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 $\theta$, yields net-benefits $N_B(\theta)$ under treatment option $t$
- The gain of information about $\theta$ following collection of samples $n$ of patients of sizes $n$ increases the value of the decision by
  $$EVSI(n) = \mathbb{E}_{\theta} \left[ \max_{t} \mathbb{E}_{\theta} \left[ N_B(\theta) \right] \right] - \mathbb{E}_{\theta} \left[ \max_{t} N_B(\theta) \right]$$
- 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
  $$ENBS(n) = PEVSI(n) - C(n)$$
  - Additional research based on studies of sizes $n$ would be efficient if $ENBS(n) > 0$
  - 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

**Strategy**
- General stochastic optimisation can be pursued via ‘brute-force’ MC\textsuperscript{3}
  - Repeated optimiser runs produce sample of ‘candidates’ $n_1, \ldots, n_m$
  - Mean $\bar{n}$ may be selected, and inferences on $\hat{ENBS}(\bar{n})$ drawn
  - The higher the MC resolution (and $m$), the more reliable the outcome
- MC noise attaching $\hat{ENBS}(\cdot)$ induces uncertainty around resulting $\bar{n}$
  - A maximin LHS $n_1, \ldots, n_k$ is selected from previous stage
  - Inferences from samples of $\hat{ENBS}(\bar{n})$ 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\textsuperscript{4}
  - $\theta_{d}$: LOR of complications and hospitalisation, symptom days reduction
  - $\theta_{e}$: probabilities of complication, hospitalisation and influenza-positive
  - $\theta_{s}$: 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 $n^*$ and $\hat{ENBS}(n^*)$
  - Relaxed 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 $\hat{\theta}$ 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)
  - Balance is required between accuracy and efficiency

**References**