Sequential Stopping for High-Throughput Experiments

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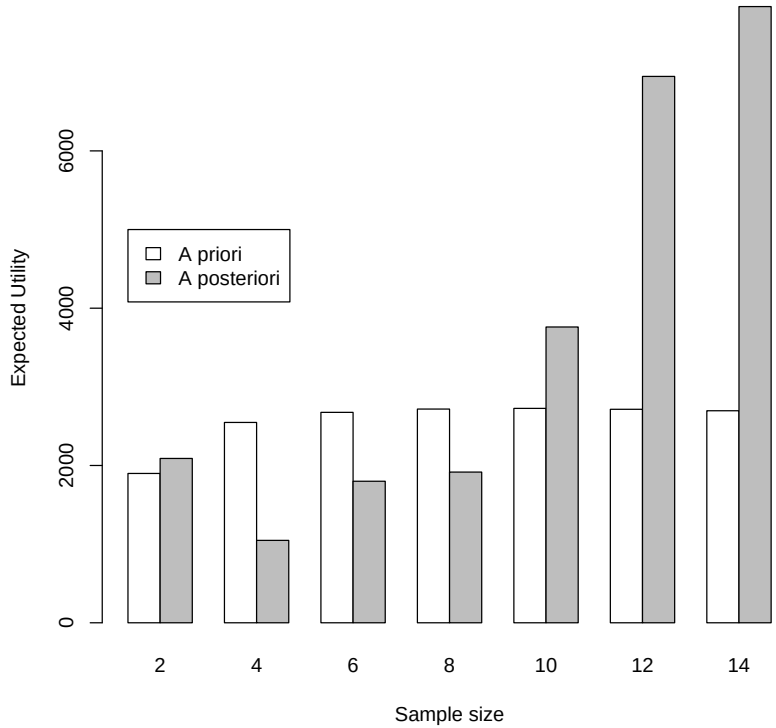
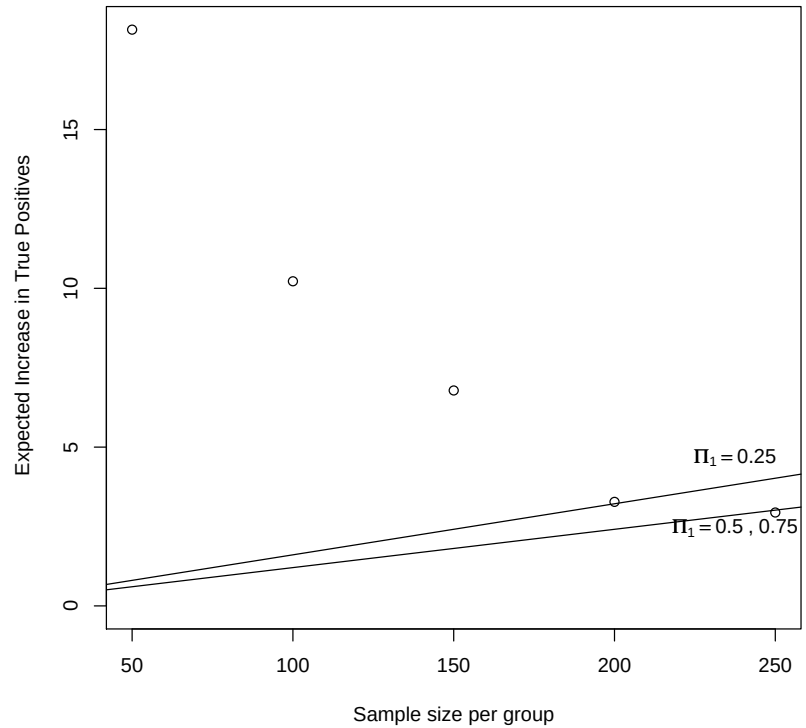
August 10, 2011

Expected Utility vs. Sample Size

Determine sample size by utility maximization.



prior expected utility at $t = 0$ (white)
for fixed sample size
vs. post exp utility ($t = \tau$) (grey)
for sequential stopping



optimal decision boundaries
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Outcome: x_{ij} outcome for gene (protein, ...) i, $i = 1, \ldots, n$ and sample j, $j = 1, \ldots, T$

