Sample size calculations using Bayesian optimisation

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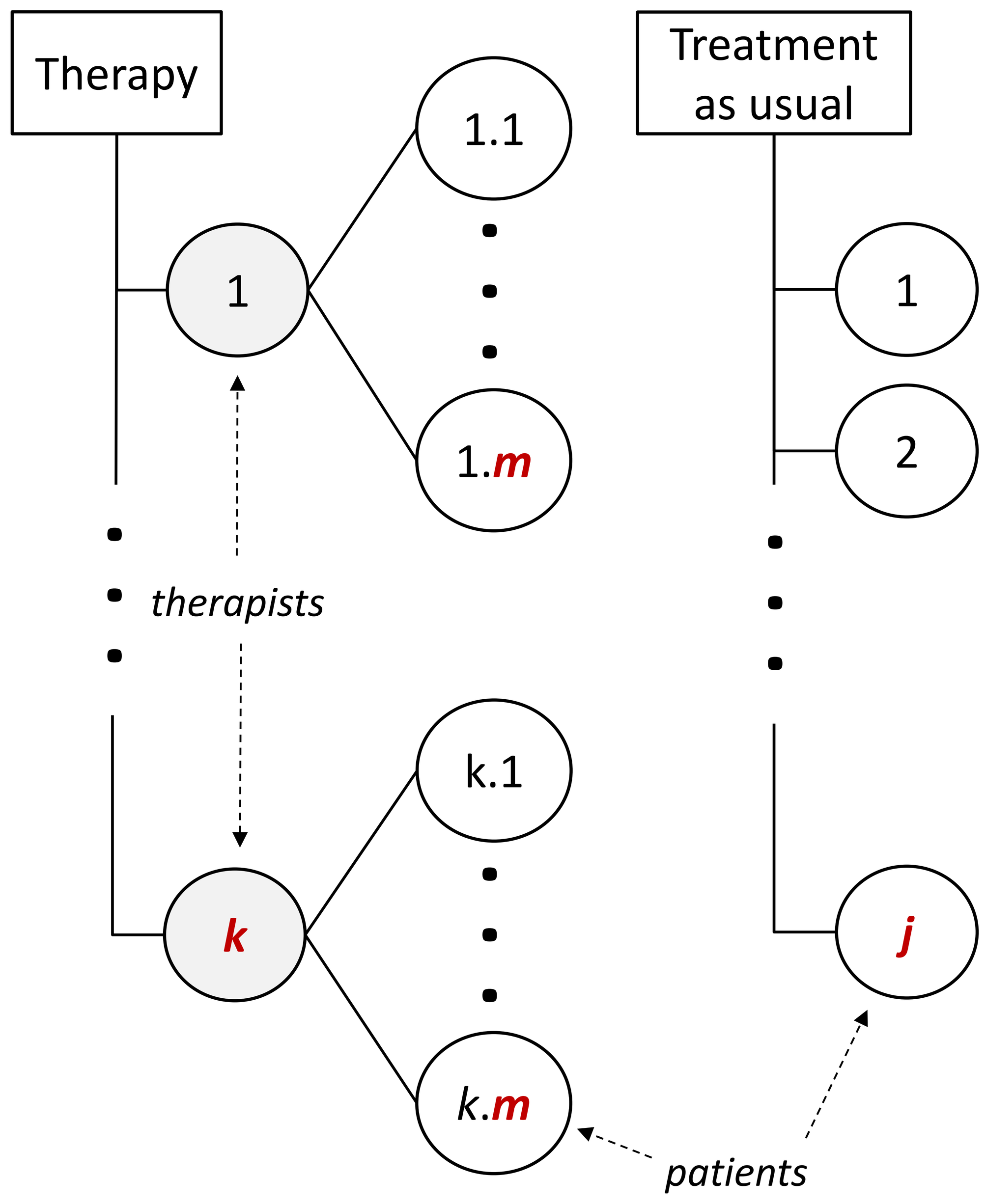
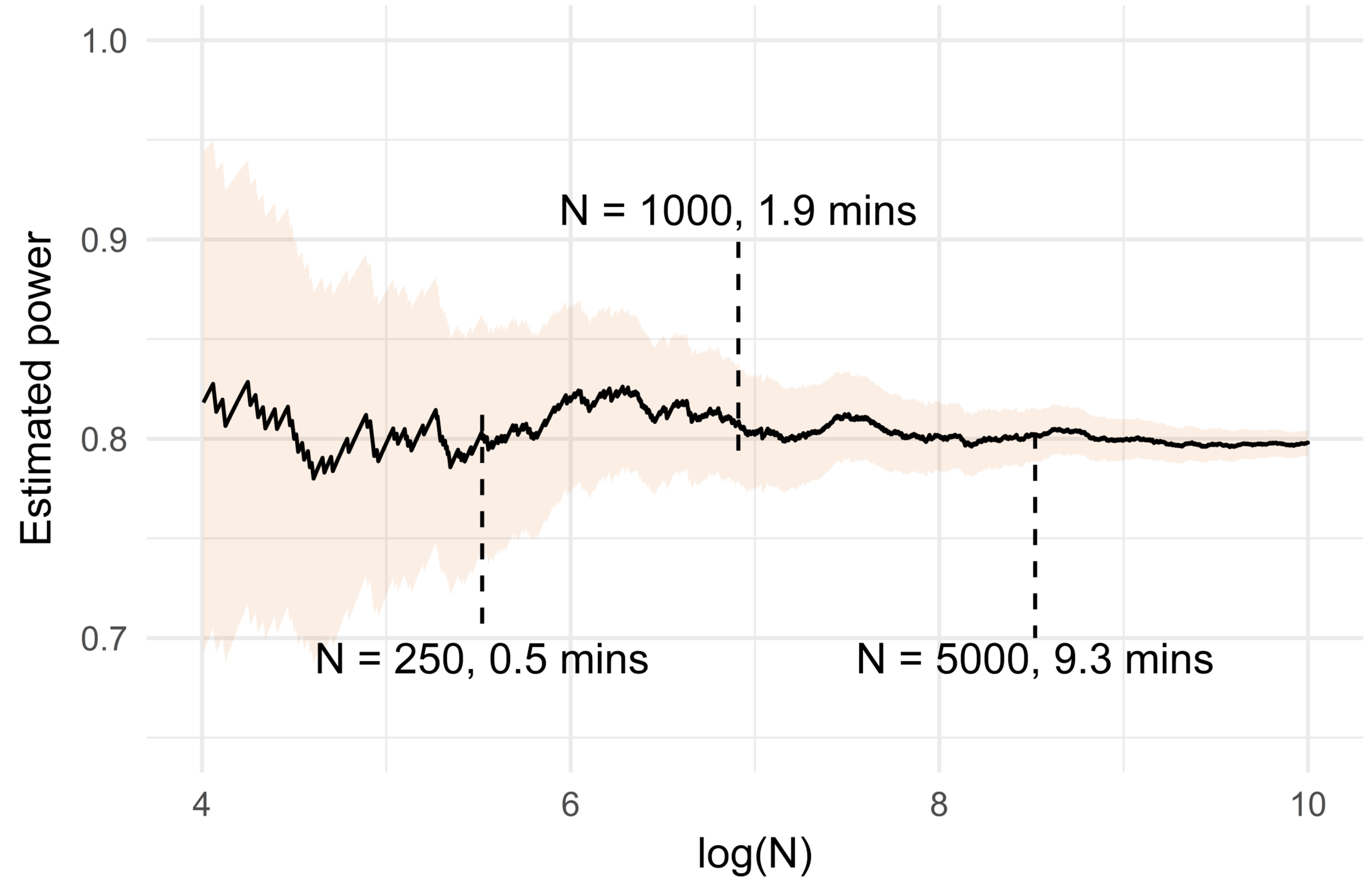
Background

