Group Sequential Tests with Data-Dependent Treatment Allocation

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for slides and full references

The Selection Problem

For each "population" or "treatment" $i = 1, \ldots, k$,

$$X_{i1},\, X_{i2},\, \ldots \;\sim\; N(\theta_i,\, \sigma^2), \quad \text{i.i.d.}$$

Aim: To select the population i with the largest mean θ_i.

Method to include:

- Group sequential comparisons
  - early elimination of weak treatments.
- Response-dependent treatment allocation
  - fewer observations on inferior treatments,
  - lower total sample size.

Earlier work

Paulson (*Ann. Math. Statist.*, 1964)

Elimination procedures based on *continuous* sequential comparisons of 2 populations at a time.

Robbins and Siegmund (*JASA*, 1974)

Adaptive sampling for a 2 population comparison with continuous monitoring.

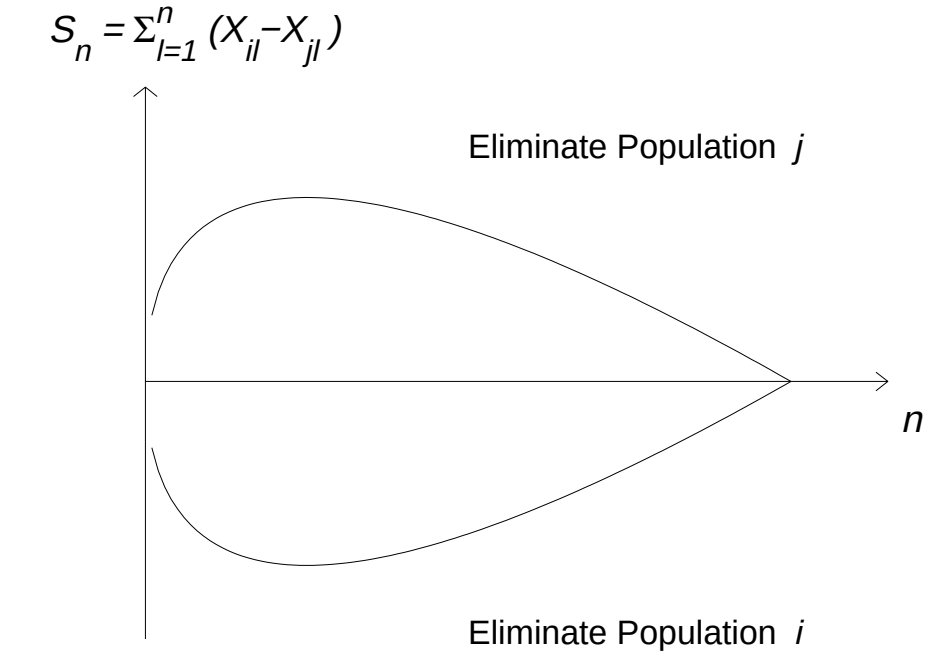
Jennison, Johnstone and Turnbull (*Purdue Symposium*, 1982)

Combining the above.

Update: To take advantage of group sequential tests, error spending, modern computation.

Paulson's procedure

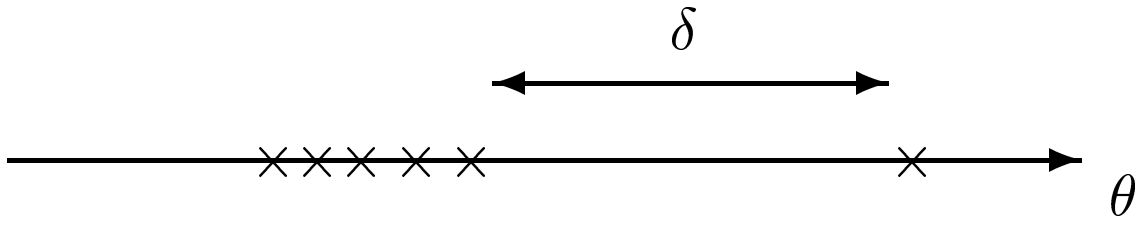
Compare all pairs Treatment i *vs* Treatment j.



If $\theta_i = \theta_j - \delta$, then $Pr\{\text{Pop. } i \text{ eliminates Pop. } j\} = \alpha/(k-1)$.

