Dimensions of Design Space: a Decision-Theoretic Approach to Optimal Research Portfolio Design

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Outline

♦ Backdrop

♦ Methodology

♦ Strategy

♦ A Test-Bed: Zanamivir vs. Standard Care

♦ Concluding Remarks
Sample size determination (SSD) is a key issue in medical study design
- in some cases (i.e. a RCT) patient allocation needs to be tuned too

Research designs can be *experimental* or *non-experimental*
- a research ‘portfolio’ combines studies of different nature
- SSD jointly optimises design sizes and allocations within the portfolio

From a CEA perspective, *EVI* lends itself as an optimality criterion
- the design portfolio expressing maximum payoff to research is sought
- both *financial* and *opportunity* costs are recognised
- fits coherently within a Bayesian decision-theoretic setting
Suppose a medical decision model, indexed by parameters $\vartheta$, yields net-benefits $NB_t(\vartheta)$ under treatment option $t$.

The gain of information about $\vartheta$ following collection of samples $x$ of patients of sizes $n$ increases the value of the decision by

$$EVSI(n) = \mathbb{E}_x \left\{ \max_t \mathbb{E}_{\vartheta|x}[NB_t(\vartheta)] \right\} - \max_t \mathbb{E}_{\vartheta}[NB_t(\vartheta)]$$

A cost of sampling function $C(n)$ is introduced to account for

- **financial** (fixed and reporting) costs attaching each sample
- **opportunity** costs
  - (i) enrolled patients forgo the study’s value of research
  - (ii) net-benefit lost by patients on sub-optimal treatments
After upscaling $EVSI$ to its population counterpart $PEVSI$, the societal payoff to proposed research is measured by

$$ENBS(n) = PEVSI(n) - C(n)$$

- further research based on studies of sizes $n$ would be efficient iff $ENBS(n) > 0$
- desired research portfolio features $n^* = \arg\max_n ENBS(n)$

In principle this defines a standard integer programming problem

- objective function normally not available in closed form
- a MC estimator $\hat{ENBS}(\cdot)$ is typically used as a proxy
- rough response surface (due to MC noise) complicates optimisation
General stochastic optimisation can be pursued via ‘brute-force’ MC (Shapiro, 2000)

- repeated optimiser runs produce sample of ‘candidates’ $\hat{n}_1, \ldots, \hat{n}_m$
- mean $\bar{n}$ may be selected, and inferences on $\hat{\text{ENBS}}(\bar{n})$ drawn
- the higher the MC resolution (and $m$), the more reliable the outcome

MC noise attaching $\hat{\text{ENBS}}(\cdot)$ induces uncertainty around resulting $\bar{n}$

- a maximin LHS $\tilde{n}_1, \ldots, \tilde{n}_L$ is selected from previous stage
- inferences from samples of $\hat{\text{ENBS}}(\tilde{n}_l)$ estimates are obtained
A Test-Bed: Zanamivir vs. Standard Care

♦ A decision tree has been proposed to model the effect of zanamivir for treating influenza in British adults (Burls, 2002)

\( \psi_{\text{trl}} \) LOR of complications and hospitalisation, symptom days reduction

\( \psi_{\text{epi}} \) probabilities of complication, hospitalisation and influenza-positive

\( \psi_{\text{utl}} \) utility of symptom day

♦ Examined research scenarios, each with a specific EVI load, comprise

1d/2d balanced/unbalanced trial of all endpoints

2d, 1d, 1d separate clinical trial, epidemiological study and utility survey

4d joint portfolio of clinical trial, epidemiological study and utility survey
Balanced trial of all endpoints

ICER = £51,662 − Arm reporting cost = £600

Arm size

£ENBS

£516,600

£2,092,100

£1,592,200

£516,600

95% C.I. = £505,200 − £527,500
95% C.I. = £2,074,500 − £2,111,900
95% C.I. = £1,577,400 − £1,606,500

Arm size

ICER = £51,662 − Arm reporting cost = £600
Unbalanced trial of all endpoints

\( \lambda = £40,000 \)
\( \lambda = £50,000 \)
\( \lambda = £60,000 \)

\[ \text{ENBS} = £529,700 \]
95% C.I. = £518,600 – £536,700

\[ \text{ENBS} = £2,092,400 \]
95% C.I. = £2,076,800 – £2,103,500

\[ \text{ENBS} = £1,618,400 \]
95% C.I. = £1,608,300 – £1,626,000

\[ \text{ICER} = £51,662 - \text{Arm reporting cost} = £600 \]
Separate research portfolio

Joint research portfolio

Reporting costs = £300 (trl), £200 (epi), £500 (utl)
Concluding Remarks

♦ Proposed approach offered useful insights on $n^*$ and $ENBS(n^*)$
  – relaxing allocation constraints generally yields higher EVI
  – research portfolio can express higher EVI than trial of all endpoints

♦ Joint research portfolio appeared to outperform separate SSD
  – optimal portfolio $\neq$ ensemble of independently optimised studies
  – intrinsically economic factors (costs, $\lambda$) are key

♦ CPU-intensive estimation and/or complex models may limit applicability
  – there is scope for improvement (e.g. MC noise appeared Gaussian)
  – a balance is required between accuracy and efficiency
References


URL: http://hera.rz.hu-berlin.de/speps/.