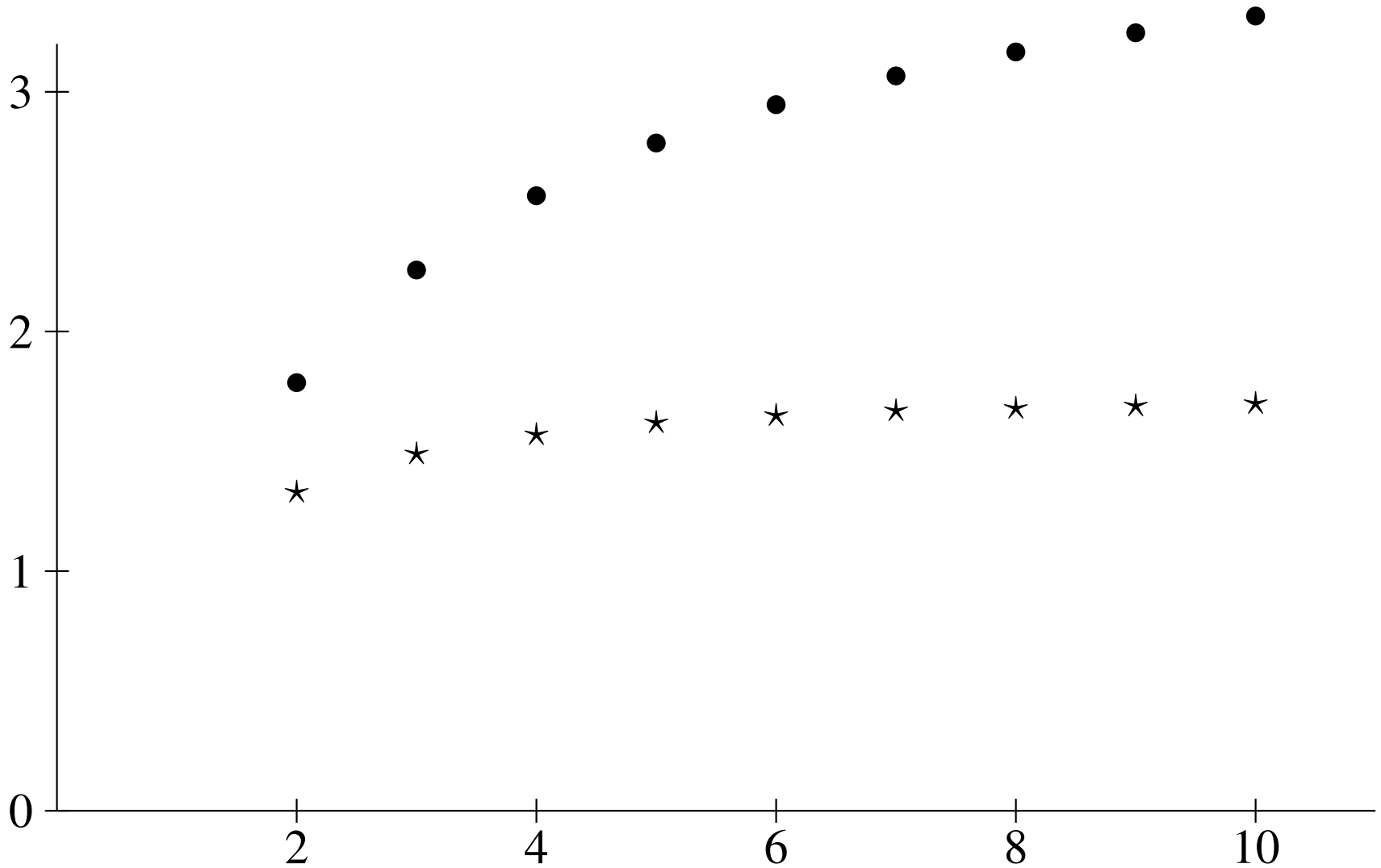
Average scaled pairwise variance (again)