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Data at time t: $x_t = \{x_{it}, 1 \leq i \leq n\}$
$x_{1:t} = \{x_{ij}, 1 \leq i \leq n,\ 1 \leq j \leq t\}$

Model

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Prior: allows gene-specific CV & $p(\lambda_{i0} = \lambda_{i1}) > 0$

- conjugate IG prior $\lambda_{i0}^{-1} \sim \text{Ga}(\alpha_0, \alpha_0/\nu)$
- pos prob for $\delta_i = I(\lambda_{i0} = \lambda_{i1})$, i.e., non-differential expression.
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Prob of DE: main summary of interst

$$p_i \equiv p(\delta_i = 1 \mid \mathbf{x}_{1:T})$$

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$$u(d, s, y, \theta)$$

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and a bit more complicated for the sequential decision s

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Utility: use two different criteria for stopping and terminal decision (not quite kosher..)

- Terminal decision: Bayes rule under FDR control. Let $D = \sum d_i$, number of $\widehat{\text{DE}}$ genes

$$\text{FDR} = \sum d_i(\mathbf{x}_{1:t})(1 - \delta_i)/D$$

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- Stopping decision

$$u(s_t = 1, \mathbf{d}(\mathbf{x}_{1:\tau}), \mathbf{x}_{1:\tau}, \boldsymbol{\delta},) = -c\tau + \sum_{i=1}^{n} \delta_i d_i(\mathbf{x}_{1:\tau}).$$

  c : # of true pos that justify one more obs.

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$$\overline{u}_t(s_t = 0, \mathbf{x}_{1:t}) = -c + \int \overline{u}_t(s^{\star}_{t+1}, \mathbf{x}_{1:t}, x_{t+1})\, dp(x_{t+1} \mid \mathbf{x}_{1:t})$$

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requires integration w.r.t. x_{t+1} and plug-in of optimal rule $s^\star_{t+1}(\cdot)$ $\rightarrow$ backward induction (arrrgh!)

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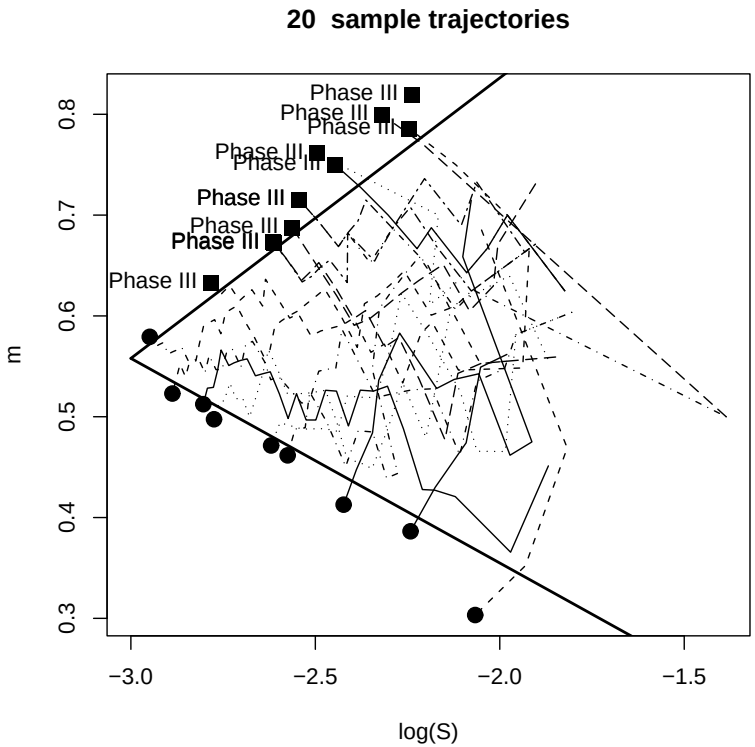

