Should phase II cancer sreening trials include a control arm?

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Objective

To evaluate the assets and drawbacks of including a control arm into Phase II cancer screening trials.

Methods

Recent literature, discussion with physicicans and statisticicans, simulations studies.

Results I

Assets:

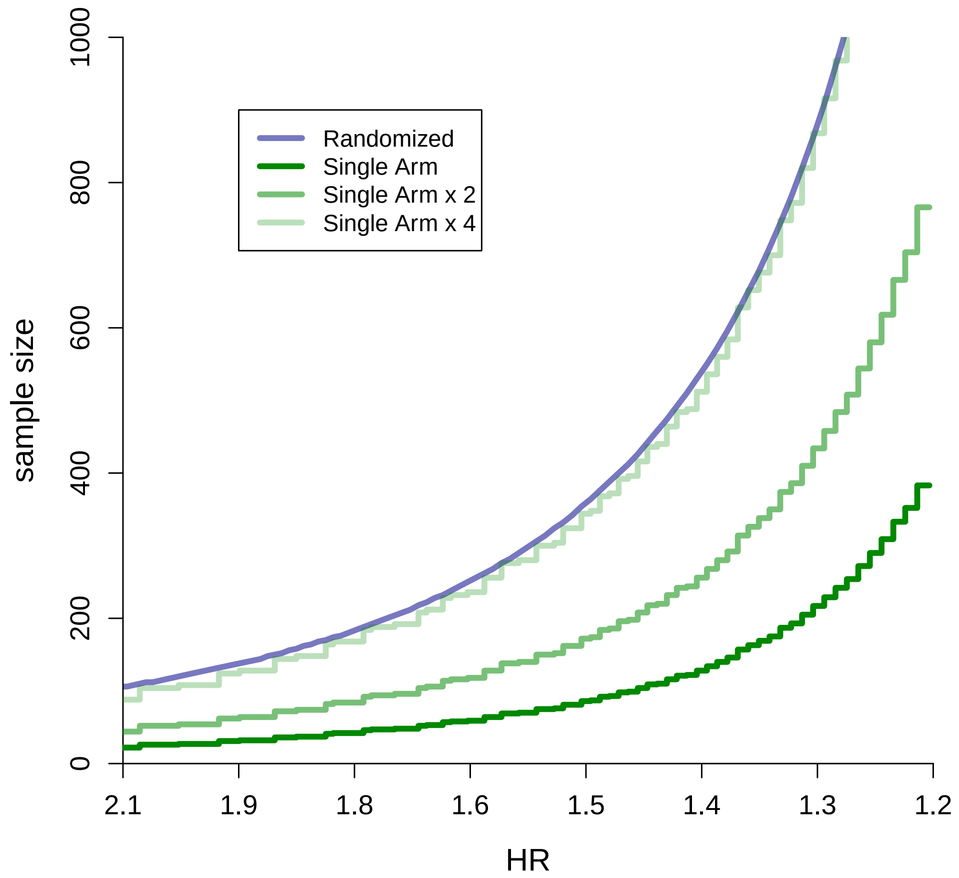
- Avoid uncertainty of historical controls and bias due to selection criteria.
- Reduce the risk of false positive results.
- Higher qualification of evidence and thus easier to be published.
- Possibly more appropriate to test combination therapies, cytostatic drugs and 'biologics' in particular.
- Appropriate if the patient population is heterogenous.

Results II

Downside:

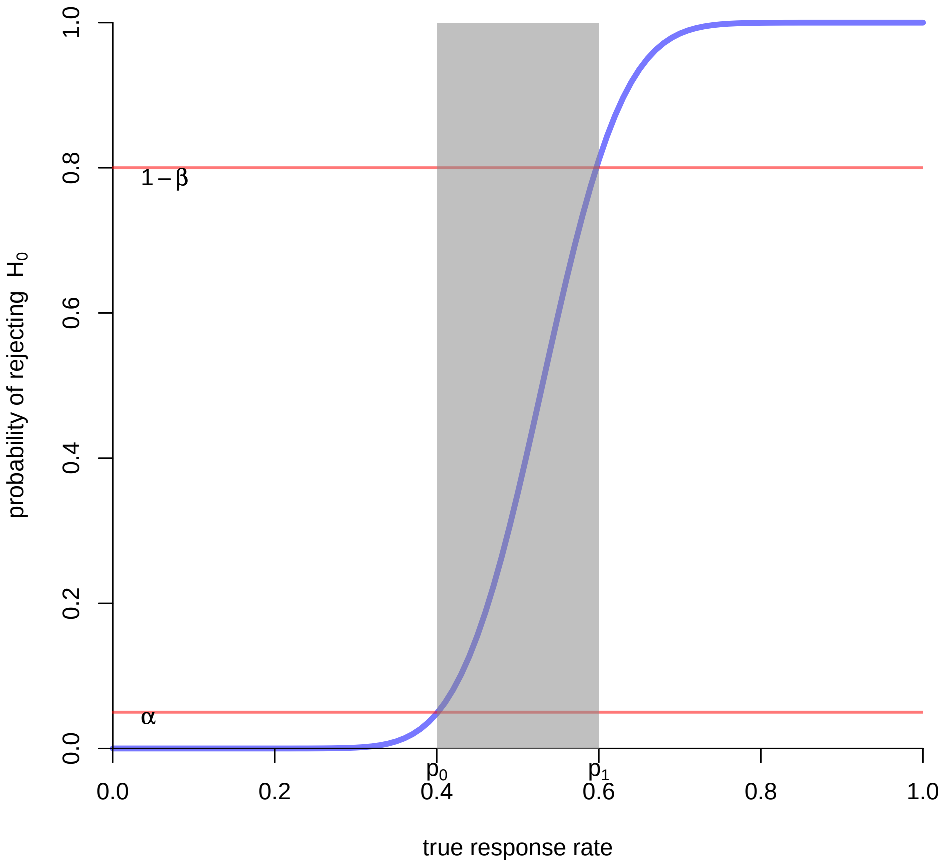
- Less feasible and more expensive.
- Not feasible for rare diseases.
- Compromise on power and significance to keep the sample size low.
- Sometimes appear merely as underpowered phase III trials and are misinterpreted by physicians.