Paulson's procedure: Probability of Correct Selection

Indifference Zone formulation



Suppose $\theta_i \leq \theta_k - \delta$ for $i = 1, \ldots, k-1$.

Then

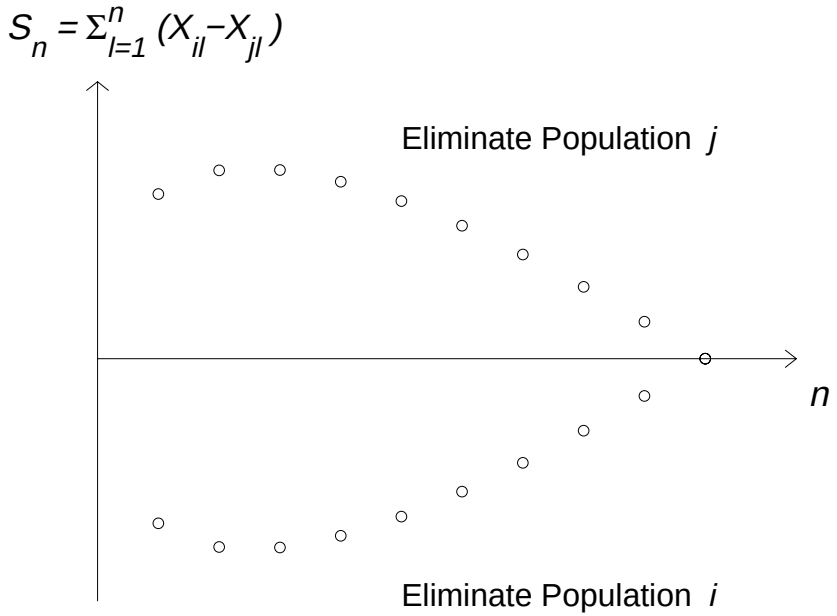
$$Pr\{\text{Pop. } k \text{ is eliminated at some stage}\}$$

$$\leq \sum_{i=1}^{k-1} Pr\{\text{Pop. } i \text{ eliminates Pop. } k \text{ at some stage}\}$$

$$\leq (k-1)\frac{\alpha}{k-1} = \alpha.$$

Paulson's procedure: Group Sequential monitoring

Compare treatments at regular interim analyses.



Choose a group sequential boundary with error rate $\alpha/(k-1)$ at $\theta_i - \theta_j = \pm\delta$ and good early stopping under likely $(\theta_1, \ldots, \theta_k)$.

Adaptive Sampling in Paulson's procedure

Motivation

Observations on the leading population are used in $k-1$ comparisons.

Allocating more observations to the leader can

- Reduce total sample size
- Reduce observations on inferior treatments
  - ethical for medical studies
  - we learn more about better treatments.

Need:

Theory to support adaptive sampling in each pair-wise comparison.

Adaptive Sampling in a Group Sequential Test

Jennison and Turnbull (*Sequential Analysis*, 2001)

For a 2-treatment comparison with

$$X_{1i} \sim N(\theta_1,\, \sigma^2) \quad i = 1, 2, \ldots ,$$

$$X_{2i} \sim N(\theta_2,\, \sigma^2) \quad i = 1, 2, \ldots .$$

At analysis m out of M, with n_{1m} observations on population 1 and n_{2m} on population 2,

$$\widehat{\theta}_1(m) - \widehat{\theta}_2(m) = \bar{X}_1(m) - \bar{X}_2(m) \;\sim\; N(\theta_1 - \theta_2,\, \sigma^2(\tfrac{1}{n_{1m}} + \tfrac{1}{n_{2m}}))$$

$$\sim\; N(\theta_1 - \theta_2,\, \mathcal{I}^{-1}(m)), \quad \text{say.}$$

Adaptive Sampling continued

The score statistic

$$S(m) \;=\; \mathcal{I}(m)(\widehat{\theta}_1(m) - \widehat{\theta}_2(m)) \;\sim\; N((\theta_1 - \theta_2)\,\mathcal{I}(m), \mathcal{I}(m)).$$

Without adaptive sampling, $\{S(1), S(2), \ldots\}$ is distributed as a Brownian motion with drift $\theta_1 - \theta_2$ observed at $\mathcal{I}(1), \mathcal{I}(2), \ldots$.

