Conflicts between Optimality Criteria in Incomplete-Block Designs for Microarray Experiments

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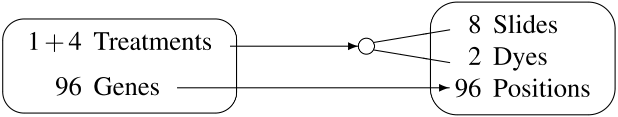
A small microarray experiment



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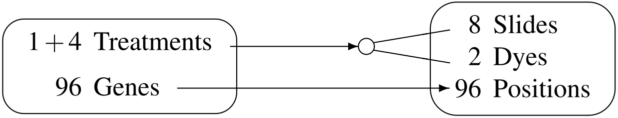

- There is 1 ‘control’ treatment (labelled 0) and 4 other treatments.

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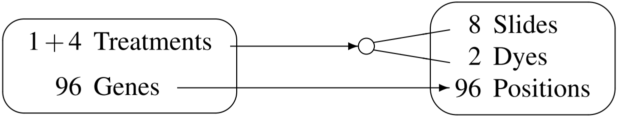

- There is 1 ‘control’ treatment (labelled 0) and 4 other treatments.
- ○ shows that we need to know a specific (non-orthogonal) design for the allocation of the treatments to the dye-slide combinations, such as

slides

	1	2	3	4	5	6	7	8
red	0	1	0	2	0	3	0	4
green	1	0	2	0	3	0	4	0

Representation of the design as an oriented graph

Treatments are vertices; slides are edges, oriented from green to red.

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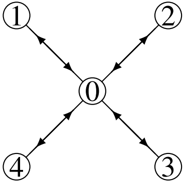

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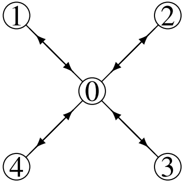

slides

	1	2	3	4	5	6	7	8
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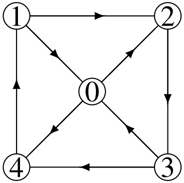
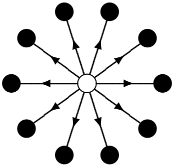
green	1	0	3	0	1	2	3	4



Two applications

Large Brazilian forestry experiment (v. Julio Bueno)

10 varieties of tree are being grown in several states for 5 years.
It is proposed to compare each with control using a single-reference design with 10 slides. Is this a good use of resources?



Large number of mutations in yeast (Hughes et al., *Cell*, **102**)

300 mutant varieties of yeast were compared with wild-type yeast using a double-reference design with 600 slides. Was that the best use of resources?

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$$\tau_i + \beta_k + \delta_l$$

and variance σ^2, independent of all other responses.

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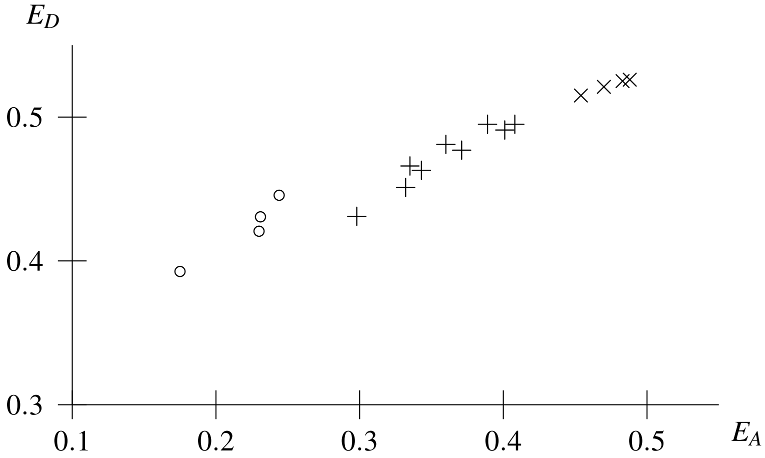
If $t = 2$ then A-optimal = D-optimal.

Temporarily ignore the dyes

We will come back to them later.