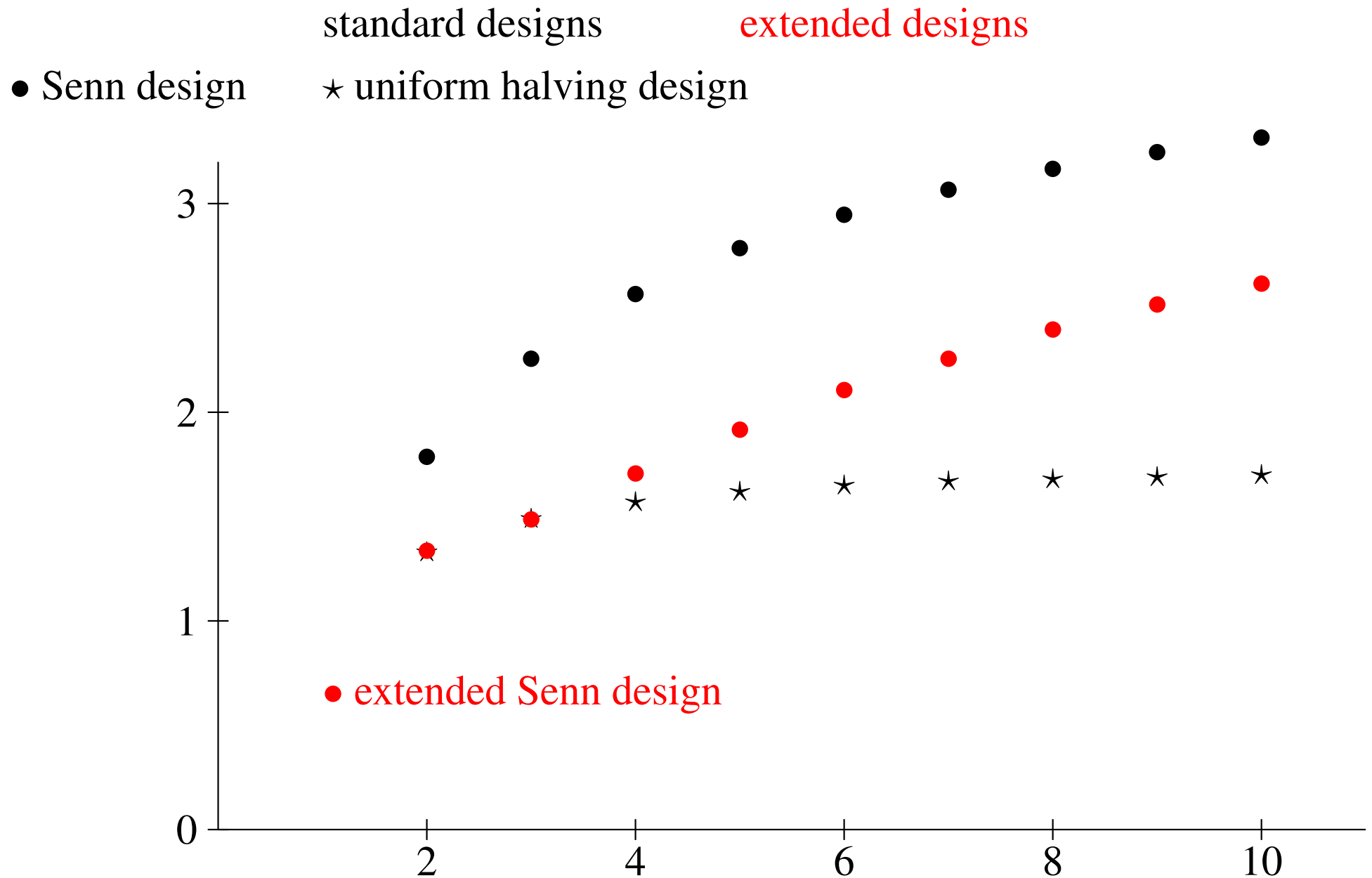
Average scaled pairwise variance: continued (again)

