Group Sequential Tests for Delayed Responses

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Superiority trials

We conduct a clinical trial comparing a new treatment versus control. As the trial progresses, we accumulate responses

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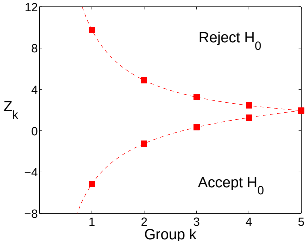
We wish to test

$$H_0 : \theta \leq 0 \quad \text{vs} \quad \theta > 0$$

with type I error rate α at $\theta = 0$ and power $1 - \beta$ at $\theta = \delta > 0$.

One-sided group sequential tests

A one-sided group sequential test of $H_0 : \theta \leq 0$ against $\theta > 0$ is of the form



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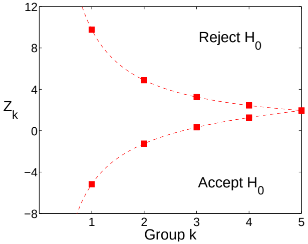

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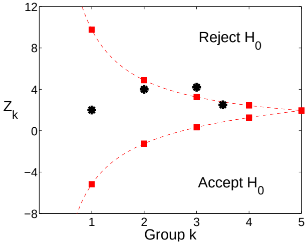

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Incorporating delayed responses into GSTs

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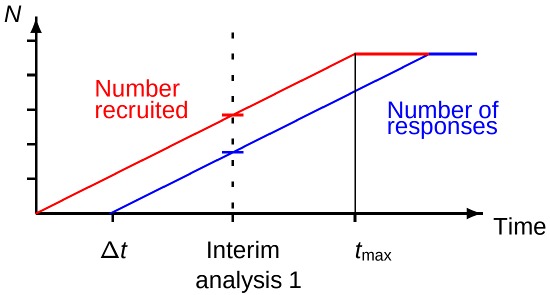

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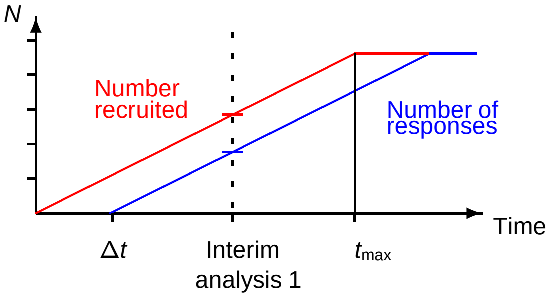

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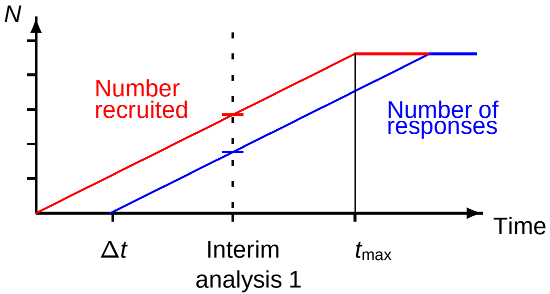

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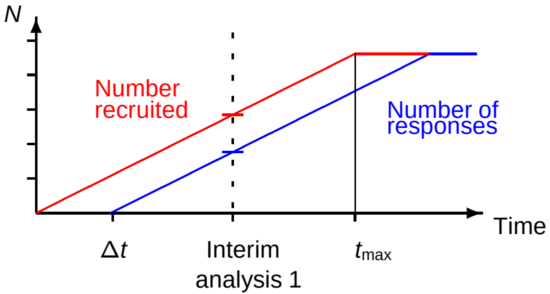

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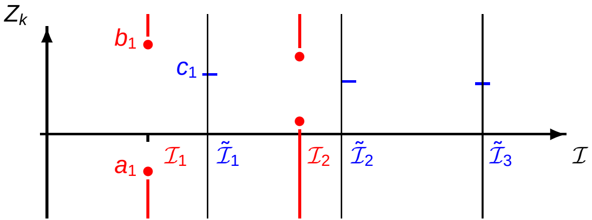
T.W. Anderson (*JASA*, 1964) considers sequential tests for delayed responses. We follow this basic structure to construct GSTs.