Typical behaviour of the optimality criteria



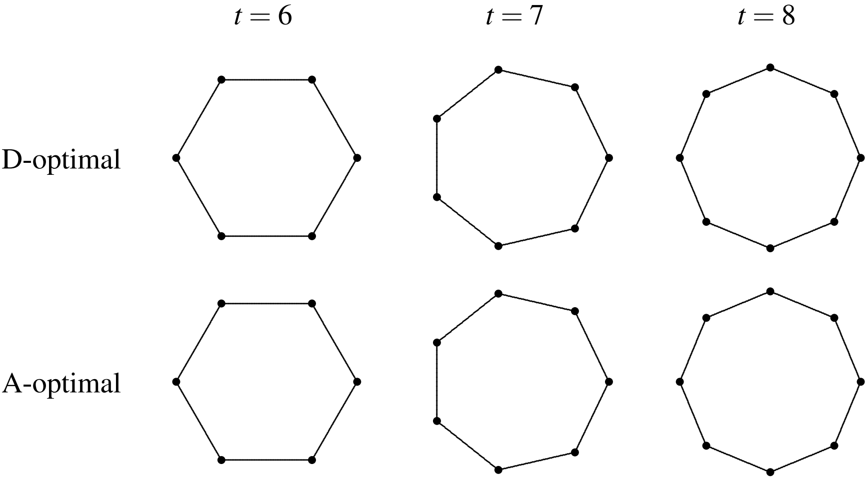
Optimality criteria for all connected equireplicate designs with 8 treatments in 12 blocks of size 2: graphs with edge-connectivity 3, 2, 1 are shown as $\times$, $+$, $\circ$ respectively

What happens when $b = t$?

Computer investigation by

- Jones and Eccleston (1980)
- Kerr and Churchill (2001)
- Wit, Nobile and Khanin (2005)
- Ceraudo (2005).

Optimal designs when $b = t$



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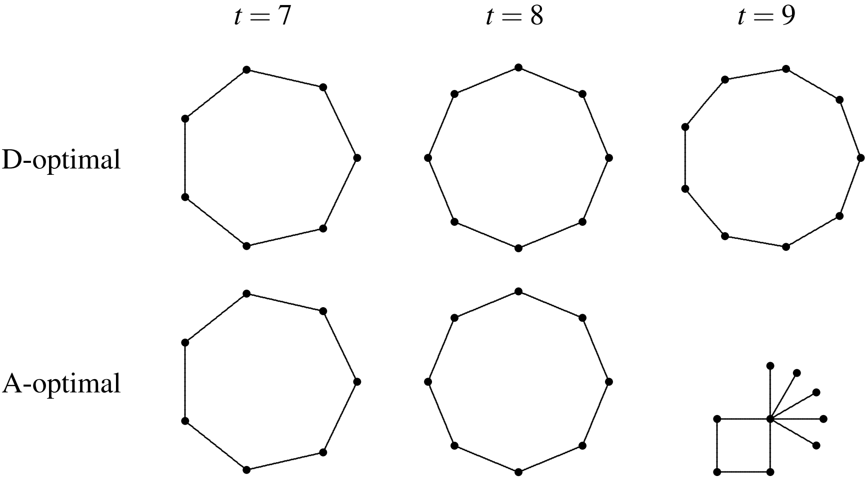

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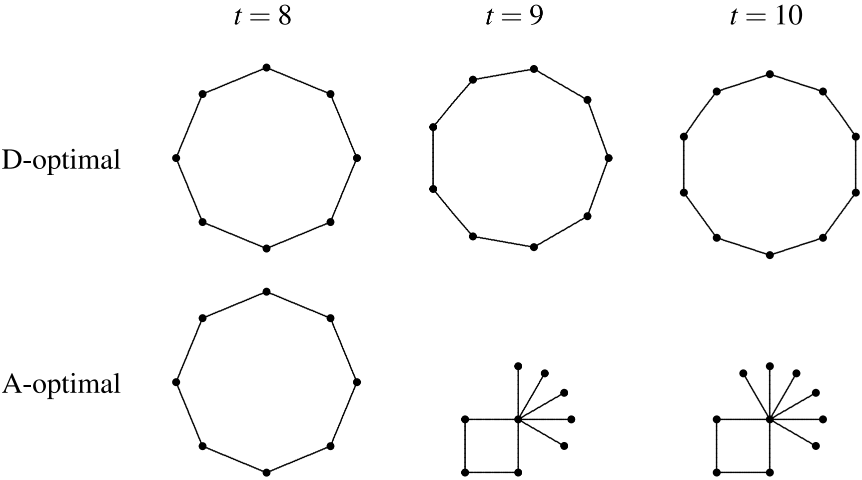

