Calculating the expected utility of a pilot trial

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Introduction

Last time

We talked about a Bayesian solution to a frequentist trial design problem:

- External pilot trial followed by a definitive trial
- Both trials to be analysed using a hypothesis test
- Needed to choose type I and II error rates $\alpha_i, \beta_i, i = 1, 2$ at each stage
- Proposed to choose the rates which maximised expected utility, w.r.t. a prior distribution

We focussed on how to choose an appropriate utility function.

A Bayesian approach

Rather than making a stop/go decision at the pilot stage through a frequentist hypothesis test, we could instead do a Bayesian decision-theoretic analysis:

- Given pilot data x_1, get the posterior $\mu|x_1$
- Choose α_2, β_2 to maximise expected utility w.r.t. this posterior

With this analysis in mind, how large should the pilot trial be?

To simplify:

- Fix $\alpha_2 = 0.025$, so just need to choose β_2 or, equivalently, the definitive sample size n_2
- Assume the pilot data can be summarised in a single sufficient statistic (e.g. a sample mean)

Notation

μ: unknown parameter(s) of interest, with prior $p(\mu)$

n_1, n_2: sample size for pilot (1) and definitive (2) trials

x_1, x_2: data from the pilot (1) and definitive (2) trials

- Utility is a function of these:

$$u(\mu, n_1, n_2.x_1, x_2)$$

Maximising expected utility

Given pilot data x_1 from a pilot of sample size n_1:

$$\max_{n_2} \ \mathbb{E}_{\mu, x_2 | x_1, n_1} \left[u(\mu, n_1, n_2 . x_2) \right]$$

Maximising expected utility

Given a pilot of sample size n_1, average over the pilot data x_1:

$$\mathbb{E}_{x_1|n_1}\Big(\quad \max_{n_2} \ \mathbb{E}_{\mu,x_2|x_1,n_1}\big[u(\mu, n_1, n_2.x_2)\big] \quad \Big)$$

Maximising expected utility

Find optimal pilot sample size n_1:

$$\max_{n_1}\left[\quad \mathbb{E}_{x_1|n_1}\left(\quad \max_{n_2}\ \mathbb{E}_{\mu,x_2|x_1,n_1}\left[u(\mu, n_1, n_2.x_2)\right]\quad\right)\quad\right]$$

Computation

Two-level nested Monte Carlo

For now, forget about choosing pilot sample size. Given some n_1, how do we calculate

$$\mathbb{E}_{x_1|n_1}\left(\quad \max_{n_2} \mathbb{E}_{\mu,x_2|x_1,n_1}\left[u(\mu, n_1, n_2.x_2)\right] \quad \right)$$

We can:

- $\mathbb{E}_{x_1|n_1}$ - sample N pilot data $x_1^{(i)} \sim p(x_1, |n_1)$
- $\max_{n_2}$ - exhaustive / bisection / other search
- $\mathbb{E}_{\mu,x_2|x_1,n_1}$ - sample M posterior parameters $\mu^{(j)} \sim p(\mu|x_1, n_1)$

Computational bottleneck: for each outer pilot data sample $x_1^{(i)}$, need to generate a set of posterior samples (through MCMC).

An alternative

Note that the inner optimisation problem maps pilot data x_1 to definitive sample size n_2:

$$f(x_1) = \underset{n_2}{\operatorname{argmax}} \; \mathbb{E}_{\mu, x_2 | x_1, n_1}\left[u(\mu, n_1, n_2.x_2)\right]$$

$$f : \mathcal{X}_\infty \to \mathbb{N}$$

We can re-write our earlier expression using $f(x_1)$:

$$\mathbb{E}_{x_1}\left(\mathbb{E}_{\mu, x_2 | x_1}\left[u(\mu, n_1, n_2 = f(x_1), x_2)\right]\right)$$

Now, with the "max" removed, we can move around our expectations:

$$\begin{aligned}
& \mathbb{E}_{x_1}\left(\mathbb{E}_{\mu, x_2 | x_1}\left[u(\mu, n_1, f(x_1), x_2)\right]\right) \\
= \; & \mathbb{E}_{\mu, x_1, x_2}\left(u(\mu, n_1, f(x_1), x_2)\right) \\
= \; & \mathbb{E}_{\mu, x_1}\left(\mathbb{E}_{x_2 | \mu, x_1}\left[u(\mu, n_1, f(x_1), x_2)\right]\right)
\end{aligned}$$

Single-level MC

We now have something we can estimate in a single-level Monte Carlo scheme:

$$\mathbb{E}_{\mu,x_1}\Big(\mathbb{E}_{x_2|\mu,x_1}\big[u(\mu,n_1,f(x_1),x_2)\big]\Big)$$

- $\mathbb{E}_{\mu,x_1}$ - sample N $(\mu^{(i)},x_1^{(i)}) \sim p(\mu,x_1|n_1) = p(x_1|\mu,n_1)p(\mu)$

$$\begin{aligned}\mathbb{E}_{x_2|\mu,x_1}\big[u(\mu,n_1,f(x_1),x_2)\big] = \; & Pr[x_2 > c_2|\mu,n_2]\; u(\mu,n_1,n_2,x_2 > c_2) + \\ & Pr[x_2 \leq c_2|\mu,n_2]\; u(\mu,n_1,n_2,x_2 \leq c_2),\end{aligned}$$

where c_2 is the critical value in the definitive trial hypothesis test.