Boundaries for a Delayed Response GST

At interim analysis k, Z_k is associated with information level $\mathcal{I}_k = \text{Var}(\hat{\theta}_k)$.



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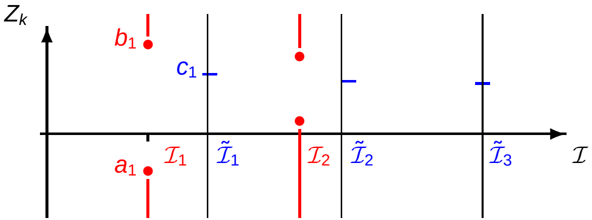

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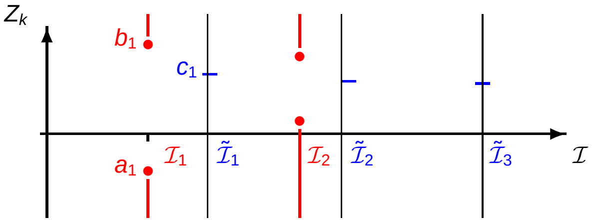

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At the decision analysis, based on information $\tilde{\mathcal{I}}_k$, reject H_0 if $\tilde{Z}_k > c_k$.

Calculating properties of Delayed Response GSTs

Calculations of test properties (type I error rate, power, $\mathbb{E}_\theta(N)$) require the joint distributions of test statistic sequences:

- $\{Z_1, \ldots, Z_k, \tilde{Z}_k\}, \qquad$ for $k = 1, \ldots, K-1$,
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Each sequence is based on accumulating datasets.

Given $\{\mathcal{I}_1, \dots, \mathcal{I}_k, \tilde{\mathcal{I}}_k\}$, the sequence $\{Z_1, \dots, Z_k, \tilde{Z}_k\}$ follows the canonical distribution for statistics generated by a GST for immediate responses (Jennison & Turnbull, *JASA*, 1997).

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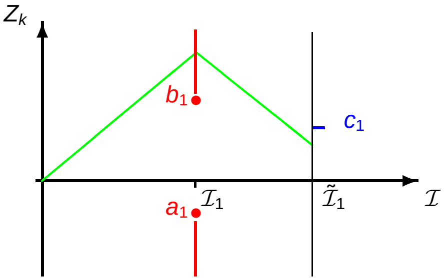
Properties of Delayed Response GSTs can therefore be calculated using numerical routines devised for standard designs.

Reversals of anticipated final decisions

Stopping with $Z_k > b_k$ or $Z_k < a_k$ indicates our *likely* final decision but there there may be a reversal. We could observe



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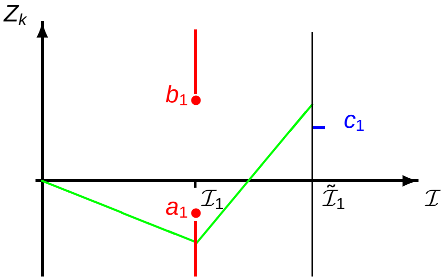

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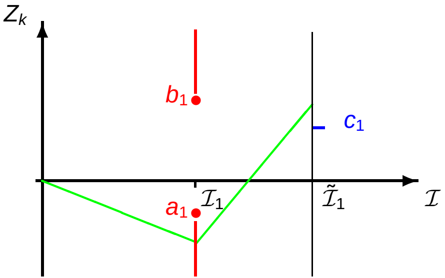

We optimise our designs to maximise the value of the additional pipeline responses for increasing the test's power.

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Objective: For a given r, maximum sample size n_{max}, stages K and analysis schedule, we find the Delayed Response GST minimising

$$F = \int \mathbb{E}_{\theta}(N) \, f(\theta) \, d\theta$$

with type I error rate α at $\theta = 0$ and power $1 - \beta$ at $\theta = \delta$. Here $f(\theta)$ is the density of a $N(\delta/2, (\delta/2)^2)$ distribution.