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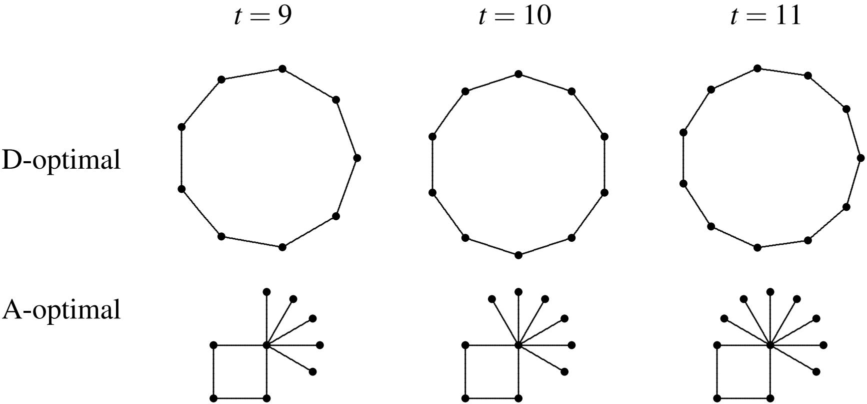

D-optimality

Cheng (1978), after Gaffke (1978), after Kirchhoff (1847):

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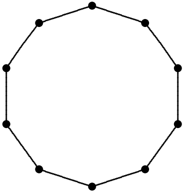
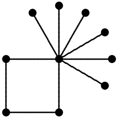


10 spanning trees

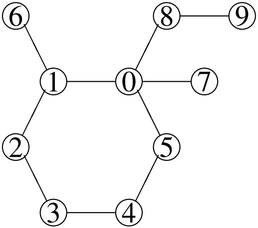


4 spanning trees

The loop design is uniquely D-optimal when $b = t$.

A-optimality

If $b = t$, the graph contains a single circuit.



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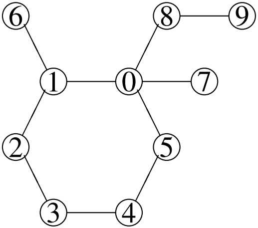

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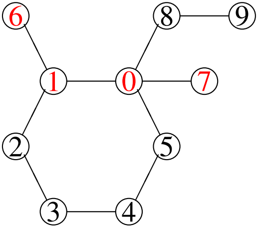

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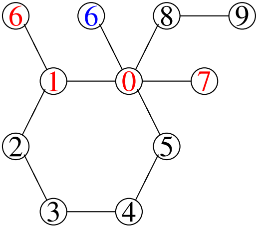

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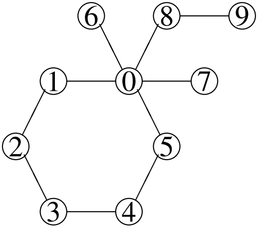

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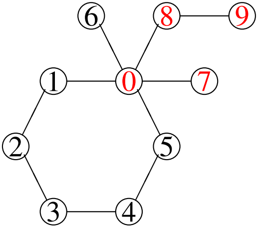

$$V_{97} = V_{98} + V_{80} + V_{07} = V_{80} + 4\sigma^2$$

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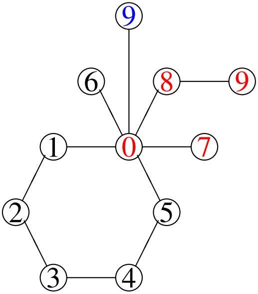

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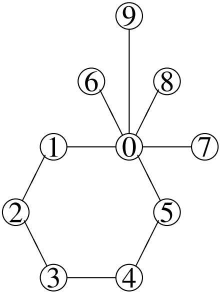

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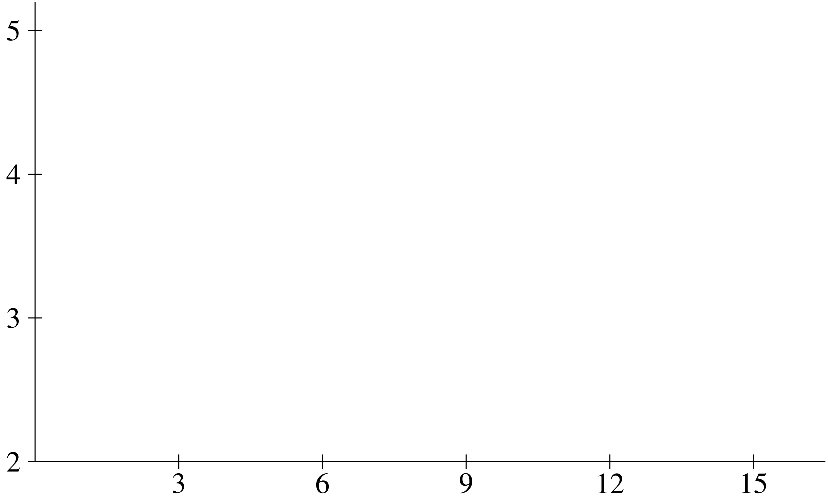
Let $V_{ij} =$ variance of estimator of $\tau_i - \tau_j$.