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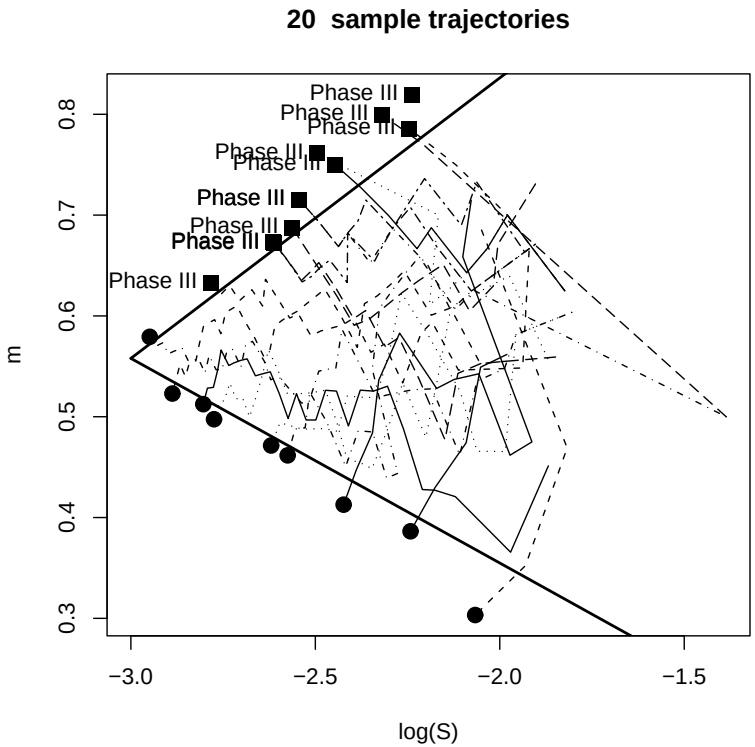

- Summary statistic $Y = (S, m)$ and decision boundaries.
  Each trajectory shows a possible trial realization.
- When the summary Y crosses decision boundary the trial stops.

Summary Statistic

Increment in true pos:

$$\Delta_t(\text{TP}) \equiv E_{\mathbf{x}_{t+1}}\left[\overline{u}_{t+1}(s_{t+1}=1, \mathbf{x}_{1:t+1}) \mid \mathbf{x}_{1:t}\right] - \overline{u}_t(s_t = 1, \mathbf{x}_{1:t})$$

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$\rightarrow$ a slight generalization of traditional myopic design

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Optimal decision: optimize $\overline{U}(\beta)$ over β.

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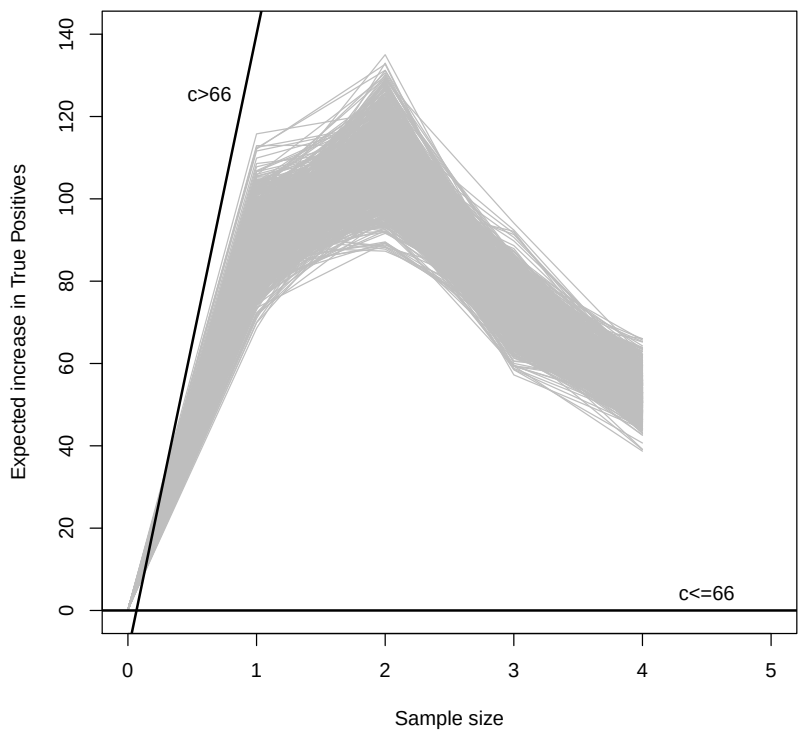
GaGa model for $x_{ij} = \log(RPKM + 1)$.