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We create an unconstrained Bayes problem by adding a prior on θ and costs for sampling and for making incorrect decisions. We search for the combination of prior and costs which gives a solution with frequentist error rates α and β.

Efficiency loss when there is a delay in response

It is required to test $H_0 : \theta \leq 0$ against $\theta > 0$ with $\alpha = 0.025$ and $\beta = 0.1$. Suppose the fixed sample test requires n_{fix} subjects and set $n_{max} = 1.1\, n_{fix}$.

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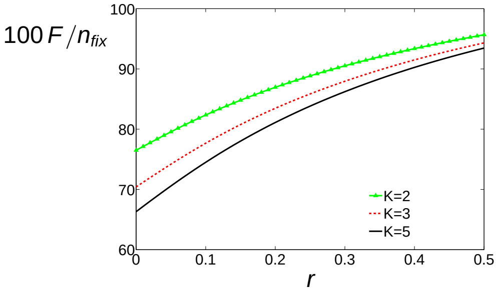
We plot the minima of F attained by optimal tests with $K = 2, 3$ and 5 stages.



When $r = 0.1$, almost 25% of the gains of group sequential testing are lost. When $r = 0.3$, this increases up to 60%.

Designing a Delayed Response GST

Example A: Cholesterol reduction after 4 weeks of treatment

Responses are assumed normally distributed with variance $\sigma^2 = 2$.

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We consider designs with a maximum sample size of 96, assuming a recruitment rate of 4 per week, giving $4 \times 4 = 16$ pipeline subjects at each interim analysis.

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We derive a Delayed Response GST minimising

$$F = \int \mathbb{E}_{\theta}(N) f(\theta) \, d\theta,$$

where $f(\theta)$ is the density of a $N(0.5, 0.5^2)$ distribution.

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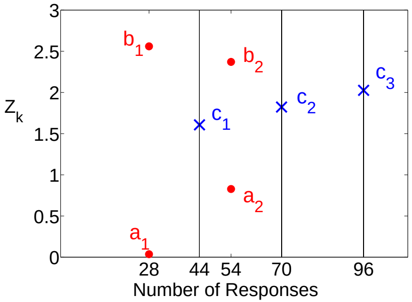
Critical values for the optimised Delayed Response GST are shown below.



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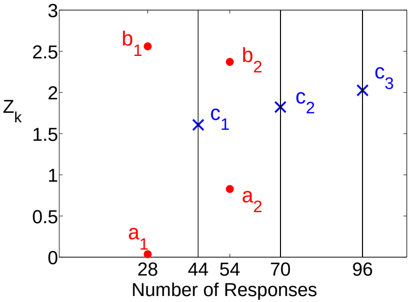

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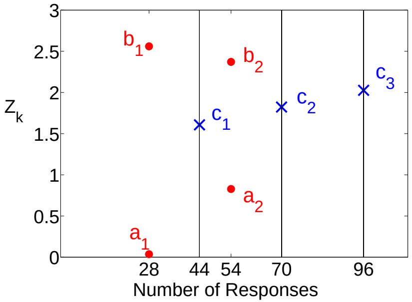

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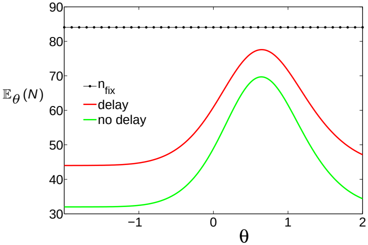
Both c_1 and c_2 are less than 1.96. If desired, these can be raised to 1.96 with little change to the design's power curve.

Designing a Delayed Response GST

The figure shows expected sample size curves for

- the fixed sample test with $n_{fix} = 85$ patients,
- the Delayed Response GST minimising F,
- the GST for immediate responses with analyses after 32, 64 and 96 responses, also minimising F.



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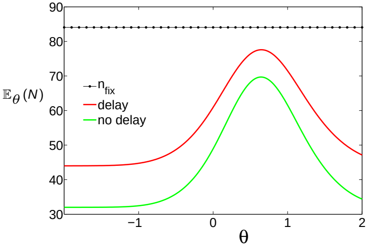

The delay in response means savings in $\mathbb{E}_\theta(N)$ are smaller than they would be if response were immediate.