- $\mathbb{E}_{x_2|\mu,x_1}$ - can be calculated exactly if the power function $Pr[x_2 > c_2|\mu,n_2]$ is known

Optimisation

But, we do not know the optimal decision rule $f(x_1)$. Note that

$$\mathbb{E}_{x_1}\Big(\max_{n_2} \; \mathbb{E}_{\mu,x_2|x_1}\big[u(\mu, n_1, n_2.x_2)\big]\Big)$$

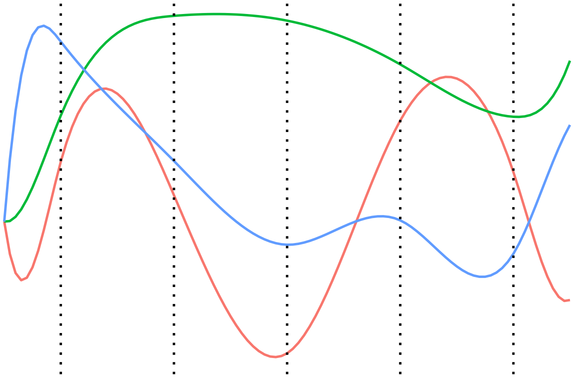
$$\geq$$

$$\mathbb{E}_{\mu,x_1}\Big(\mathbb{E}_{x_2|\mu,x_1,n_1}\big[u(\mu, n_1, f(x_1), x_2)\big]\Big), \text{ for all } f.$$

$\Rightarrow$ if we can search over functions $f(x_1)$ and find that which maximises expected utility, this will coincide with the optimal decision rule.

Splines

Spline: a piecewise polynomial defined by a set of *knots* and by the degree of the polynomial pieces.



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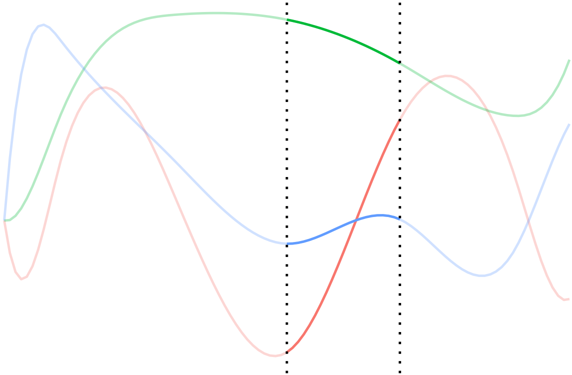


B-splines

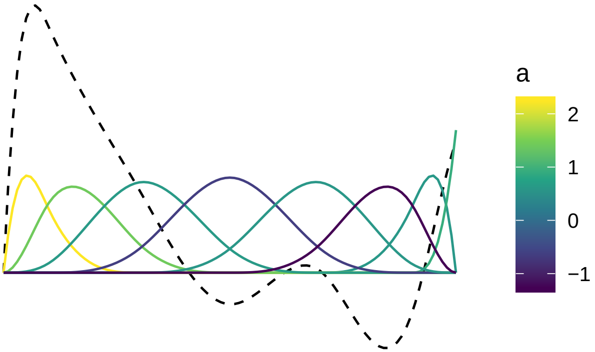
For a specific set of k knots, there is a set of cubic splines which serves as a basis for the space of all cubic splines defined over the same knots.

Denoting these so-called b-splines by $\phi_i(x), k = 1, \ldots, k + 4$, a function can then be written as

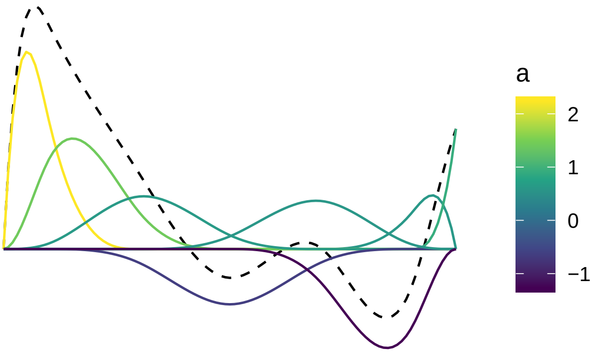
$$f_{\mathbf{a}}(x) = \sum_{i=1}^{k+4} a_i \phi_i(x),$$

So, functions are then defined by a vector of coefficients $\mathbf{a} \in \mathbb{R}^{k+4}$.