Results


c>66
c<=66
Expected increase in True Positives
Sample size
0
20
40
60
80
100
120
140
0
1
2
3
4
5

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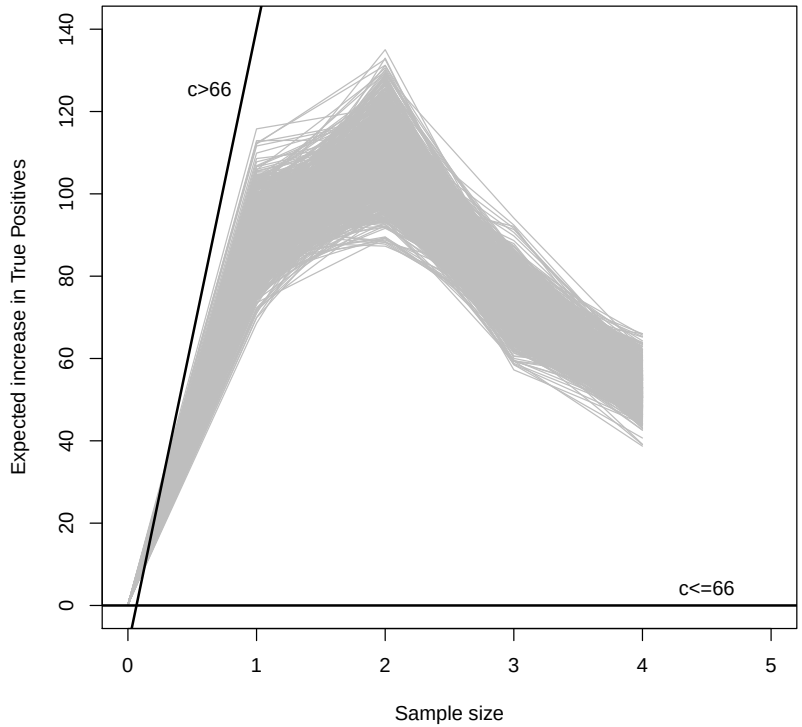
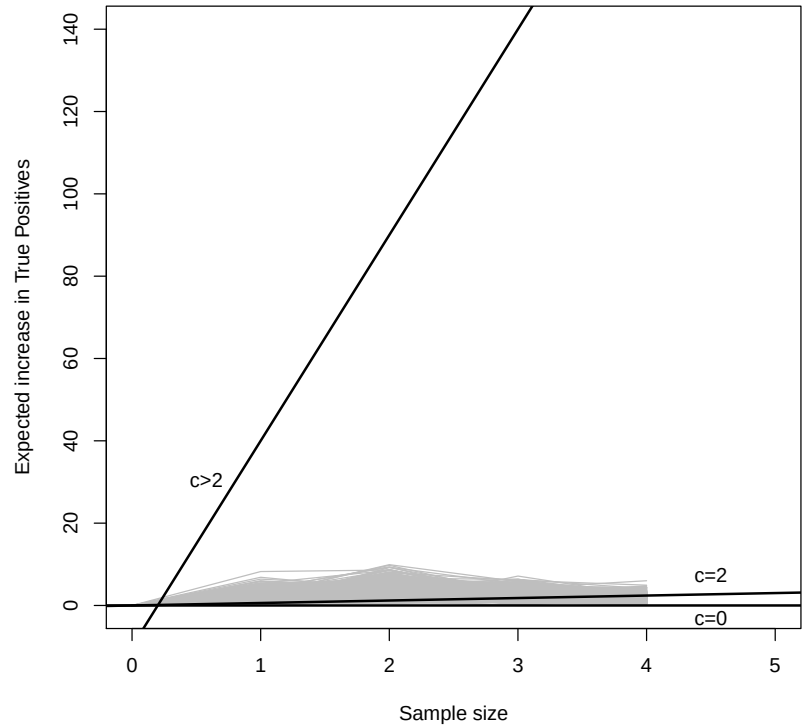


(a) brain vs. muscle
$s_t = 0$
for most posterior pred simulations



(b) muscle vs. muscle
$s_t = 1$
(unless $c < 2$)

Example 2: Microarray Data

Study: Campo Dell'Orto et al. (2007), leukemia microarray; 21 ALL & 15 MLL patients, 54,675 genes, Affymetrix array

Design: collect data in batches of 2 arrays each per group, max of $T = 7$ batches.