Information is costly

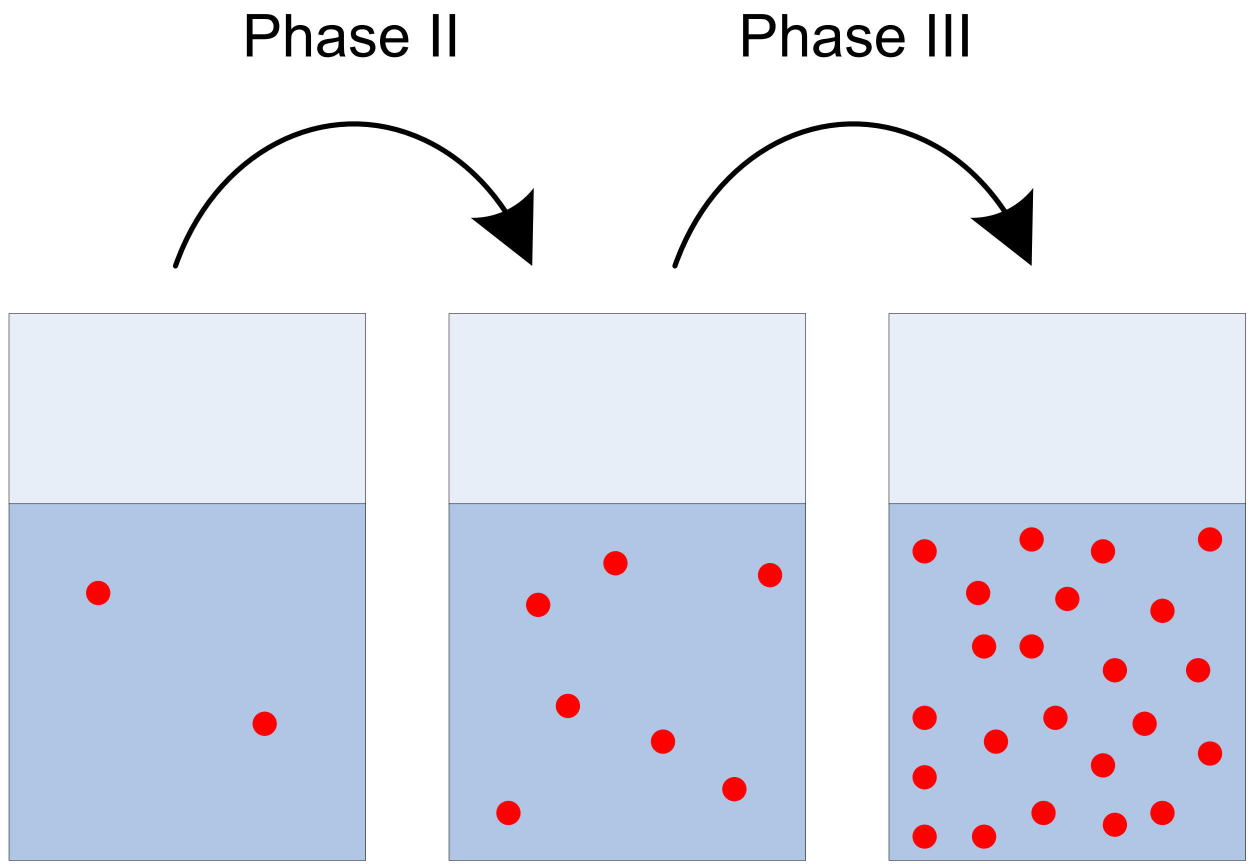


Twilight zone in Simon's design

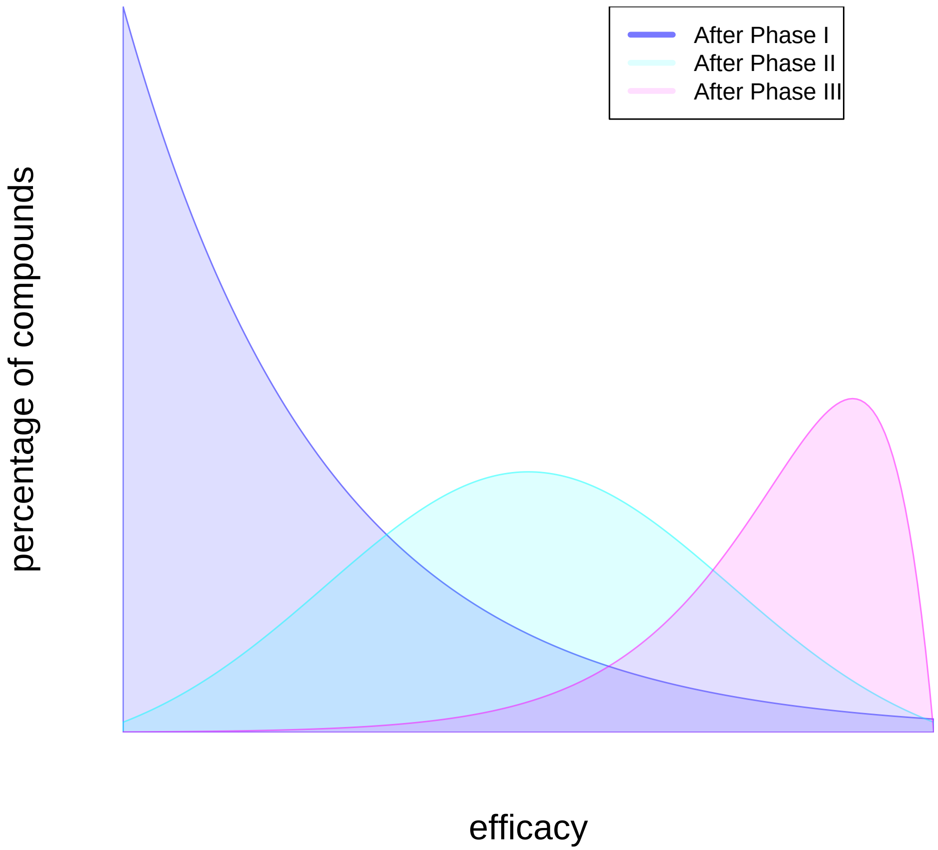
$\left(p_0 = 0.4, p_1 = 0.6, \alpha = 0.05, 1 - \beta = 0.8\right)$



Model of the 3 buckets



"Enrichment" of effective compounds (aka model of the 3 buckets)



Simulation of the first bucket (after Phase I)

a. Poor

Draw 10000 normally distributed numbers ($i \in R, \mu = 0, \sigma = 1$)

Calculate $i = |(\frac{-\log_2 i}{10})|$

If $i > 1$: $i = i/2$

b. Medium

Pick a random sample of $n = 100$ and replace them with uniformly distributed numbers $0 < i < 1$, $i \in R$

c. Rich

Pick a random sample of $n = 1000$ and replace them with uniformly distributed numbers $0 < i < 1$, $i \in R$

