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

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Backdrop

- 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

Methodology

- Suppose a medical decision model, indexed by parameters $\boldsymbol{\vartheta}$, yields net-benefits $NB_t(\boldsymbol{\vartheta})$ under treatment option t
- The gain of information about $\boldsymbol{\vartheta}$ following collection of samples $\boldsymbol{x}$ of patients of sizes $\boldsymbol{n}$ increases the value of the decision by

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

- A cost of sampling function $C(\boldsymbol{n})$ 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

$$ENBS(\boldsymbol{n}) = PEVSI(\boldsymbol{n}) - C(\boldsymbol{n})$$

  - additional research based on studies of sizes $\boldsymbol{n}$ would be efficient *iff* $ENBS(\boldsymbol{n}) > 0$
  - desired research portfolio features $\boldsymbol{n}^\star = \arg\max_{\boldsymbol{n}} ENBS(\boldsymbol{n})$
- In principle this defines a standard integer programming problem
  - objective function normally not available in closed form
  - a MC estimator $\widehat{ENBS}(\cdot)$ is typically used as a proxy
  - rough response surface (due to MC noise) complicates optimisation

Strategy

- General stochastic optimisation *can* be pursued via 'brute-force' MC[3]
  - repeated optimiser runs produce sample of 'candidates' $\hat{\boldsymbol{n}}_1, \ldots, \hat{\boldsymbol{n}}_m$
  - mean $\bar{\boldsymbol{n}}$ may be selected, and inferences on $\widehat{ENBS}(\bar{\boldsymbol{n}})$ drawn
  - the higher the MC resolution (and m), the more reliable the outcome
- MC noise attaching $\widehat{ENBS}(\cdot)$ induces uncertainty around resulting $\bar{\boldsymbol{n}}$
  - a maximin LHS $\tilde{\boldsymbol{n}}_1, \ldots, \tilde{\boldsymbol{n}}_L$ is selected from previous stage
  - inferences from samples of $\widehat{ENBS}(\tilde{\boldsymbol{n}}_l)$ 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[2]

  ϑ_{trl} LOR of complications and hospitalisation, symptom days reduction

  ϑ_{epi} probabilities of complication, hospitalisation and influenza-positive

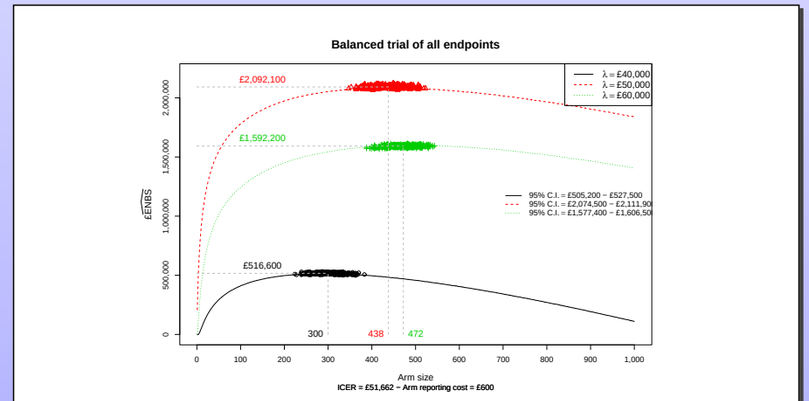
  ϑ_{utl} utility of symptom day

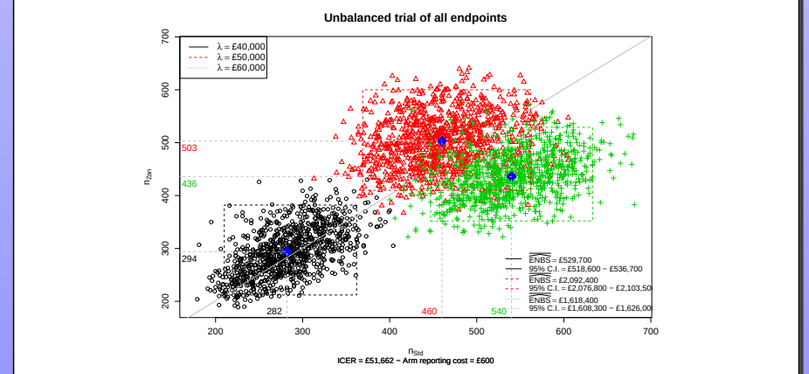
- Examined research scenarios, each with a *specific* EVI load, comprise

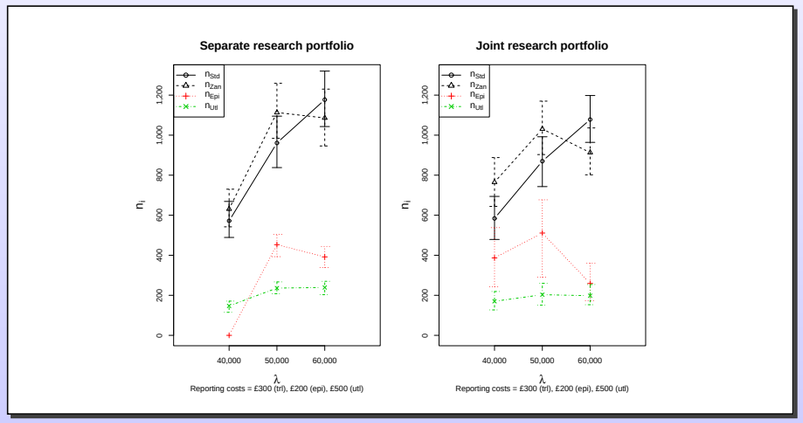
  1d/2d balanced/unbalanced trial of all endpoints

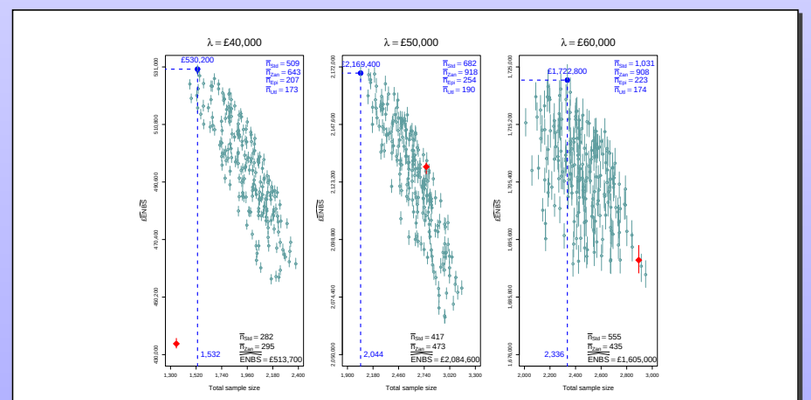
  2d, 1d, 1d separate clinical trial, epidemiological study and utility survey

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









Concluding Remarks

- Proposed approach offered useful insights on $\boldsymbol{n}^\star$ and $ENBS(\boldsymbol{n}^\star)$
  - 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, λ) 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

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[3] A. Shapiro. Stochastic Programming by Monte Carlo Simulation Methods. **Stochastic Programming E-Print Series**, 2000. URL: http://hera.rz.hu-berlin.de/speps/.