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GaGa model on x_{ij} = GCRMA pre-processed scores (Wu & Irizarry, 2007).

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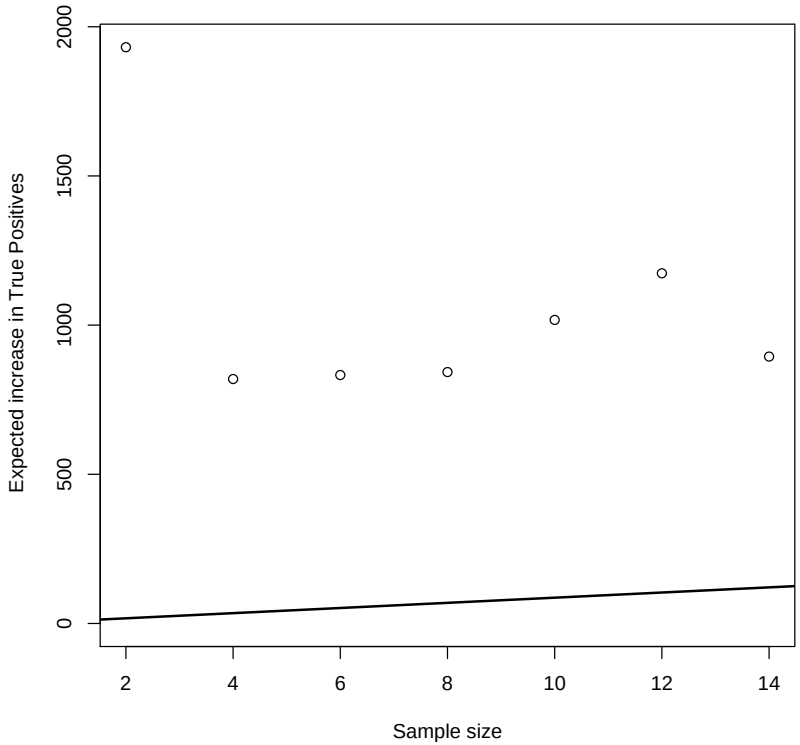
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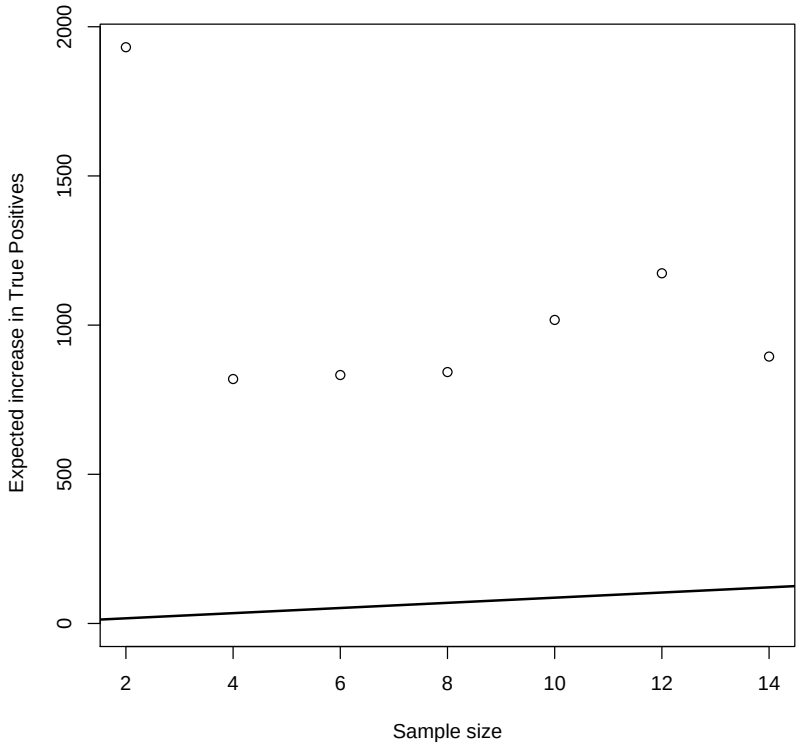
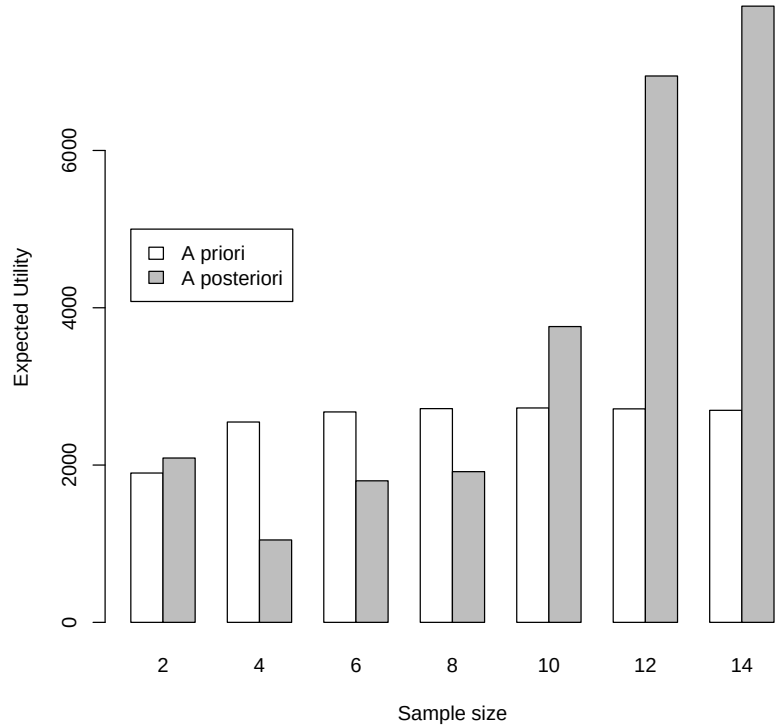