standard designs

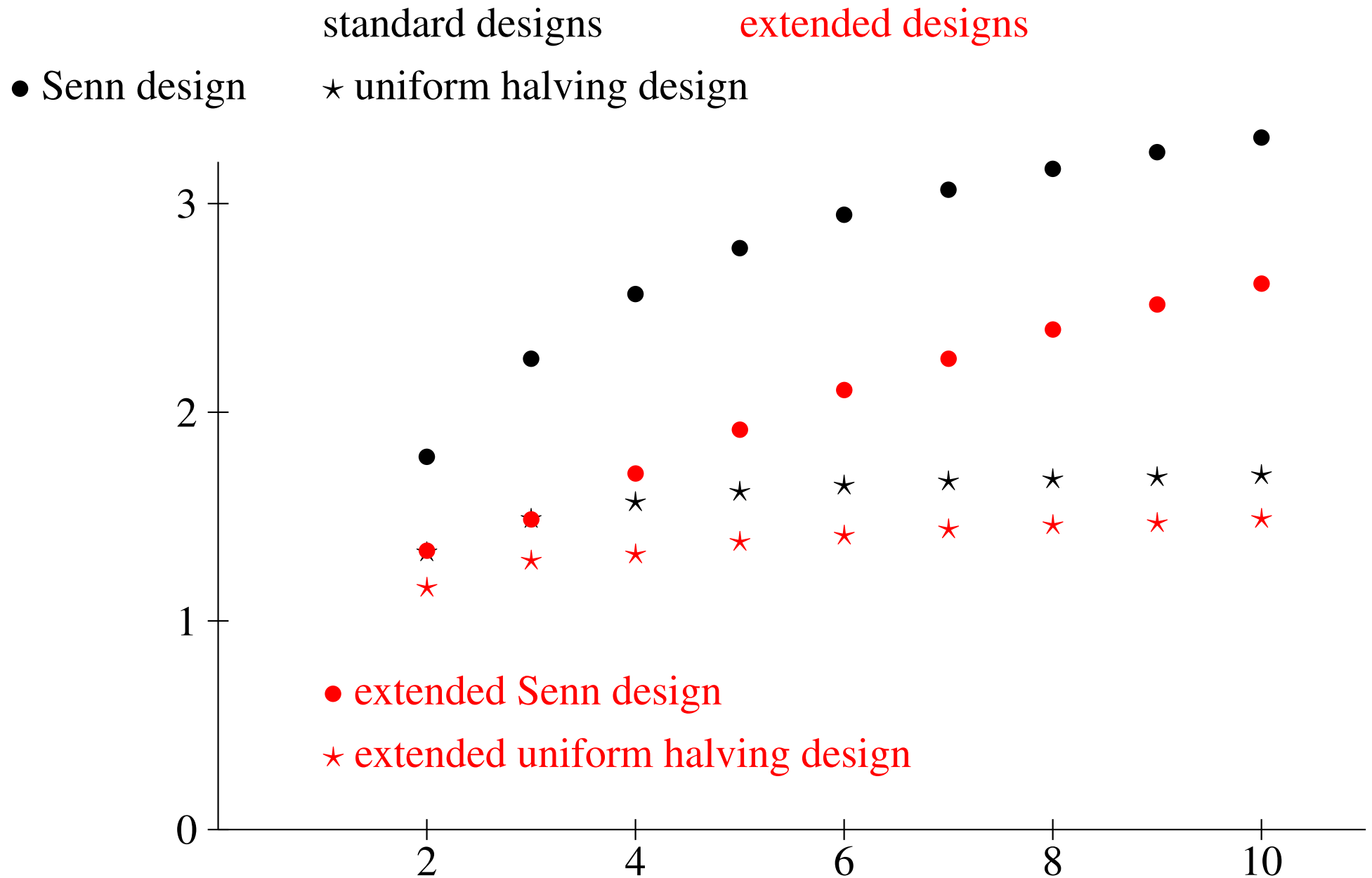
• Senn design ⋆ uniform halving design



Average scaled pairwise variance: continued (again)



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
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
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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	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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Cohort 1	4	4	0	0	0
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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

average 0.33

Random cohort effects

Now assume that the expectation of the response of a subject who gets dose i in cohort k is τ_i, and that cohort effects are uncorrelated random variables with common variance σ_C^2.

$$\text{Put } \mathbf{C}_{\alpha\beta} = \begin{cases} 1 & \text{if subjects } \alpha \text{ and } \beta \text{ are in the same cohort} \\ 0 & \text{otherwise.} \end{cases}$$