Making inferences on termination

How can we calculate a p-value for $H_0 : \theta \leq 0$ and a CI for θ?

On termination of the test at stage T, $(\tilde{\mathcal{I}}_T, \tilde{Z}_T)$ is a sufficient statistic for θ. We base inferences on a "stage-wise" ordering of the test's sample space for this pair.

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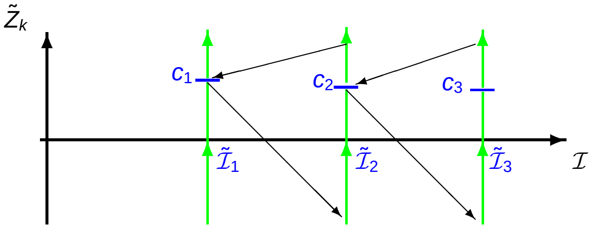

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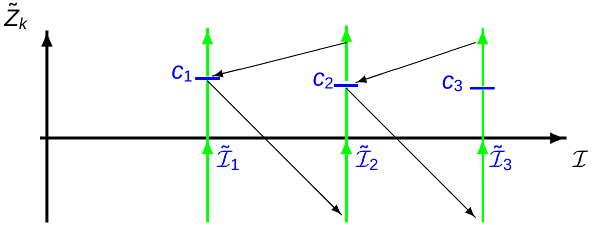

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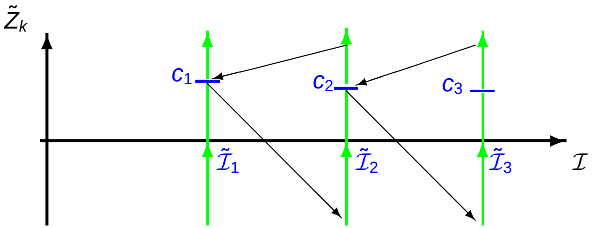

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This ordering ensures p-value calculations do not depend on future, possibly *unpredictable*, information levels.

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Choosing c_k to balance reversal probabilities under $\theta = 0$ implies we may choose (a_k, b_k) to satisfy

$$\mathbb{P}_{\theta=0}\{Z_1 \in \mathcal{C}_1, \ldots, Z_{k-1} \in \mathcal{C}_{k-1}, Z_k \geq b_k\} = \pi_k - \pi_{k-1}$$
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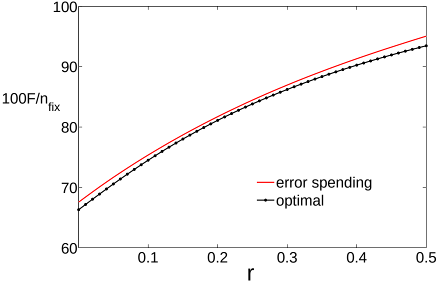
Under this construction, the stage k stopping rule can be set without knowledge of $\tilde{\mathcal{I}}_k$.

Efficiency of error spending tests

In the figure below, error spending tests are designed using the ρ-family of error spending functions.

Values of F are attained by tests designed and conducted with $K = 5$, $n_{max} = 1.1\, n_{fix}$, $\alpha = 0.025$ and $\beta = 0.1$.



Error spending Delayed Response GSTs are flexible and closely match the optimal tests for savings in $\mathbb{E}_\theta(N)$.

Dealing with unexpected overrunning

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Solution: We partition the sample space at $\tilde{\mathcal{I}}_{k^\star}$ such that

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Requiring $c_{k^\star}$ to balance the probabilities of reversing decisions under $\theta = 0$ at stage $k^\star$ preserves the test's overall type I error rate.

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Requiring $c_{k^\star}$ to balance the probabilities of reversing decisions under $\theta = 0$ at stage $k^\star$ preserves the test's overall type I error rate.

In addition, p-value calculations do not depend on $\tilde{\mathcal{I}}_1, \ldots, \tilde{\mathcal{I}}_{k^\star-1}$, nor on information levels beyond stage $k^\star$.