optimal decision boundaries



fixed sample size design (prior) (white)
seq stopping
(posterior at $t = \tau$) (grey)

Example 3: RPPA

Study: Korenblau et al. (2006), protein abundance in bone marrow (BMA) vs. peripheral blood (PB), using RPPA

Data: 168 proteins, 435 BMA + 282 PB samples.

Design: batches of 50 samples per group, max of $T = 250$. RPPA is cheap $\rightarrow$ $c = 5$ or 10.

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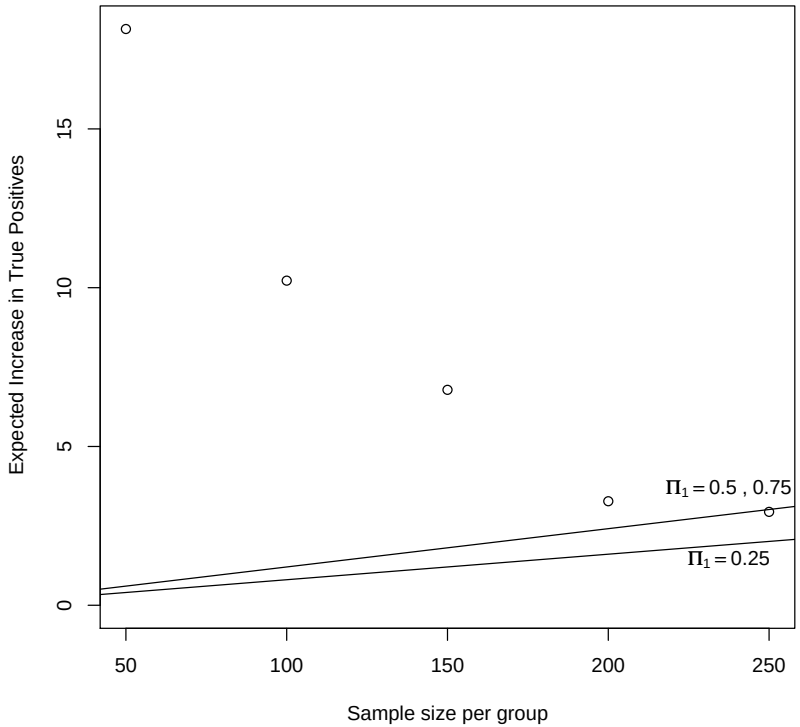
$x_{ij} = \exp(superCurve)$, Super-Curve pre-processed data (Shannon et al. 2009, Bioinformatics)

