Untitled

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Introduction

Last time

- 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

Maximising expected utility

- Rather than making a stop/go decision at the pilot stage through a hypothesis test, we could instead use MEU
- Given pilot data x_1, get the posterior $\mu | x_1$ and choose α_2, β_2
- With this analysis in mind, how large should the pilot be?

Simplifications

- 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

MEU

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

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

MEU

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

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

MEU

Find optimal pilot sample size n_1:

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

Computation

Nested MC

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

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

Extremely computationaly intensive.

An alternative

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

$$f(x_1) : \mathcal{X}_\infty \to \mathbb{N}$$

Ignoring optimising over n_1 for now, we can re-write our eearlier expression:

$$\begin{aligned} & \mathbb{E}_{x_1}\Big(\mathbb{E}_{\mu, x_2 | x_1}\big[u(n_1, n_2 = f(x_1), x_2)\big]\Big) \\ = \ & \mathbb{E}_{\mu, x_1, x_2}\Big(u(n_1, f(x_1), x_2)\Big) \\ = \ & \mathbb{E}_{\mu, x_1}\Big(\mathbb{E}_{x_2 | \mu, x_1}\big[u(n_1, f(x_1), x_2)\big]\Big) \end{aligned}$$

Single-level MC

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

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

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

$$\begin{aligned}\mathbb{E}_{x_2|\mu,x_1}\left[u(n_1, f(x_1), x_2)\right] = \; & Pr[x_2 > c_2|\mu, n_2] \; u_1(\mu, n_1, n_2, x_2 > c_2) + \\ & Pr[x_2 \leq c_2|\mu, n_2] \; u_1(\mu, n_1, n_2, x_2 \leq c_2)\end{aligned}$$

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

Optimisation

All very well, but we do not know what the optimal decision rule $f(x_1)$ is. But note that

$$\mathbb{E}_{x_1|n_1}\Big(\max_{n_2}\ \mathbb{E}_{\mu,x_2|x_1,n_1}\big[u(n_1,n_2.x_2)\big]\Big)$$
$$\geq$$
$$\mathbb{E}_{\mu,x_1}\Big(\mathbb{E}_{x_2|\mu,x_1,n_1}\big[u(n_1,f(x_1),x_2)\big]\Big),\ \text{for all } f.$$

$\Rightarrow$ 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.

B-splines

For a specific set of k knots, there is a set of cubic splines which serve 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 thewn be written as

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

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 $(\mu^{(i)}, x_1^{(i)}) \sim p(\mu, x_1 | n_1), i = 1, \dots, N$
- 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.

OK-Diabetes

- Model, prior and utility parameterised as before
- Three approaches to compare:
  - Semi-analytic
  - Two-level nested MC
  - Proposed method

Objective

$$\frac{1}{N}\sum_{i=1}^{N}\mathbb{E}_{x_2|\mu^{(i)},x_1^{(i)}}\left[u\left(\mu^{(i)},n_1,f_{\mathbf{a}}\left(x_1^{(i)}\right),x_2\right)\right]$$

OK-Diabetes

Derivatives:

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

Introduction

"What is the principal distinction between Bayesian and classical statistics? It is that Bayesian statistics is fundamentally boring. There is so little to do: just specify the model and the prior, and turn the Bayesian handle" - Phil Dawid commenting on Lindley's The Philosophy of Staistics (2000)

Not just prior and model, but utility, and we can make any decision optimally.

Two major challenges in practice: - specifying a utility (assuming model and prior are correct) - doing the calculations

We will consider a specific problem in clinical trial design, and attempt to say something interesting about each of these challenges.

Motivation

- Assessing effectiveness in complex intervention pilot trials to improve efficiency
- Testing not advised due to low power, an artefact of sharing the same endpoint and small pilot sample

Part 1

Problem

- Pilot and definitive trial, shared normal endpoint, known variance, unknown effect, two-arm etc.
- Normal conjgate prior on effect
- Make progression decision at each stage using a z-test of means
- Programme design defined by ns and cs at each stage

Optimisation

- Search over the four parameters to maximise expected utility

MEU theory

- Doing MEU is not a hueristic, but axiomatic
- Given some basic axioms about our preferences and how we want to behave (coherence), there exists a utility function s.t. preferences between distributions is encoded by its expectation
- Need to be able to find this specific utility, which means asking the right questions
- Contrast with ad-hoc “utilities”, e.g. Thall

Part 2

Problem

- If we have set up our utility, we can analyse the pilot through MEU
- Assume definitive type I set at default
- Now just need to choose the pilot sample size

Nested MC algorithm

- Simple
- Computationally demanding
- Automating Bayesain inference without checks

Surrogate decision rules

- Re-casting the problem as searching over rules mapping pilot data to definitive sample sizes
- Need a way to represent functions and search over them

Splines

- Defined by their order and their knots
- Some example functions for a given set of knots

Summary