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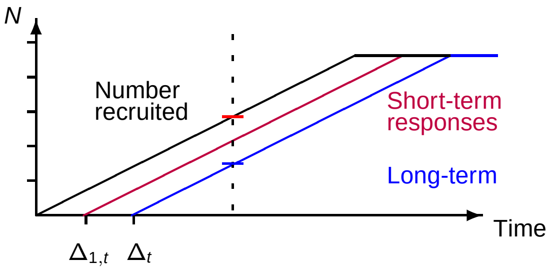

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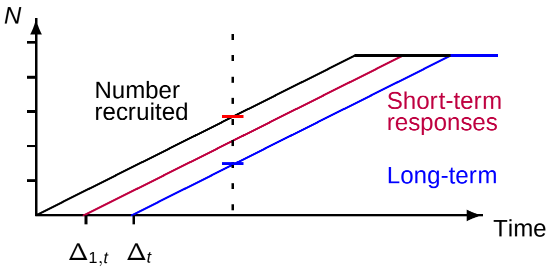

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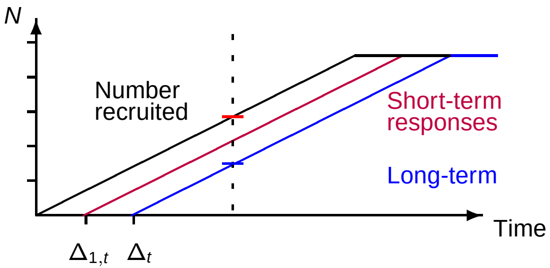

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Suppose each pair $(Y_{T,i}, X_{T,i})$ has joint distribution

$$\begin{pmatrix} Y_{T,i} \\ X_{T,i} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{T,1} \\ \mu_{T,2} \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \tau\sigma_1\sigma_2 \\ \tau\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix} \right).$$

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At interim analysis k, we estimate $\theta = \mu_{A,2} - \mu_{B,2}$ from all available data, using maximum likelihood estimation to fit the full model then extracting $\widehat{\theta}_k$ and $\mathcal{I}_k = \text{Var}(\widehat{\theta}_k)$.

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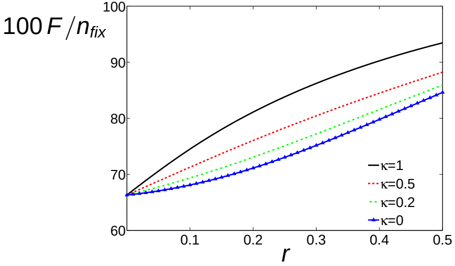
At decision analysis k when all subjects are fully observed, short-term responses don't contribute any additional information for θ.

Revisiting Example A

Example A: Incorporating a second, short-term endpoint



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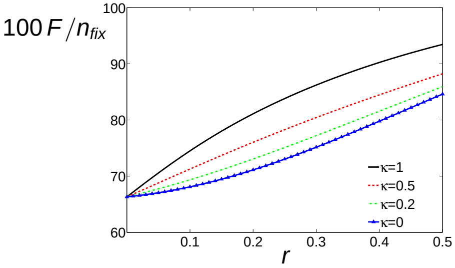

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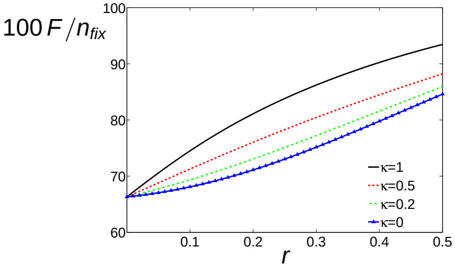

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The solid line for $\kappa = 1$ is the case of no short-term endpoint.

Conclusions

In this presentation, we have presented

- Delayed Response GSTs as a coherent approach to handling delayed data in a sequential setting.
- Versions of Delayed Response GSTs that can accommodate unpredictable group sizes and unexpected overrunning.
- P-values and confidence intervals on termination.

The impact on efficiency of a delay in response can be ameliorated by

- incorporating information on correlated short-term endpoints
- slowing recruitment rates
- ensuring rapid data cleaning before an analysis.