RPPA – Results



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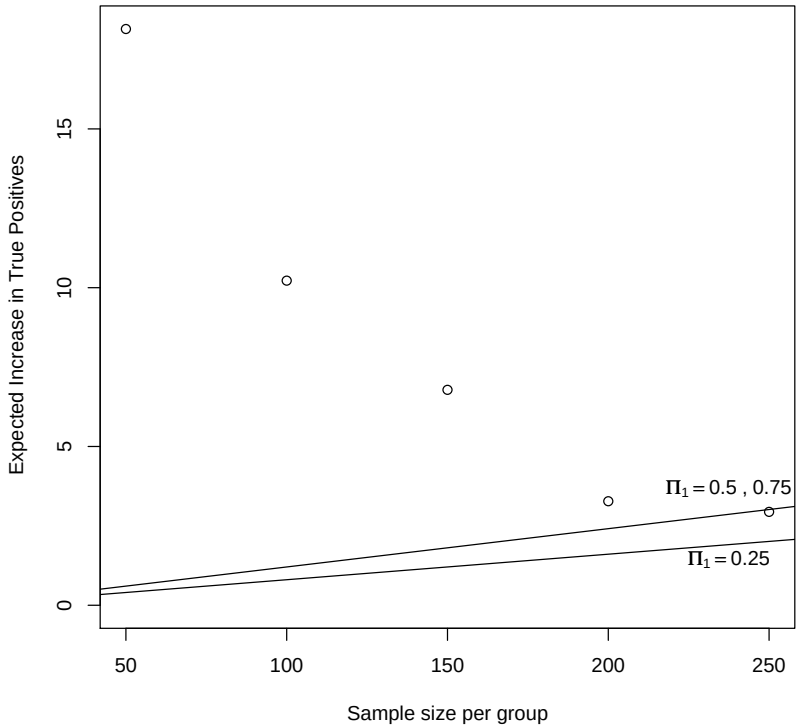
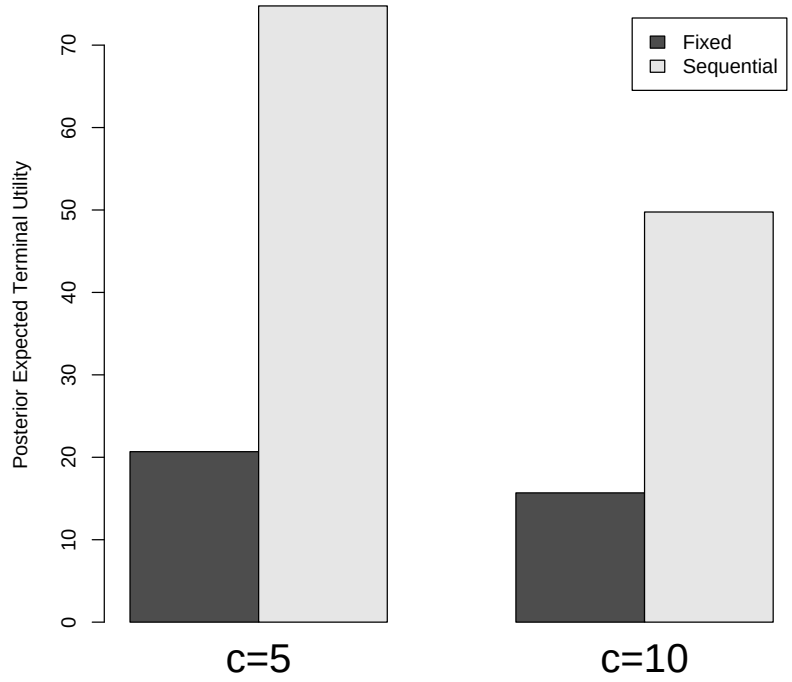


decision boundary



post expected terminal utility

Summary

- Approx sequential design by decision boundaries
- Need informative priors (post predictive | pilot data; historical data)
- Sequential stopping makes design robust against bad prior choices.
- Utility function, can reflect study goals
- Examples were group comparison, but could be anything: classification, clustering, network discovery ...