- We consider a partially nested design where there are ***k*** therapists in the intervention arm, each treating an average of ***m*** patients, and there are ***j*** patients in the control arm (*see right*).
- To analyse, we will fit a **partially nested heteroskedastic model** for a continuous patient outcome, accounting for clustering in the intervention arm **[1]**. A likelihood ratio test will be used to test the hypothesis of no treatment effect.
- For $k \in \{3, 30\}$, $m \in \{3, 40\}$, $j \in \{100, 500\}$, we have **over 500,000 possible designs** to choose from.

Questions:
1) Which designs give sufficient power?
2) Which of these minimise the size of the trial?
3) To what extent can we trade-off the number of therapists against the total number of patients?

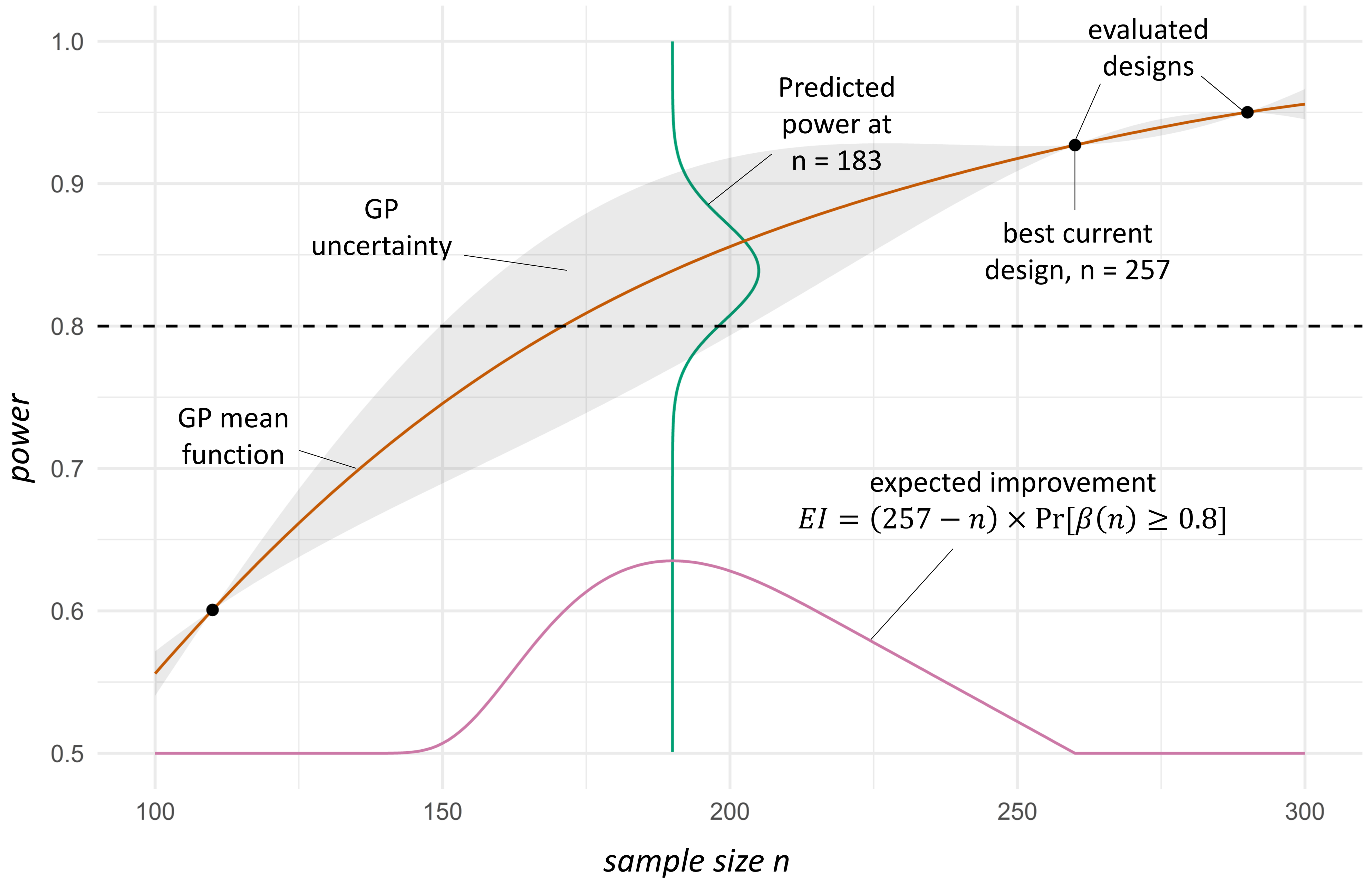


No closed form expression for power calculation Is available, but we can **estimate power using Monte Carlo simulation [2]**. However, this can require a considerable number of Monte Carlo samples N, and therefore considerable time, to deliver a precise estimate (*see below*).



Methods

- Because estimating power takes so long, we can only do so for a small (< 200) number of designs.
- However, given some estimates, we can construct a **surrogate model** of the true power function.
- We use a **Gaussian process** (GP) model, which is both flexible and leads to tractable calculations.
- A GP model characterises our belief about the power of a design by a normal distribution, giving both a point prediction (the mean) and a measure of the uncertainty in that prediction (*see below*).
- GP models are commonly used in a wide variety of fields, and several R packages for fitting GPs are available.