Simulation of the second bucket (after Phase II)

Draw a sample of 10000 with replacement.

a. Blunt:

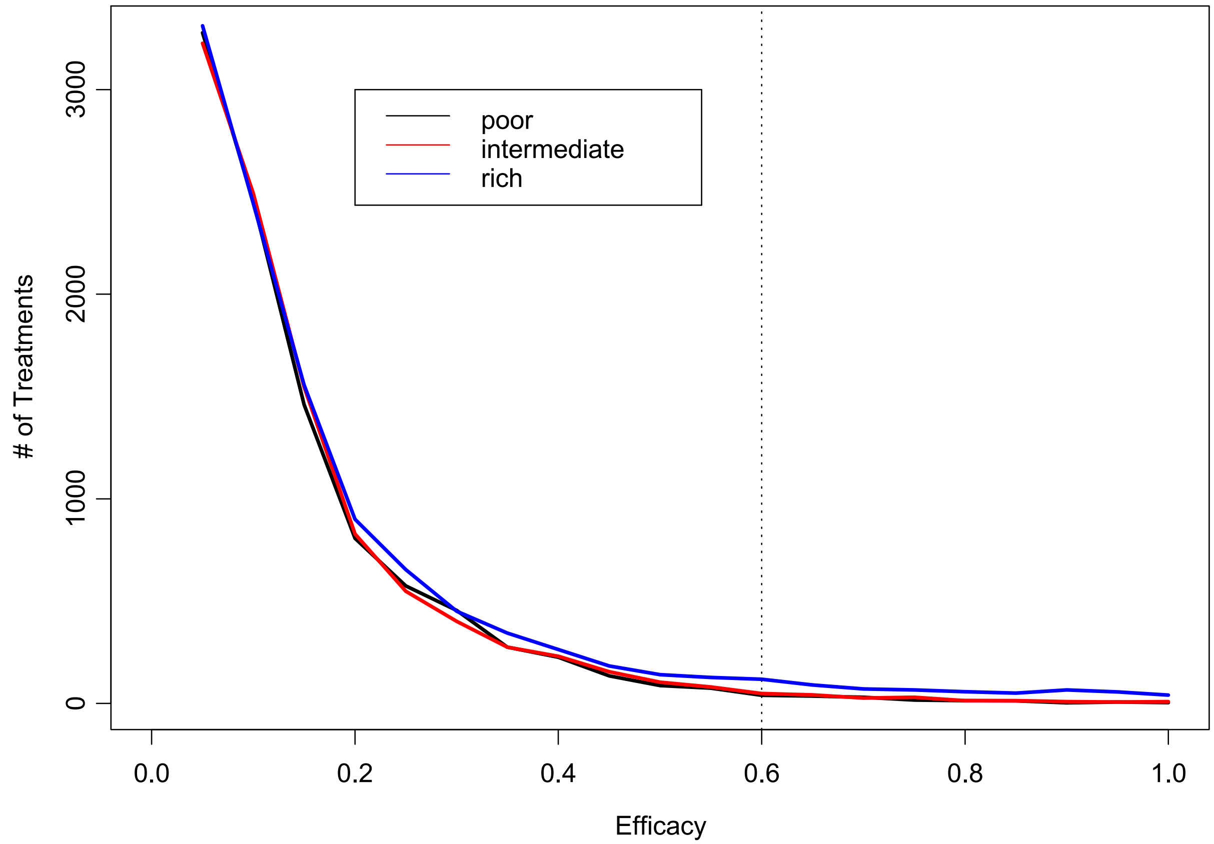
$$p = \begin{cases} \alpha & p_t \leq p_1 \\ 1-\beta & p_t > p_1 \end{cases} \quad (1)$$

b. Simon's two stage design:

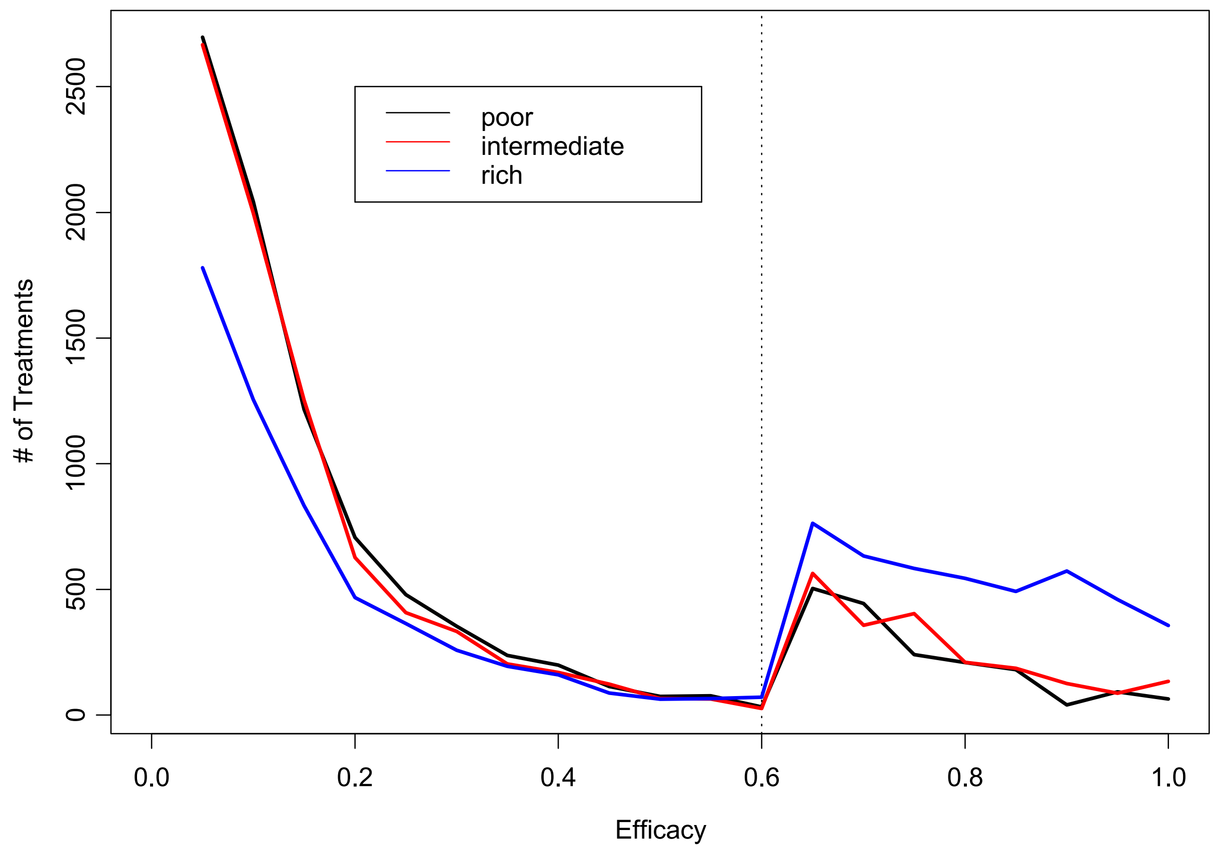
$$p = 1 - \left(B(r_1, p_t, n_1) + \sum_{x=r_1+1}^{min(n_1,r)} b(x, p_t, n) B(r - x, p_t, n_2)\right) \quad (2)$$

