Independent Increments in Group Sequential Tests: A Review

KyungMann Kim
kmkim@biostat.wisc.edu

University of Wisconsin-Madison, Madison, WI, USA

July 13, 2013

Outline

Why do I look the way I do?

Sequential Probability Ratio Test by Wald

- Test simple hypotheses H_0 against H_1
- Decisions D_0 and D_1 favoring H_0 and H_1, respectively
- After each observation, with L_{n0} and L_{n1}, the likelihoods of H_0 and H_1, respectively, stop sampling when

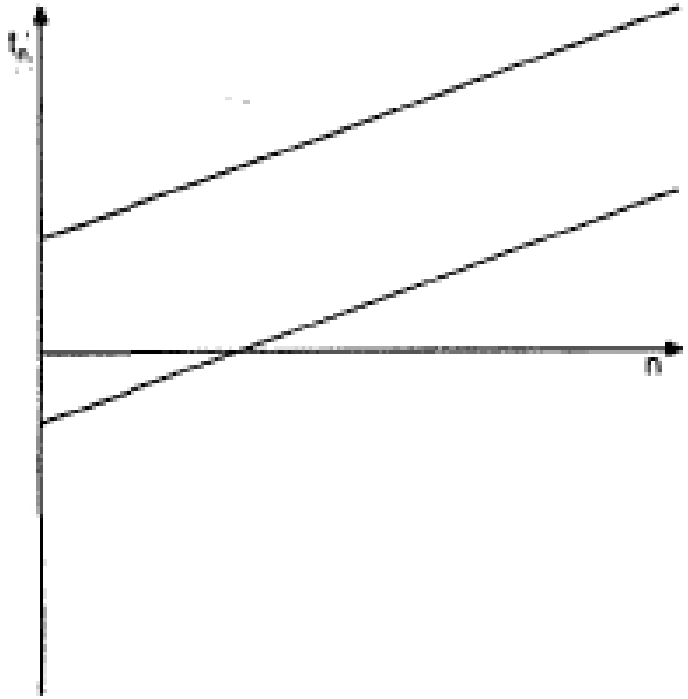
$$L_{n1}/L_{n0} \geq (1-\beta)/\alpha$$

and

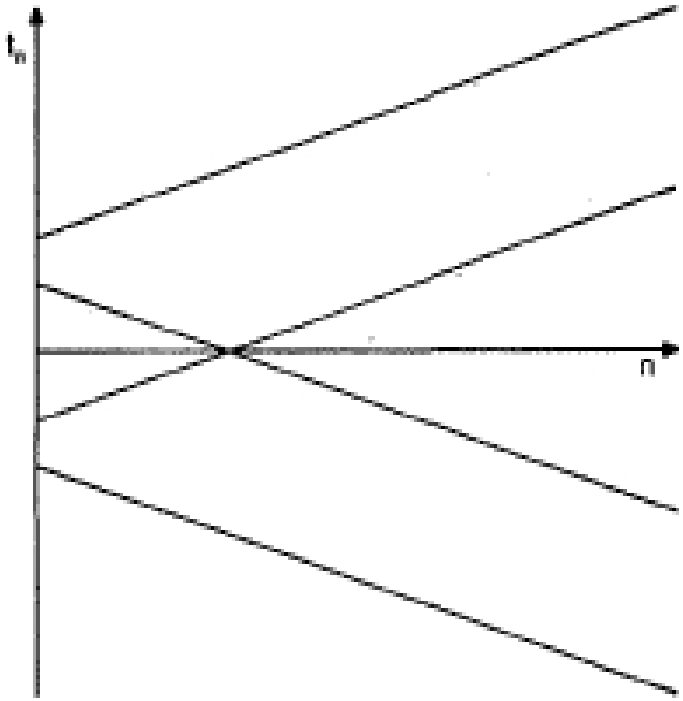
$$L_{n1}/L_{n0} \leq \beta/(1-\alpha),$$