Then the variance-covariance matrix of the responses is

$$\sigma^2\mathbf{I} + \sigma_C^2\mathbf{C}$$

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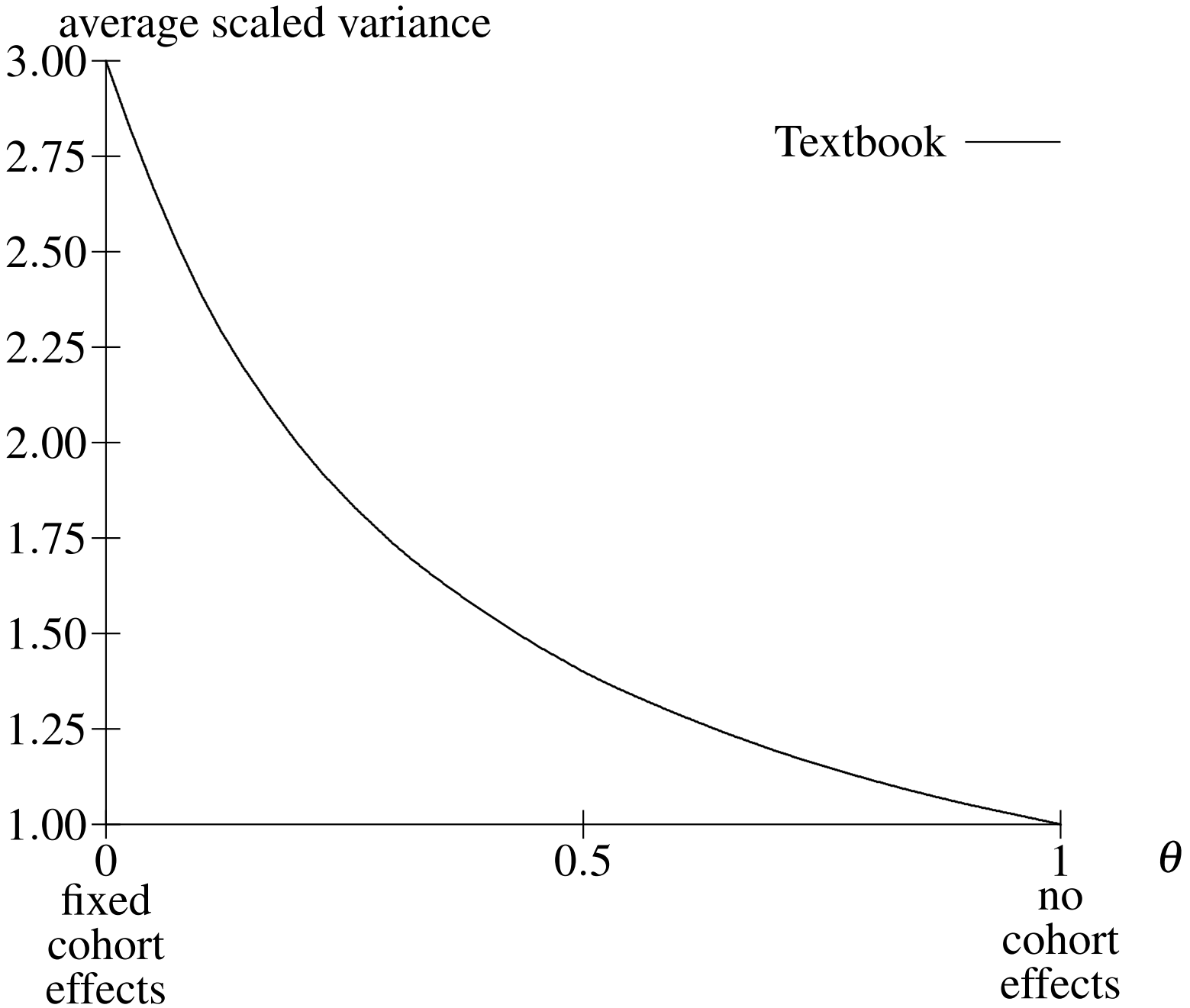
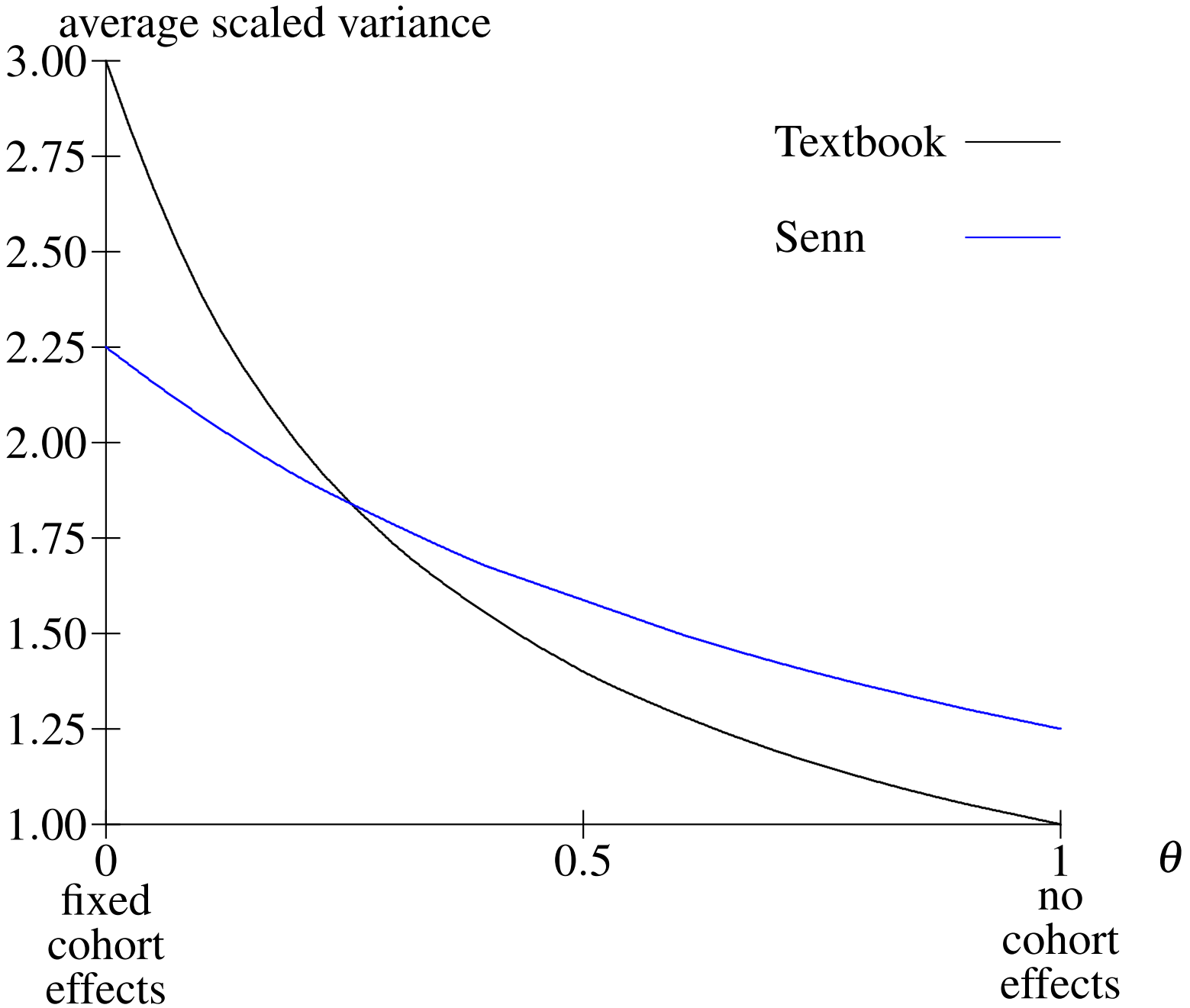
$$\sigma^2\mathbf{I} + \sigma_C^2\mathbf{C} \quad = \quad \sigma^2 \underbrace{\left(\mathbf{I} - \frac{1}{m}\mathbf{C}\right)}_{\text{within cohorts}} \quad + \quad \sigma^2\theta^{-1} \underbrace{\frac{1}{m}\mathbf{C}}_{\text{between cohorts}}$$