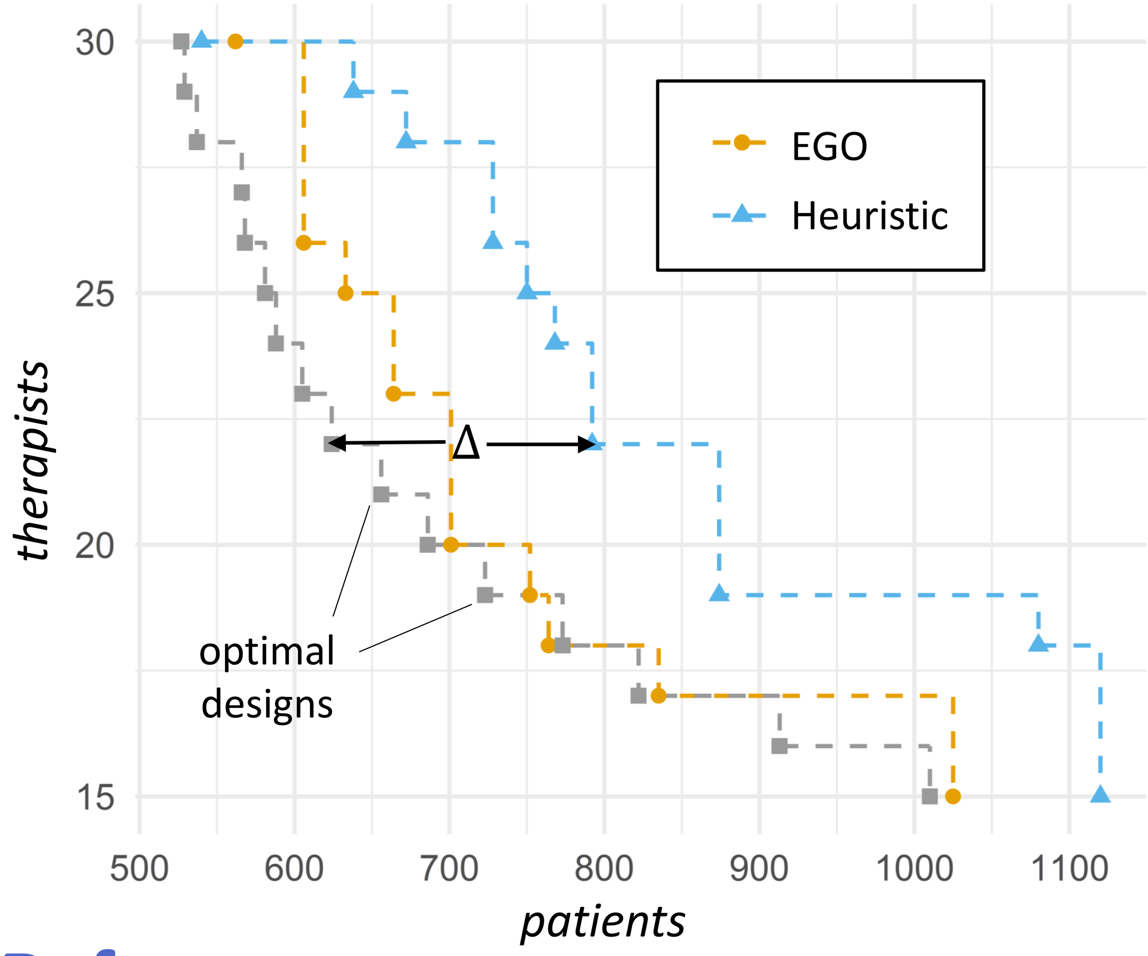
Model-assisted Efficient Global Optimisation (EGO)

- Given a GP model of the power function and the uncertain predictions it provides, we can ask questions like:
  - If I estimate the power of a new design, what is the probability that it will be sufficient?
  - Compared with the best design I have found so far, what improvement can I expect to see if I estimate the power of this new design?
- When minimising a single criteria, we can guide the search process by estimating the power of the design which gives the largest **expected improvement [3]** (*see left*).
- Our partially nested design is more complex – we want to minimise both the number of therapists *k* and the total number of patients *n*.
- At each iteration in the algorithm (*see below*) we select a random weight w and define the quality of a design as *wk* + (1-*w*)*n.* We then treat this as the single criteria we want to minimise, subject to power.
- By selecting a random weight *w* at each iteration, we find a range of designs with different trade-offs between the two criteria.