This remains true if group sizes $n_{1m} - n_{1,m-1}$ and $n_{2m} - n_{2,m-1}$ depend on $\widehat{\theta}_1(m-1) - \widehat{\theta}_2(m-1)$ — but sampling *cannot* depend more generally on $(\widehat{\theta}_1(m-1), \widehat{\theta}_2(m-1))$.

Theory generalises to normal linear models containing θ_1 and θ_2.

This extends Robbins and Siegmund (1974) to the group sequential case.

Adaptive Sampling: Problem 1

Problem 1

With $k \geq 3$, interesting sampling rules do not satisfy

"m th group sizes for populations 1 and 2 depend only on $\widehat{\theta}_1(m-1) - \widehat{\theta}_2(m-1)$".

Solution

- Fix sampling ratios at the start of each group,
- estimate $\theta_i - \theta_j$ within each group of data,
- combine estimates with weights $\propto$ variance^{-1}.

This equates to fitting a linear model with additive "stage" effects — recommended in medical studies to avoid bias from time trends.

Adaptive Sampling: Problem 1

JT (2001) assess performance of 2-treatment tests:

With stage effects in the model, one cannot compensate later on for sub-optimal sampling ratios in early stages. Savings in Inferior Treatment Numbers are reduced by about a half.

- Fitting stage effects to avoid bias from a time trend is reasonable.
- If modelling such a trend is not really necessary, data are being used inefficiently
  - ethically dubious for medical studies
  - at best pragmatic in other applications.

Adaptive Sampling: Problem 2

Problem 2

Information levels for comparing populations i and j

$$\mathcal{I}_{ij}(1), \mathcal{I}_{ij}(2), \mathcal{I}_{ij}(3), \ldots ,$$

depend on the sampling rule, which involves $S_{ij}(1), S_{ij}(2), \ldots .$

Standard group sequential designs, including error spending tests, do not allow such a dependence.

Solution A

Reported studies of such "data-dependent analysis times" show only minor effects on error probabilities — trust these studies and ignore the problem!

Adaptive Sampling: Problem 2

Solution B

Recent designs which "adapt" to observed data offer a precise solution:

Denne (*Statistics in Medicine*, 2001),

Müller and Schäfer (*Biometrics*, 2001).

Procedure

- Set up an error spending test for anticipated $\{\mathcal{I}_1, \mathcal{I}_2, \ldots\}$
- Recursively for $m = 1, 2, \ldots,$
  - At analysis m, compute conditional error probabilities given $S(m)$
  - Run stages $m+1$ to M as an error spending test with this conditional error.

A sampling rule (JJT, 1982)

In comparing $N-1$ populations with a control, the most efficient allocation is

$\sqrt{N-1}$ observations on the control to

1 observation on each other population.

Adaptive rule:

At stage m, with N_m non-eliminated populations, sample

$\sqrt{N_m-1}$ observations on the leading population to

1 observation on each other population.

An updated procedure

Eliminate populations using Paulson's pair-wise comparisons.

Run these comparisons as error spending group sequential tests.

a) Base tests on overall population means (cf JJT, 1982)

Sample in stage m to achieve ratios $\sqrt{N_m} : 1 : \ldots : 1$ of total observations on the N_m surviving populations.

b) Combine stage-wise estimates of each $\theta_i - \theta_j$

Sample in ratios $\sqrt{N_m} : 1 : \ldots : 1$ within stage m.

Problem 1 is dealt with properly in (b); Problem 2 is ignored (Solution A!)

Modern applications: Medical

Aim: Combine phase II and phase III clinical trials by running a single study to select a treatment (e.g., dose level) and compare this treatment with a control.

References:

Thall, Simon and Ellenberg (*Bmka*, 1988)

Schaid, Wieand and Therneau (*Bmka*, 1990)

Proschan, Follmann and Geller (*Statist. in Med.*, 1994)

Stallard and Todd (*Univ. Reading Technical Report*, 1999)

The need to compare with a control treatment changes the problem.