where $\sigma^2 + m\sigma_C^2 = \theta^{-1}\sigma^2$,
so $\theta \in [0,1]$ with $\theta = 0$ if cohort effects are fixed
$\theta = 1$ if cohort effects are zero.

Average scaled variance for 3 doses in 3 cohorts



Average scaled variance for 3 doses in 3 cohorts



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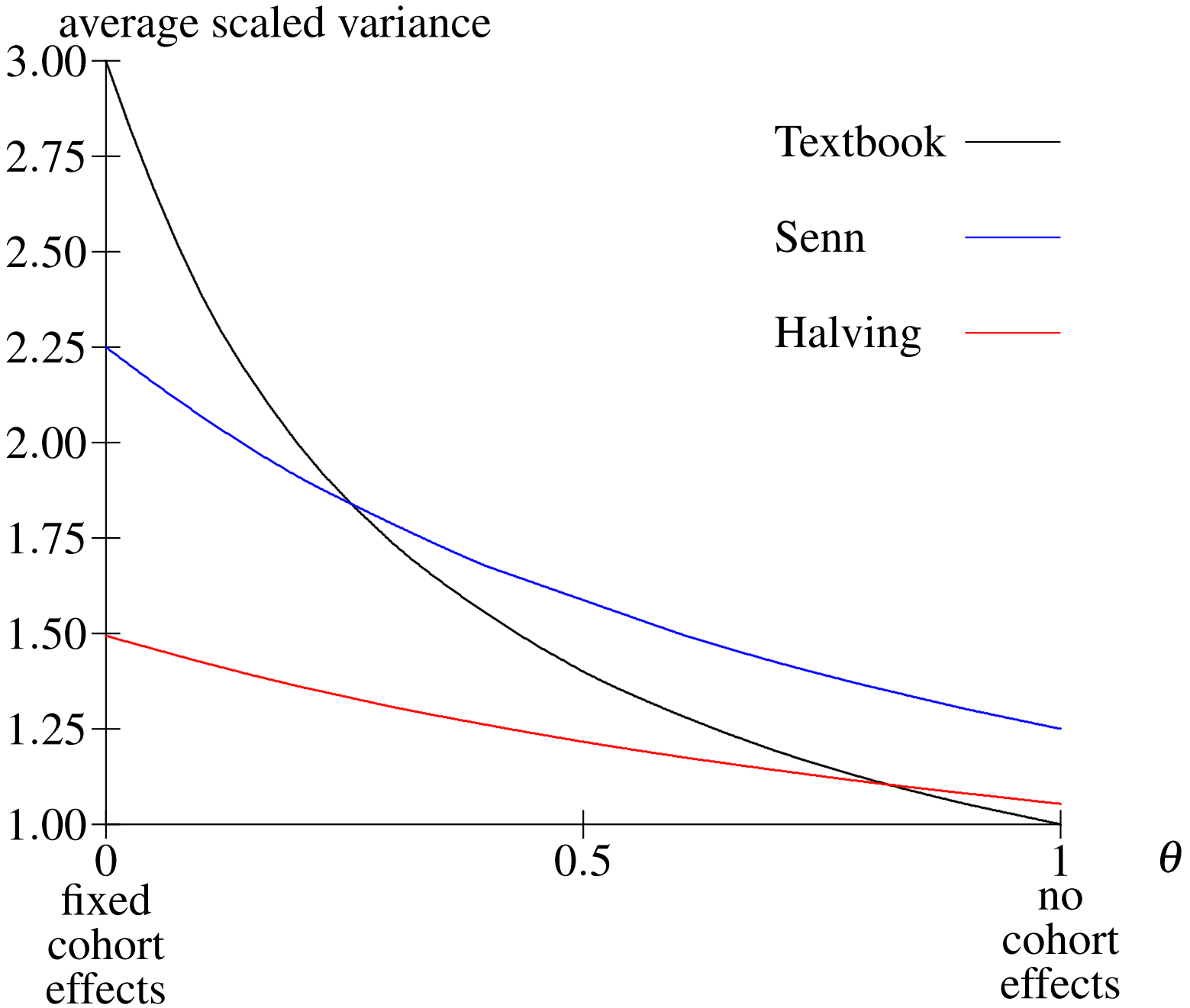
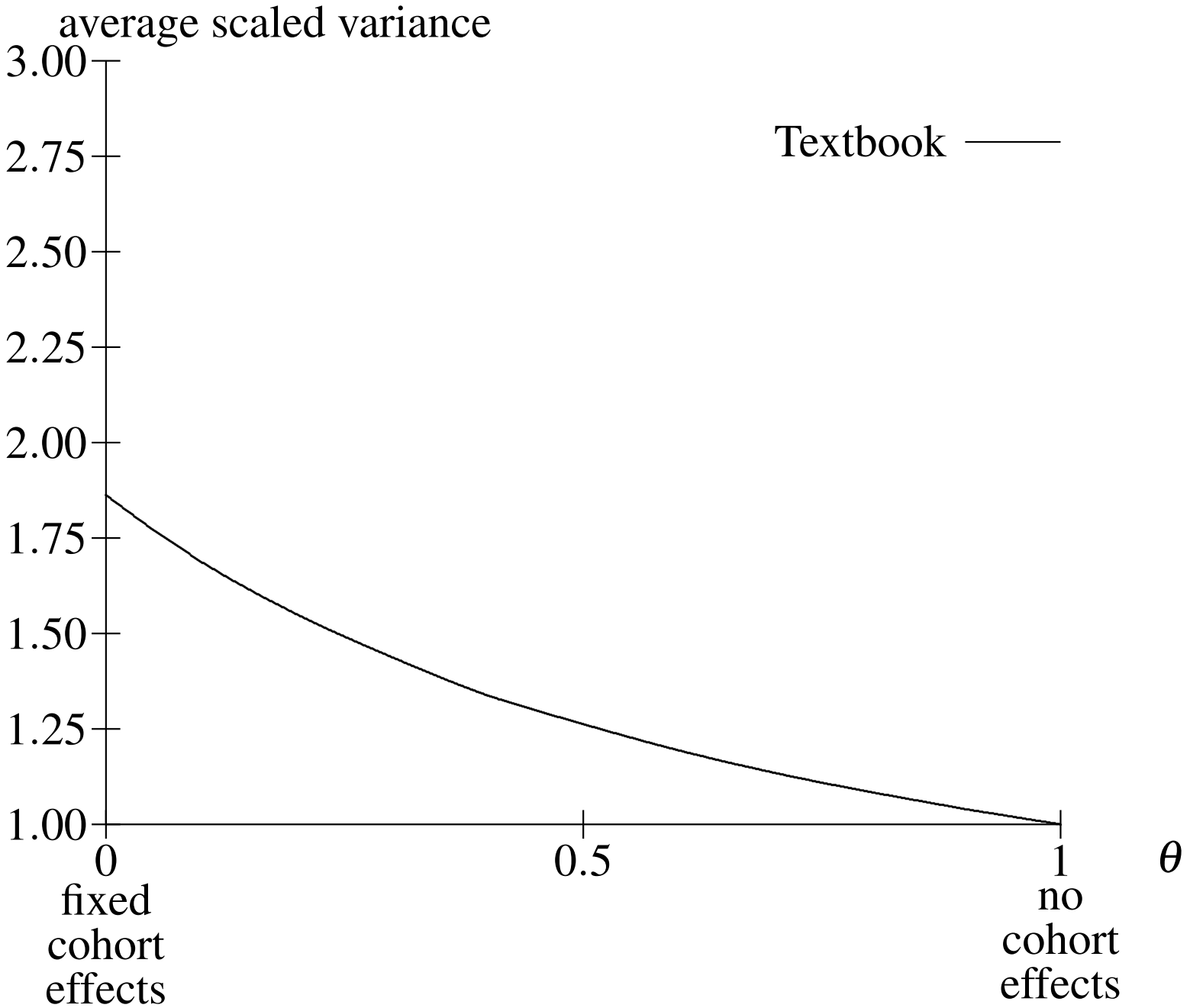