The algorithm

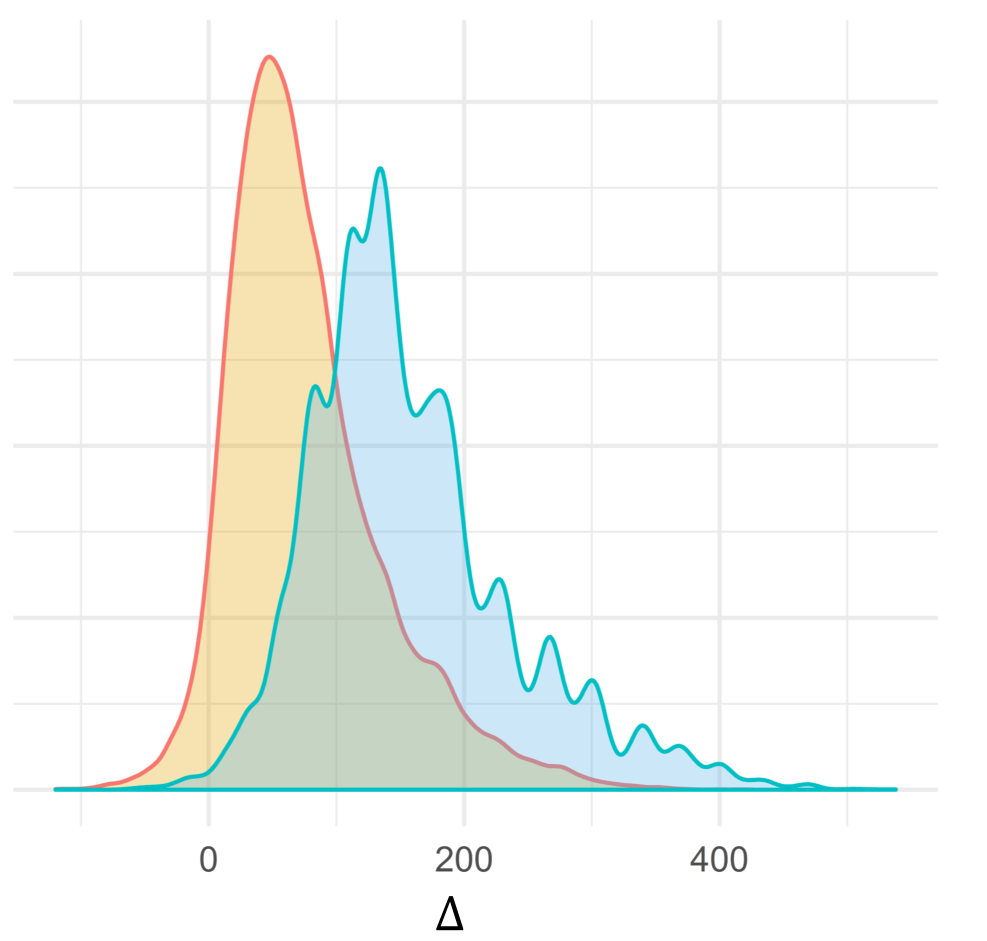
1. Choose an initial set of designs X.
2. Compute the Monte Carlo power estimate at each $x \in X$.
3. Using a random weight w, calculate the value y of each $x \in X$.
4. Fit a Gaussian process model $f(x)$ as a surrogate for $\beta(x)$.
5. Find the value y_* of the best design $x \in X$ which is almost certainly adequately powered, according to the model f.
6. Find the design $x \notin X$ with the largest expected improvement.
7. Compute the Monte Carlo estimate of the power at x and add x to X.
8. Repeat steps 3 – 7 until the computational budget is exhausted.

Illustration



To illustrate and evaluate the EGO method, we contrast it with a simple heuristic when determining sample size for the above partially nested psychotherapy example.

- In a single application, we compare the performance of EGO and the heuristic.
- The EGO algorithm finds **more efficient designs** – for equal numbers of therapists, EGO designs can require as many as 220 fewer patients.
- The EGO designs are quite close to the optimal designs (*see left*).
- Over 1000 applications, we count the differences Δ between the obtained and optimal designs' patients.
- On average, the EGO algorithm requires 80 fewer patients than the heuristic.
- EGO is also more likely to locate a design for each feasible k – the heuristic will miss a feasible k around 15% of the time.



References

[1] Roberts, C. & Roberts, S. A. (2005), Design and analysis of clinical trials with clustering effects due to treatment, *Clinical Trials*, 2, 152-162. **[2]** Landau, S. & Stahl, D. (2013), Sample size and power calculations for medical studies by simulation when closed form expressions are not available, *Statistical Methods in Medical Research*, 22, 324-345. **[3]** Jones, D. R. (2001), A Taxonomy of Global Optimization Methods Based on Response Surfaces, *Journal of Global Optimization*, 21, 345-383.

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