$\alpha = 0.05, \beta = 0.2, p_1 = 0.6, p_0 = 0.4$

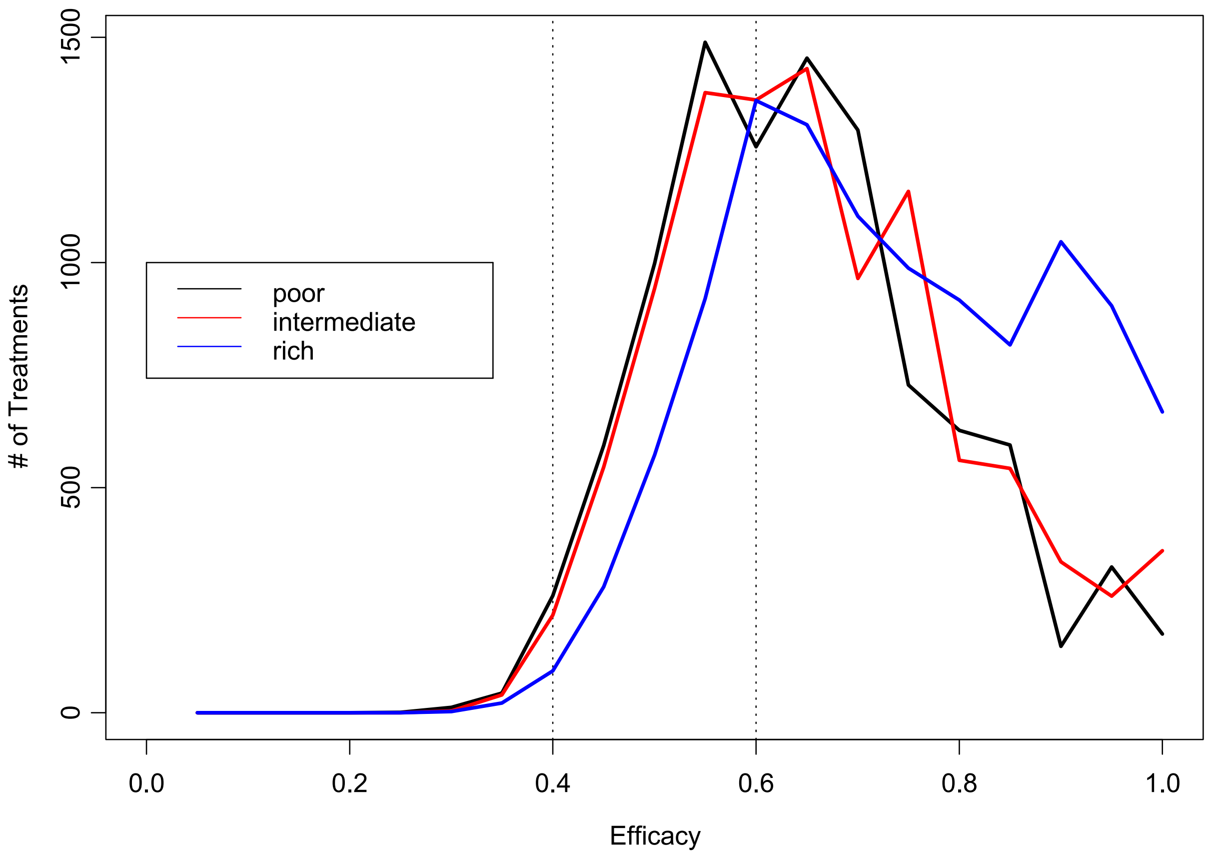
After Phase I (aka 1st bucket)



After Phase II (aka 2nd bucket)



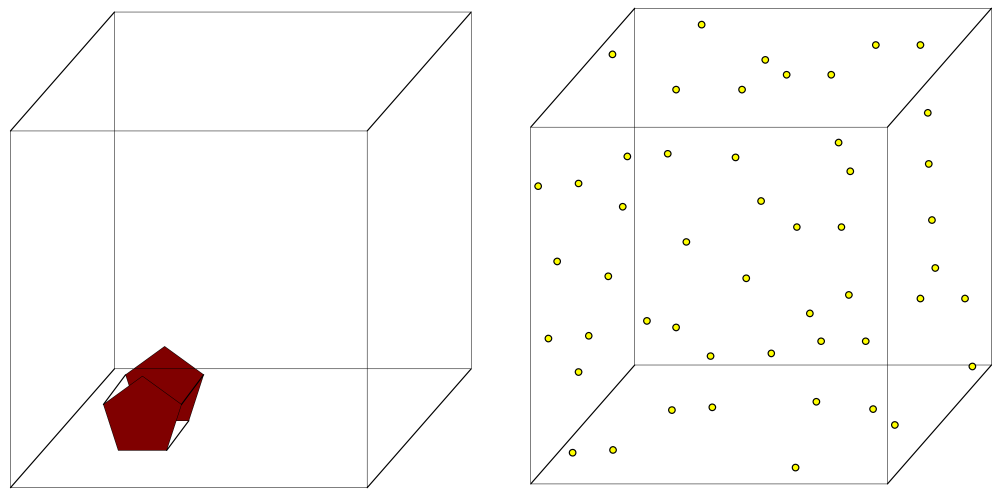
After Phase II, Simon's $(n_1 = 21, n_2 = 20, r_1 = 9, r = 21)$



Dirk observed:

"It is a convolution of Simon's function and the prior distribution of treatments"

Perspective I: Prior distribution determines the search algorithm — learn from the treasure seekers!



Perspective II: Beware of local maxima!