For a given size of circuit, the total variance is minimized when everything outside the circuit is attached to the same vertex of the circuit.

A-optimality: continued

Average pairwise variance is a cubic function of the size of the circuit.



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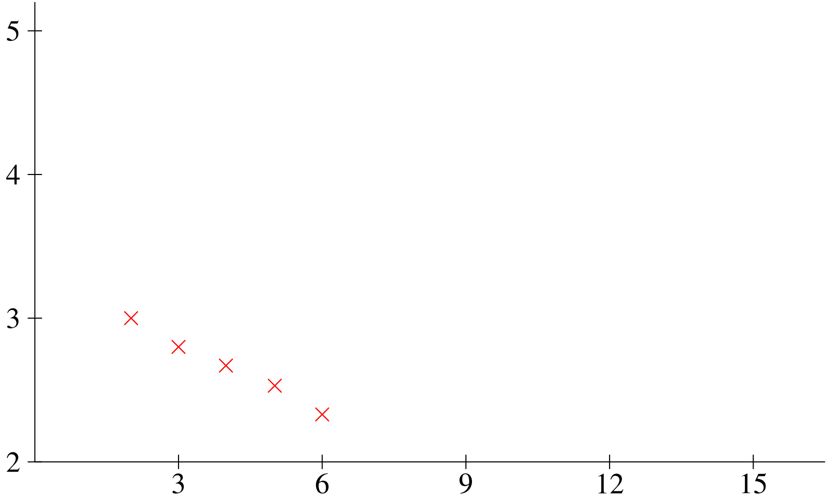

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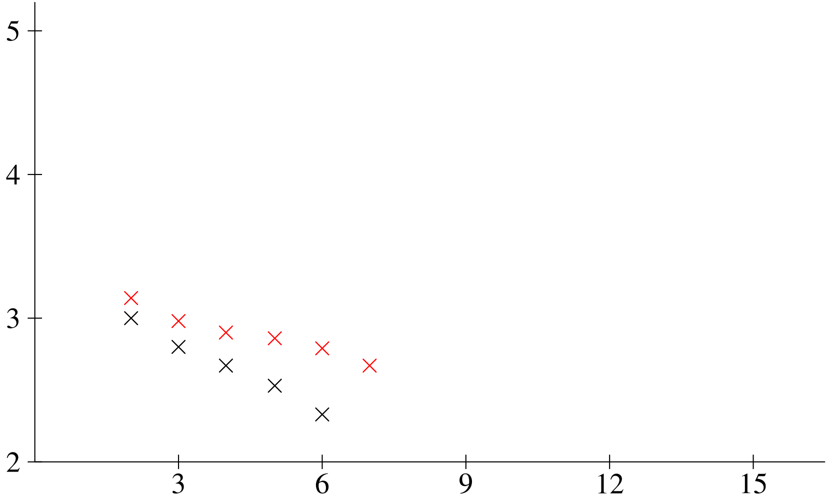

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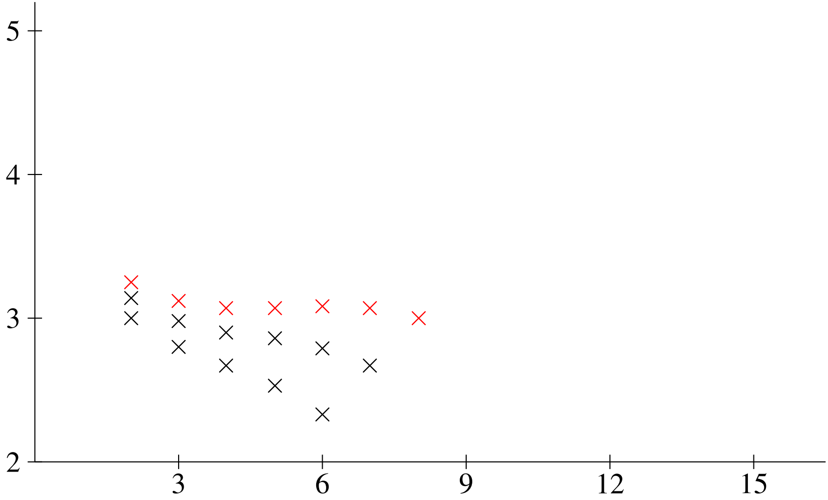