Sequential elimination offers scope for improvement on proposed designs — but there are computational complications.

Modern applications: Computer learning

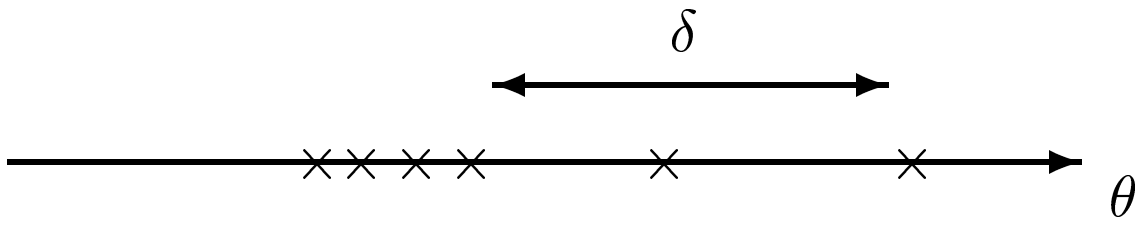
Aim: To select and rank algorithms for their performance on randomly chosen problems.

Experimentation is on a computer, hence any well-defined procedure is easily implemented.

In selecting the best s out of k competitors, k can be large, e.g., 10,000. Clearly, sequential methods are desirable — or, with parallel processing, group sequential methods.

Computer scientists are discovering the selection and ranking literature!

Beyond the indifference zone



What if there is a θ_i within δ of the highest θ_j?

It should be OK to select a population within δ of the best. But can a non-optimal population eliminate the best, then be eliminated itself?

Kao and Lai (*Comm. Statist. Th. Meth.*, 1980) provide a solution, raising the boundary for any pair-wise elimination before the final decision.

This method works for Paulson's procedure with adaptive sampling and can be extended to choosing the best s populations out of k.

Conclusions

- Solutions found in 1982 are still very appropriate.
- Applications for selection procedures are appearing in important research areas.
- Interesting challenges remain.

References

Denne, J.S. (2001). Sample size recalculation using conditional power. *Statistics in Medicine* **20**, 2645–2660.

Jennison, C., Johnstone, I. M. and Turnbull, B. W. (1982) Asymptotically optimal procedures for sequential adaptive selection of the best of several normal means. In *Statistical Decision Theory and Related Topics III, Vol. 2*, (eds S. S. Gupta and J. Berger) New York: Academic Press **2**, 55–86.

Jennison, C. and Turnbull, B. W. (2000) *Group Sequential Tests with Applications to Clinical Trials*, Chapman and Hall/CRC, 390 pages.

Jennison, C. and Turnbull, B. W. (2001) Group sequential tests with outcome-dependent treatment assignment. *Sequential Analysis*, **20**, 209–234.

Kao, S. C. and Lai, T. L. (1980). Sequential selection procedures based on confidence sequences for normal populations. *Comm. Statist. Theory and Methods*, **A9(16)**, 1657–1676.

Müller, H-H. and Schäfer, H. (2001). Adaptive group sequential designs for clinical trials: Combining the advantages of adaptive and of classical group sequential procedures. *Biometrics* **57**, 886–891.

Paulson, E. (1964) A sequential procedure for selecting the population with the largest mean from k normal populations. *Ann. Math. Statist.*, **35**, 174–180.

Proschan, M.A., Follmann, D.A and Geller, N.L. (1994). Monitoring multi-armed trials. *Statistics in Medicine*, **13**, 1441–1452.

Robbins, H. and Siegmund, D.O. (1974). Sequential tests involving two populations. *J. Amer. Statist. Assoc.*, **69**, 132–139.

Schaid, D.J., Wieand, S. and Therneau, T.M. (1990). Optimal two-stage screening designs for survival comparisons. *Biometrika*, **77**, 507–513.

Stallard, N. and Todd, S. (1999). Sequential designs for phase III clinical trials incorporating treatment selection. Technical Report 99/1, Department of Applied Statistics, The University of Reading.

Thall, P.F., Simon, R. and Ellenberg, S.S. (1988). Two-stage selection and testing designs for comparative clinical trials. *Biometrika*, **75**, 303–310.