Average scaled variance for 3 doses in 4 cohorts



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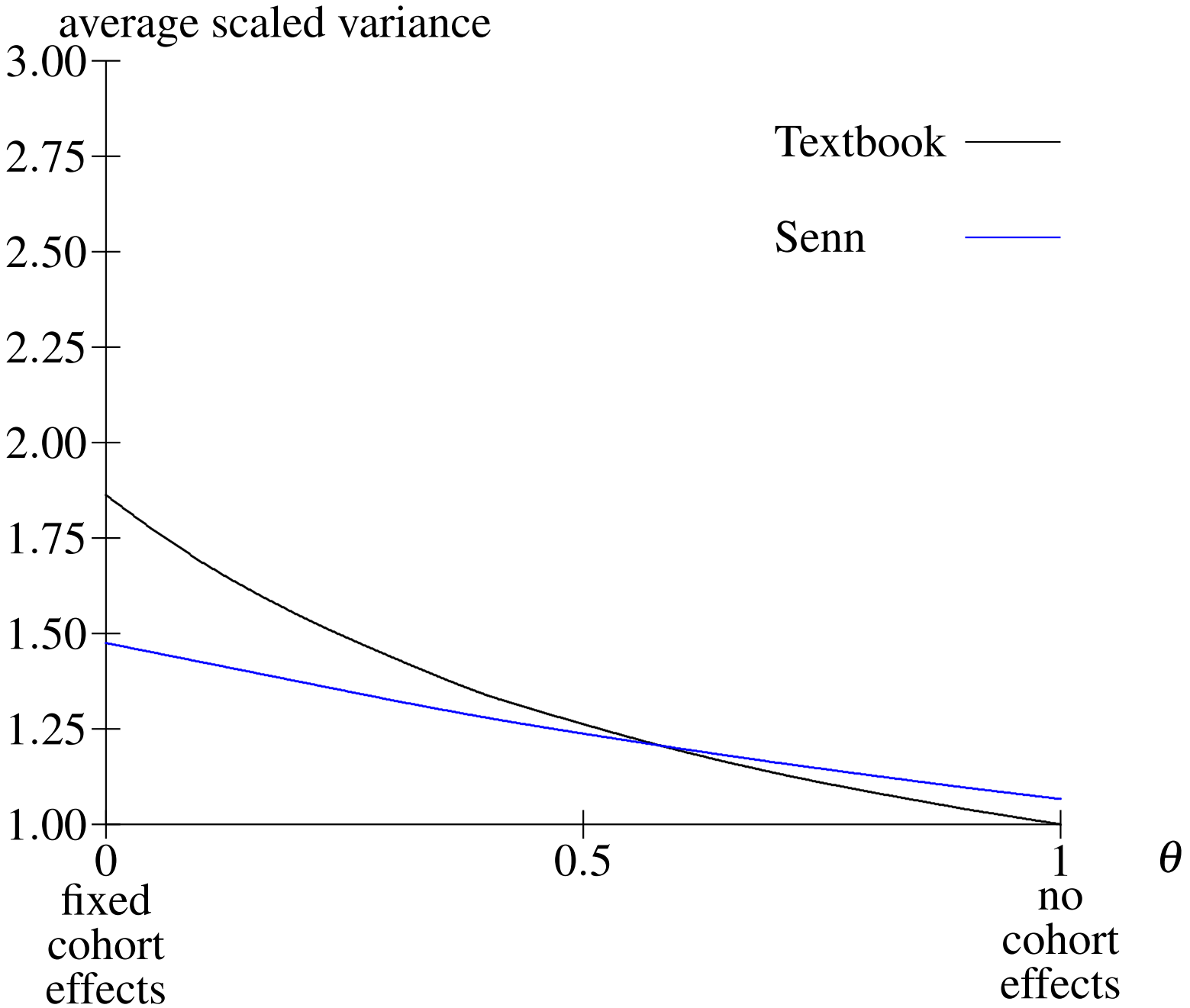