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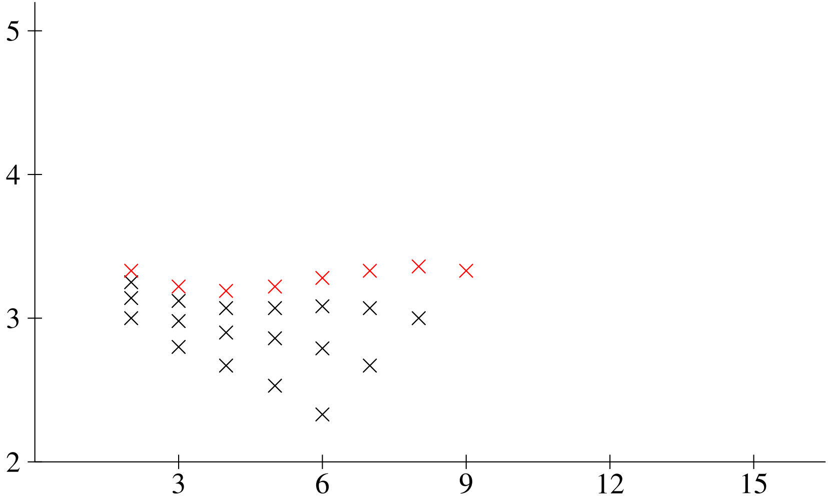

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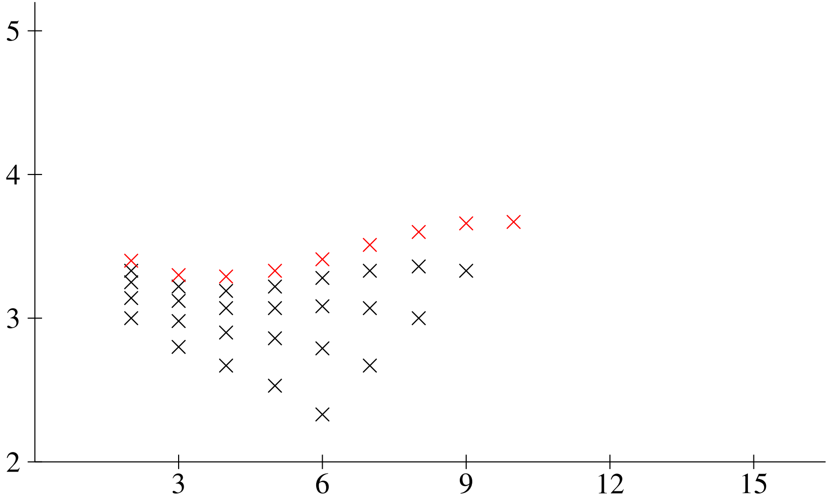

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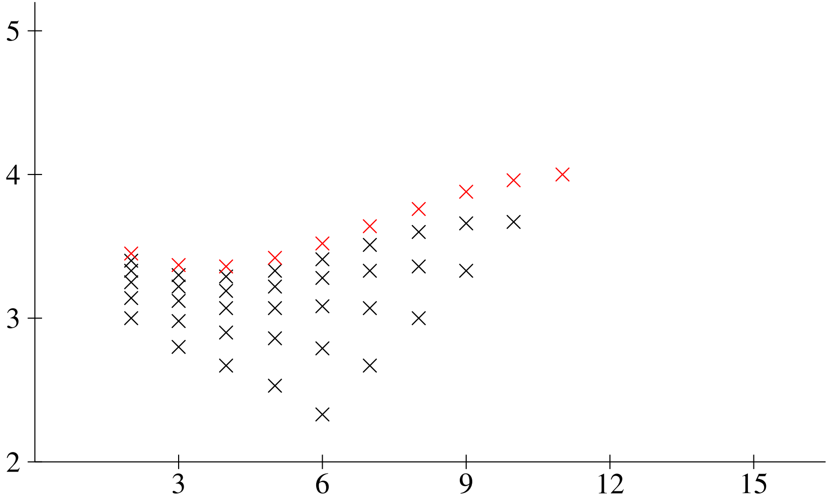

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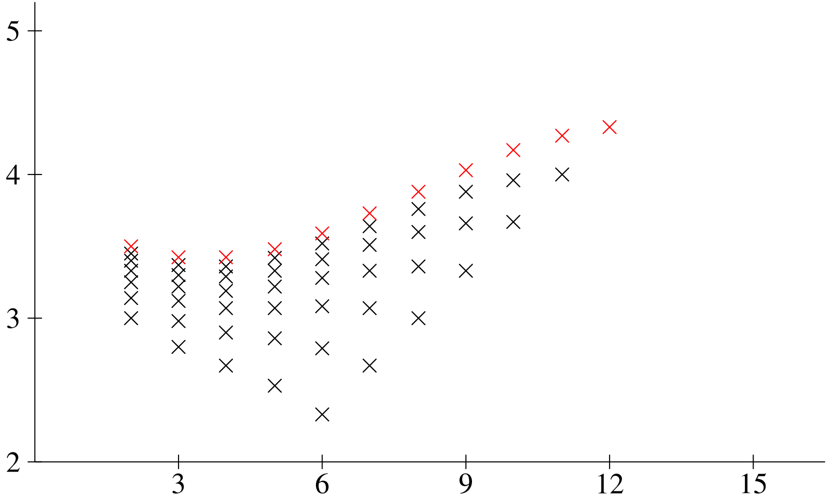