Example



Example



Optimisation

An algorithm for estimating the expected utility of a pilot trial with sample size n_1:

- Choose a set of k knots
- Generate a sample $(\mu^{(i)}, x_1^{(i)}) \sim p(\mu, x_1 | n_1), i = 1, \ldots, N$
- While not convereged:
  - select candidate $\mathbf{a} \in \mathbb{R}^{k+4}$
  - calculate $\frac{1}{N} \sum_{i=1}^{N} \mathbb{E}_{x_2 | \mu^{(i)}, x_1^{(i)}} \left[u(\mu^{(i)}, n_1, f_{\mathbf{a}}(x_1^{(i)}), x_2) \right]$
  - check convergence
- Return maximum

Note that we use the same sample from $p(\mu, x_1 | n_1)$ at each iteration.

Application

OK-Diabetes

- Two-arm parallel group pilot and definitive trials, normally distributed primary outcome
- Known outcome variance
- Unknown parameter μ: mean difference, with (conjugate) normal prior
- Utility function from last time (based on change in outcome, total sample size, and treatment costs of the intervention)

Derivatives

The function we are maximising is:

$$
\begin{aligned}
& \frac{1}{N}\sum_{i=1}^{N}\mathbb{E}_{x_2|\mu^{(i)},x_1^{(i)}}\left[u(\mu^{(i)}, n_1, f_{\mathbf{a}}(x_1^{(i)}), x_2)\right] \\
= \ & \frac{1}{N}\sum_{i=1}^{N}\Big[pow(n)(1-e^{-\rho(k_d\mu+k_n(n_1+n_2))})+ \\
& (1-pow(n))(1-e^{-\rho(k_n(n_1+n_2)+k_c)})\Big],
\end{aligned}
$$

where

$$
pow(n) = \Phi\left(z_{1-\alpha/2} - \frac{\mu}{\sqrt{(2\sigma^2/n)}}\right).
$$

We can get the derivative of this function with respect to the vector **a** - helps dramaticaly with optimisation.

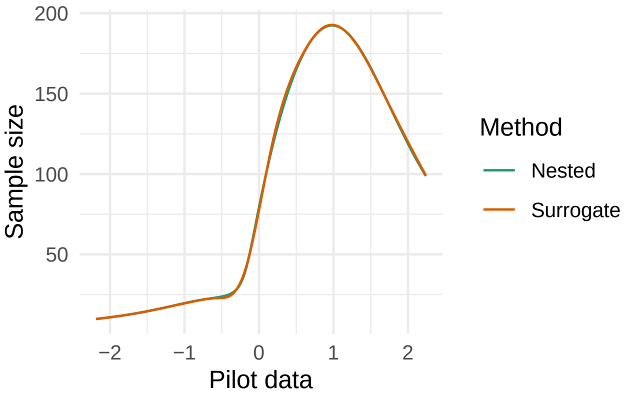
Comparisons

In this case (normal outcome, known variance, conjgate prior) we can get an exact expression for the expected utility of the definitive trial.

So, no need for MCMC sampling or numerical integration for the inner expectation $\rightarrow$ a more accurate answer.

Application

Computation time: 9s (surrogate), 66s (nested)



Extensions

- Optimising over n_1
- Adding a stop/go point
- Adding a decision rule mapping pilot data x_1 to optimal definitive type I error rate α_2
- Allowing for unknwon variance

Unknown variance

Suppose we don't know the variance of the outcome, and have a prior on that as well as the mean.

- The pilot data can now be summarised by a 2D sufficient statistic, the sample mean x_1 and the sample variance y_1
- Now need to map this 2D space to choice of definitive trial sample size

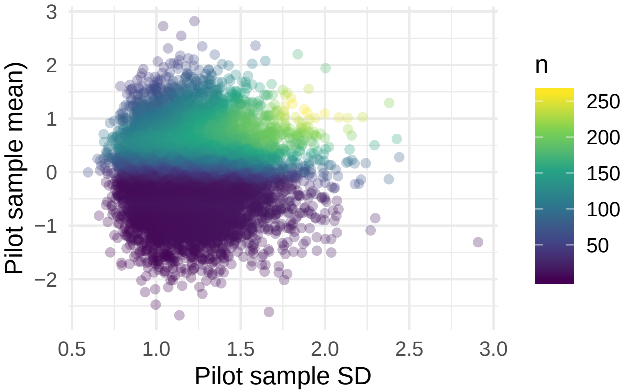
We can use tensor product splines:

$$\sum_{i=1}^{k+4} \sum_{j=1}^{k+4} a_{i,j} \phi_i(x_1) \psi_j(y_1)$$

- Still defined by vector $\mathbf{a}$, but now $\mathbf{a} \in \mathbb{R}^{(k+4)^2}$
- In our example with $k = 10$, solution space dimensions go from 14 to 196
- Impact is managable *if* we have derivatives

Unknown variance

Computation time: 79s



Summary

We can now quickly calculate and maximise the expected utility of pilot trials, making a Bayesian decision-theoretic approach to pilot design and analysis feasible.

But:

- Need only 1 or 2 dimension sufficient statistic
- If 2 dimensions, need derivatives of objective function
- Need an analyticpower function for the definitive trial
- How can we be sure of converegnce to true global optimum?