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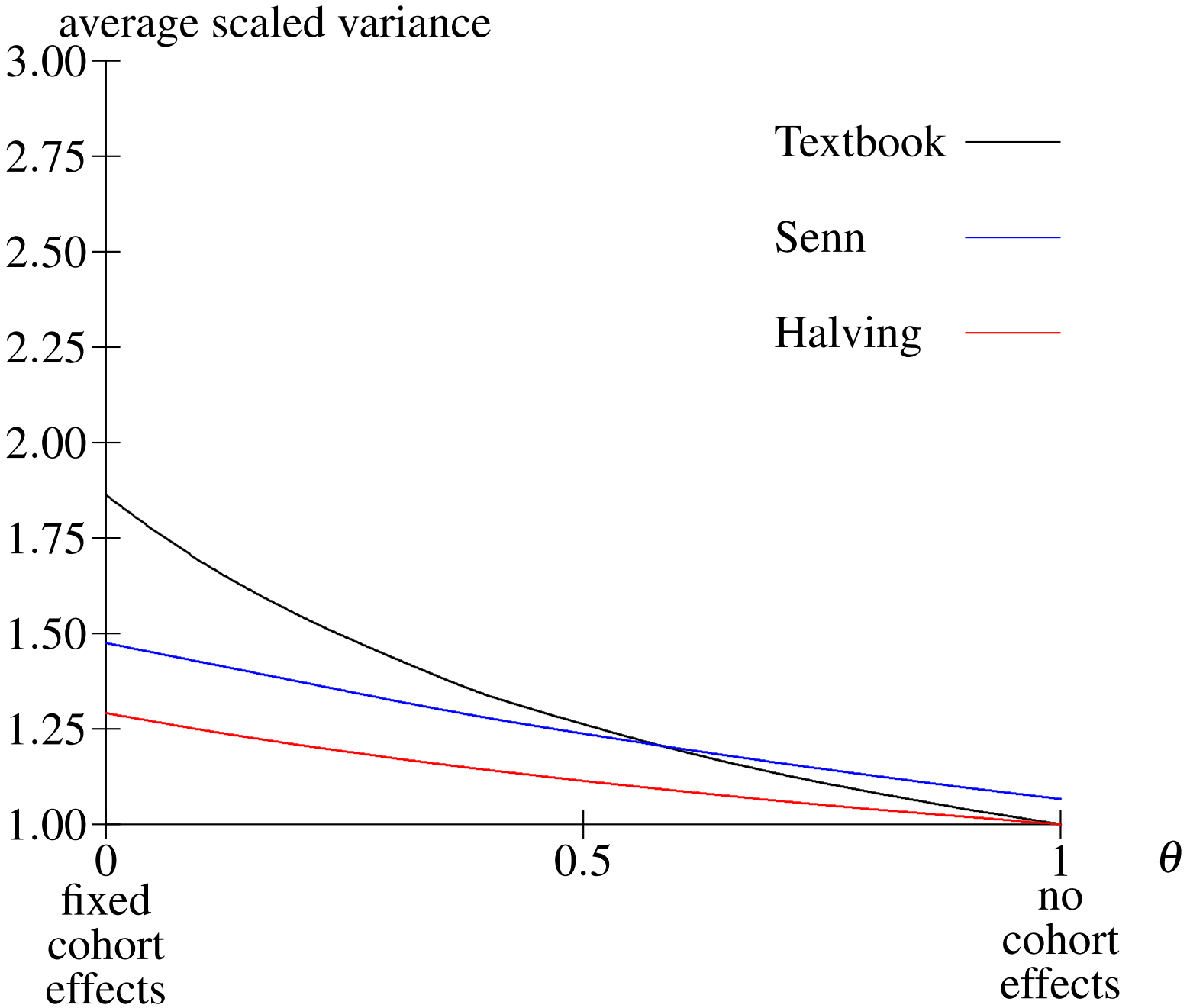

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Principle

In each cohort,
half of the subjects should be distributed (approximately) equally among all the treatments that have been used in any previous cohort;
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.
- 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 $\sum_{i=0}^{n} s_{ki} = m$

More recent work: I. Integer optimization

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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
Cohort 1	w_{10}	w_{11}	...	0
...				
Cohort k	w_{k0}	w_{k1}	...	w_{kn}
...				

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

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Dose	0	1	...	n
Cohort 1	w_{10}	w_{11}	...	0
...				
Cohort k	w_{k0}	w_{k1}	...	w_{kn}
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Brendan O'Neill optimized the proportions w_{ki}, but cut down the search by restricting a design for c cohorts to use the best design for $c-1$ cohorts and just optimize the proportions in the final cohort.

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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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Given the number m of volunteers per cohort,

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

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

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

More recent work: III. Continuous designs, using constant ratios

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

(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	0.27	0.27	0.46

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

More recent work: IV. Other criteria

Vlad Dragalin said that the aim of Phase I trials is to find the maximum tolerable dose, so suggested that we we should minimize $\mathrm{Var}(\hat{\tau}_i - \hat{\tau}_{i-1})$ if the trial stops with i as the maximal tolerable dose.

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Since we do not know i in advance, these both need a best-so-far approach, and the results are slightly different if we intend to have an 'extra' cohort.

Examples of optimized designs

If we take the average of those two criteria,
we want to minimize $\mathrm{Var}(\hat{\tau}_i - \hat{\tau}_{i-1}) + \mathrm{Var}(\hat{\tau}_i - \hat{\tau}_0)$
if the trial stops with i as the maximal tolerable dose.

For dose 2, here are the optimal standard and extended designs.

Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.257	0.257	0.486

Examples of optimized designs

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Dose	0	1	2
Cohort 1	0.500	0.500	0
Cohort 2	0.265	0.265	0.470
Cohort 3	0.265	0.265	0.470

More recent work: V. Integer programming for other criteria

Radoslav Harman and his PhD student Samuel Rosa are using integer programming to find

- E-optimal designs (designs which minimize the largest variance of any normalized treatment contrast);
- designs which minimize $\mathrm{Var}(\hat{\tau}_{\mathrm{last}} - \hat{\tau}_0)$.

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4. Brendan O'Neill: A-optimal continuous designs and statistical issues in clinical trials. MSc dissertation, Queen Mary, University of London, 2011.
5. Linda M. Haines and Allan E. Clark: The construction of optimal designs for dose-escalation studies. *Statistics and Computing* **24** (2014), 101–109.