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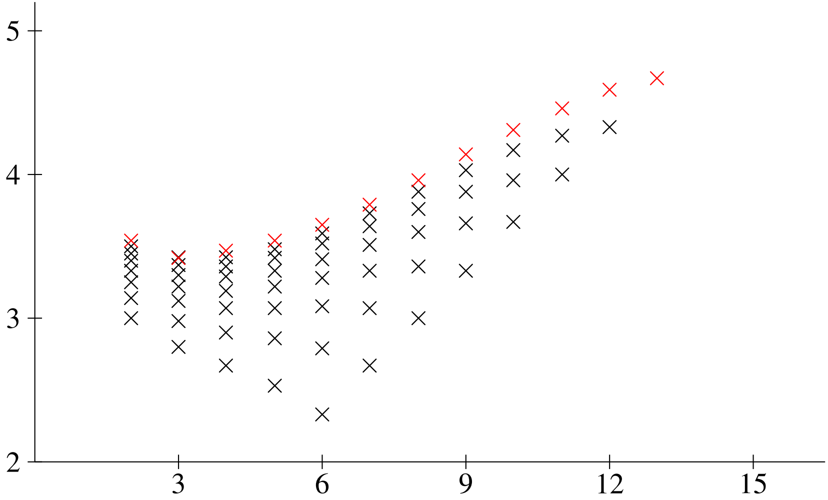

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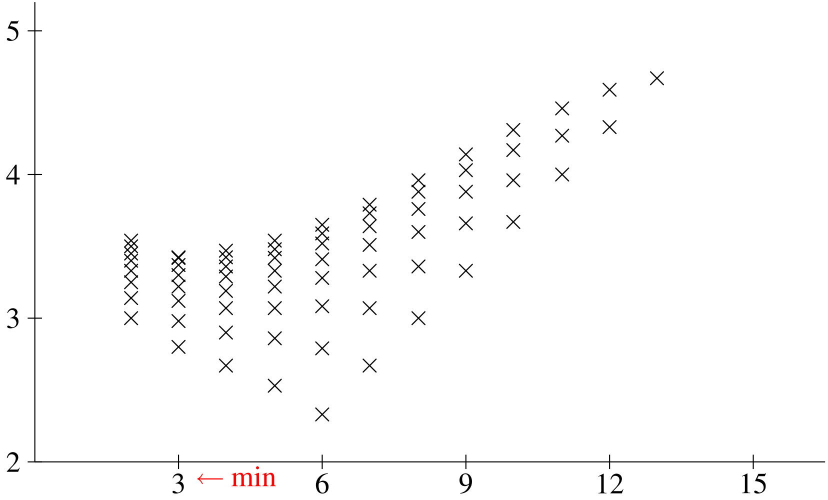
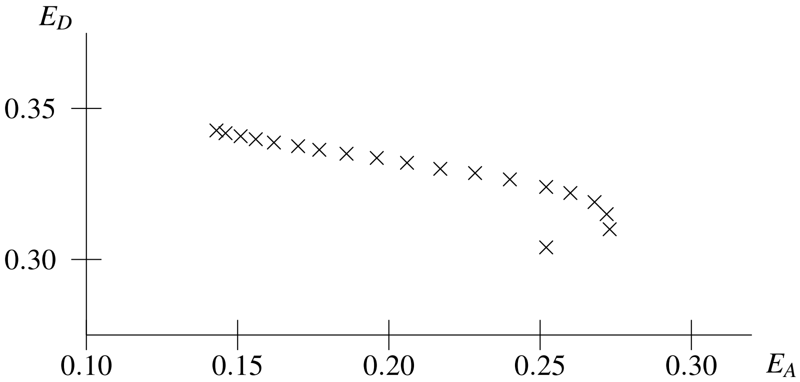


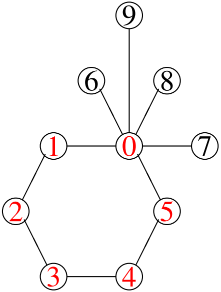
Optimality criteria for designs for 20 treatments in 20 blocks



The two criteria give essentially reverse rankings.

Assigning colours to a circuit with leaves

The difference between the colours can be estimated only from the circuit.



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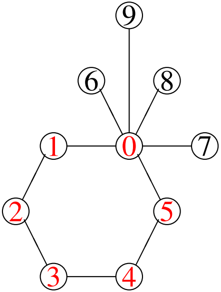

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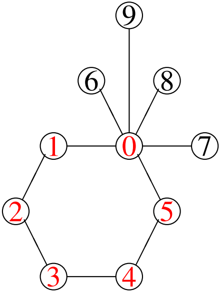

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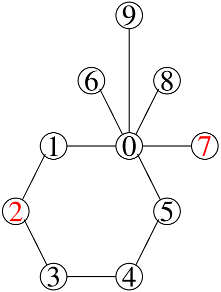

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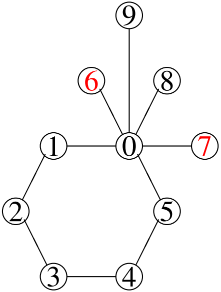

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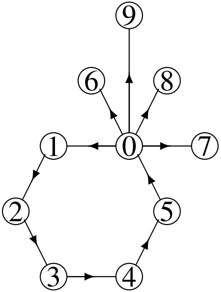
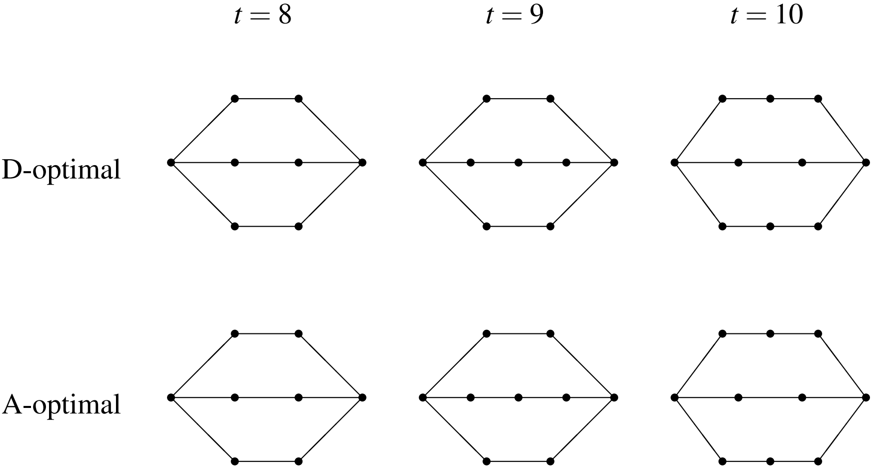


What happens when $b = t + 1$?

A similar analysis shows that the A-optimality and D-optimality criteria conflict when $t \geq 12$.

Optimal designs when $b = t + 1$



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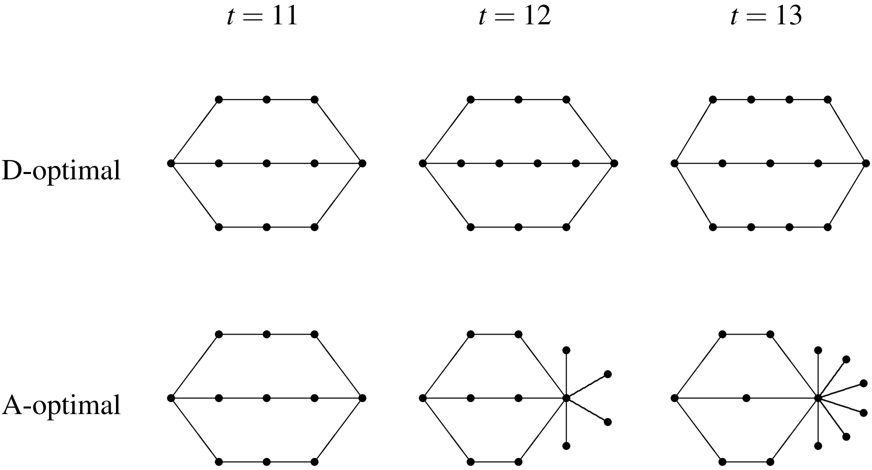

What happens for larger values of $b - t$?

Bad news theorem

Given any fixed value of $b - t$, there is a threshold T such that when $t \geq T$ the A- and D-optimality criteria conflict.

In fact, when $t \geq T$, the A-better designs have many vertices of valency 1 (leaves) attached to single vertex of some small graph, whereas the D-better designs have no leaves.

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Good news theorem

Inserting 1 or 2 (or sometimes 3) vertices into the edges of a graph with no leaves gives a lower average pairwise variance than attaching the extra vertices to a single vertex of that graph.

Strategy for choosing a design when $t/8 \le b - t \le t/2$

1. Choose the best equireplicate design for $2(b-t)$ treatments in $3(b-t)$ blocks, including dye allocation.
2. Insert up to 2 treatments in each edge.

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Forestry example

$t = 10 + 1 = 11$

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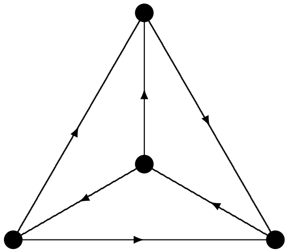

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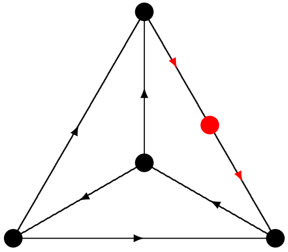

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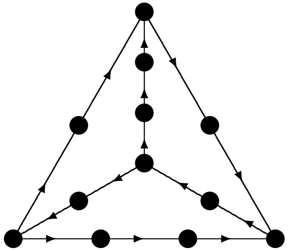

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   1.3 Using the algorithm from Hall's Marriage Theorem, (also König's Theorem) orient the edges so that each lower vertex has 2 out-edges and 1 in-edge and each upper vertex has 1 out-edge and 2 in-edges.
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$t = 216$

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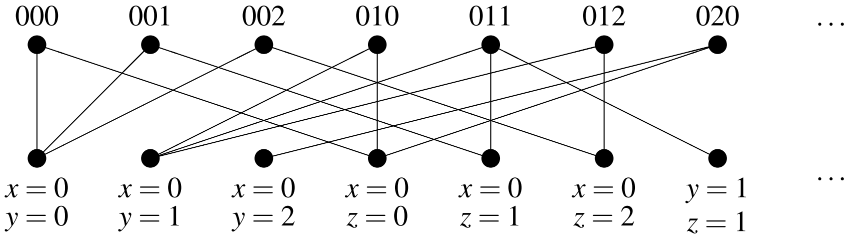
Its Levi graph has 54 vertices and 81 edges.



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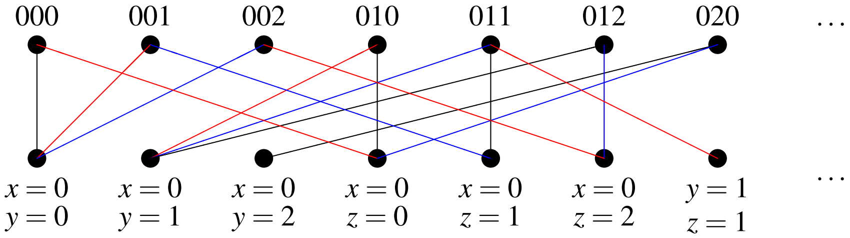

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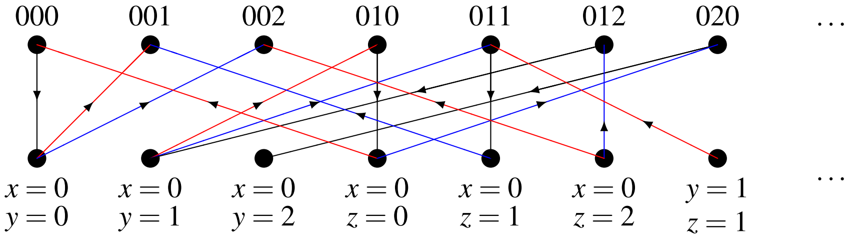

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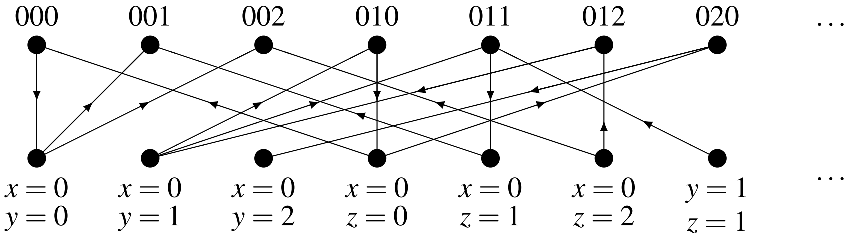

Inserting 2 vertices into each edge gives 216 vertices and 243 edges.