with decisions D_1 and D_0, respectively

SPRT by Wald



(a) SPRT

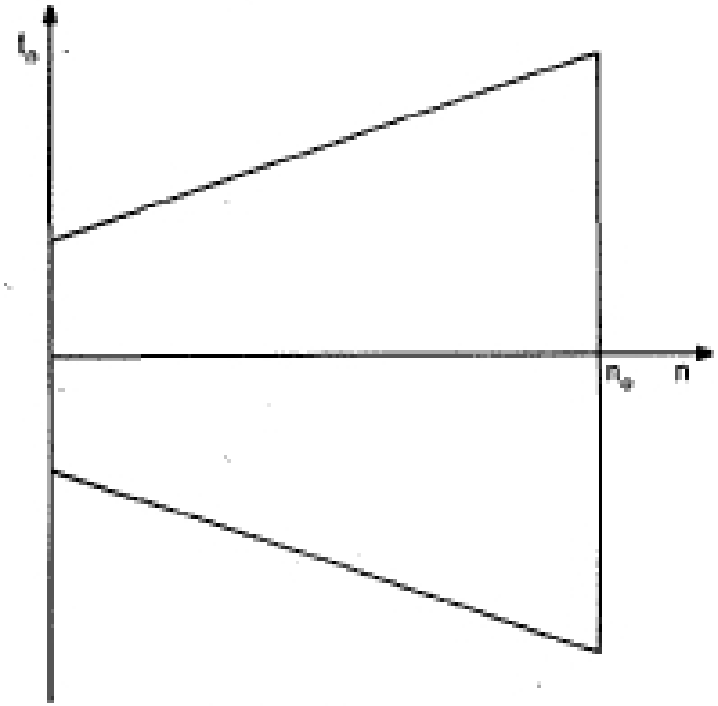


(b) Combination of two SPRTs

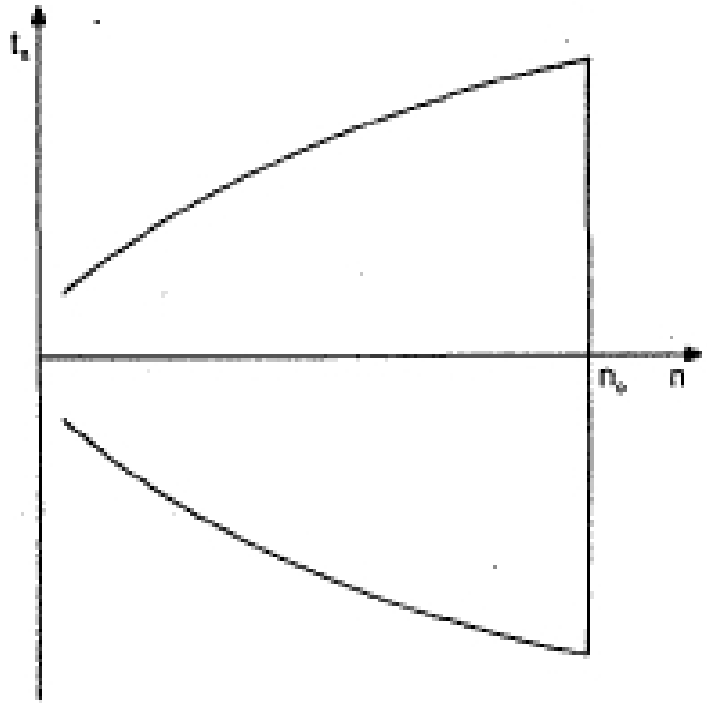
Sequential Methods for Clinical Trials

- Armitage (1960)
- Ethical imperatives in considering early termination in clinical trials
- Restricted plan (Armitage, 1957) as a modification of the two-sided version of SPRTs by Sobel and Wald (1949)
- Repeated significant test (RST) by Armitage, McPherson & Rowe (1969) as a means to adjust the critical value to account for multiple testing leading to a constant critical value for repeated significance tests

Sequential Tests by Armitage



(c) Restricted plan



(d) RST plan

Group Sequential Methods for Clinical Trials

- Wald (1947, pp 101–3) refers to taking groups of observations and applying SPRTs for binary outcome
- Elfring & Schultz (1973) was the first to specifically use the term “group sequential" for clinical trials with binary outcome
- Pocock (1977), following the repeated significance test by Armitage, McPherson & Rowe (1969), popularized the group sequential tests for clinical trials with Gaussian outcome

Why Independent Increments?

- In group sequential tests, one has to solve the following multivariate integral

$$\int_{-b_1}^{b_1} \cdots \int_{-b_K}^{b_K} f(s_1, \ldots, s_K) ds_1 \cdots ds_K = 1 - \alpha$$

where f is the joint density of the sequentially computed test staistics

- However, if the following holds

$$Cov(S_k, S_{k'}) = Var(S_k), k < k'$$

i.e., if the test statistics have independent increments, the multivariate integration above becomes univariate integration involving recursion

Armitage, McPherson & Rowe (1969)

- Repeated significant tests
- Assume that $Y_1, Y_2, \ldots$ are independent Gaussian observations with mean μ and variance 1, and let $S_k = \sum_{j=1}^{k} Y_j$
- To test $H_0 : \mu = 0$ against $H_1 : \mu \neq 0$, sampling is terminated the first time when

$$|S_k| > b_k$$

- Denote by f_k the probability density function of S_k in the sequential procedure:

$$f_k(s;\mu) = \int_{-b_{k-1}}^{b_{k-1}} f_{k-1}(u;\mu)\phi(s-u-\mu)du$$

- The probability of stopping at or before k is

$$P_k = \Pr(k^\star \leq k; \mu) = 1 - \int_{-b_k}^{b_k} f_k(u; \mu) du$$

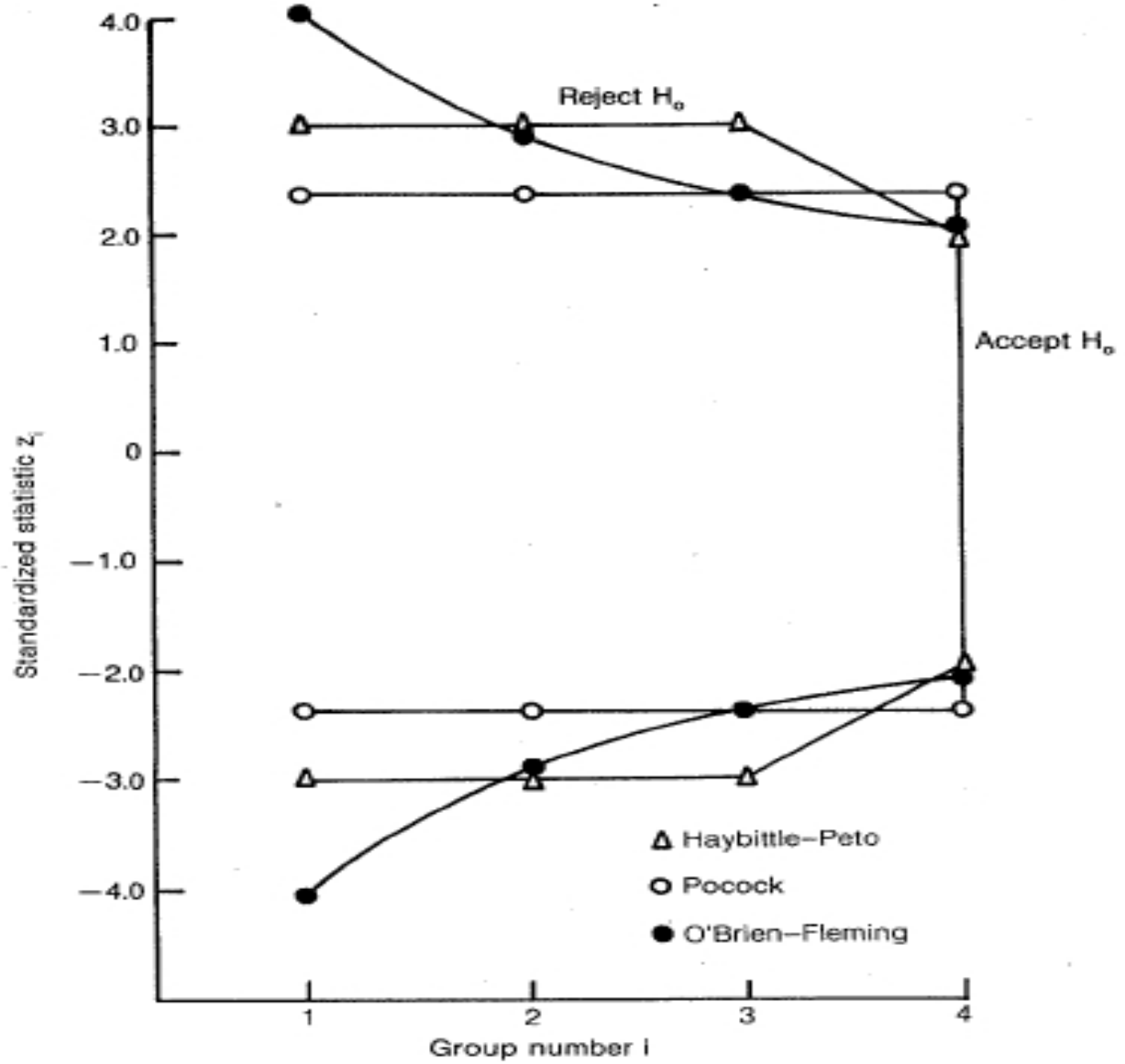
- The probability of stopping, i.e. exit probability, at $k^\star = k$ is

$$P_k - P_{k-1} = \int_{-b_{k-1}}^{b_{k-1}} f_{k-1}(u; \mu)\{1 - \Phi(b_k - u; \mu) + \Phi(-b_k - u; \mu)\} du$$

- This can be done by application of a Newton-Cotes formula of the second order, i.e. Simpson's rule

Classical Group Sequential Tests

- Pocock (1977)
- O'Brien & Fleming (1979)
- Slud & Wei (1982)
- Lan & DeMets (1983)


4.0
3.0
2.0
1.0
0
−1.0
−2.0
−3.0
−4.0
Standardized statistic z_i
Reject H_o
Accept H_o
Haybittle–Peto
Pocock
O'Brien–Fleming
1
2
3
4
Group number i

Intuition about Independent Increments

- With Gaussian outcome, it is intuitive that group sequential test statistics would have independent increments, thus allowing application of the classical group sequential methods
- With time to event outcome, it is unclear since each subject contributes follow-up data possibly multiple times over group sequential tests
  - Conjecture by Armitage (1975, pp 140–2) for time to event data subject to random censoring
- With longitudinal outcome, again it is unclear since each subject contributes follow-up data multiple times longitudinally

Tsiatis (1981)

- The asymptotic joint distribution of the efficient scores test for the proportional hazards model calculated over time
- The score statistic of the proportional hazards model calculated at different points in time is shown to converge asymptotically to a multivariate Gaussian process with independent increments when individuals enter randomly throughout the course of the study
- This allows group sequential methods to be based on the logrank test in clinical trials with time to event outcome subject to random censoring, thus proving Armitage's conjecture

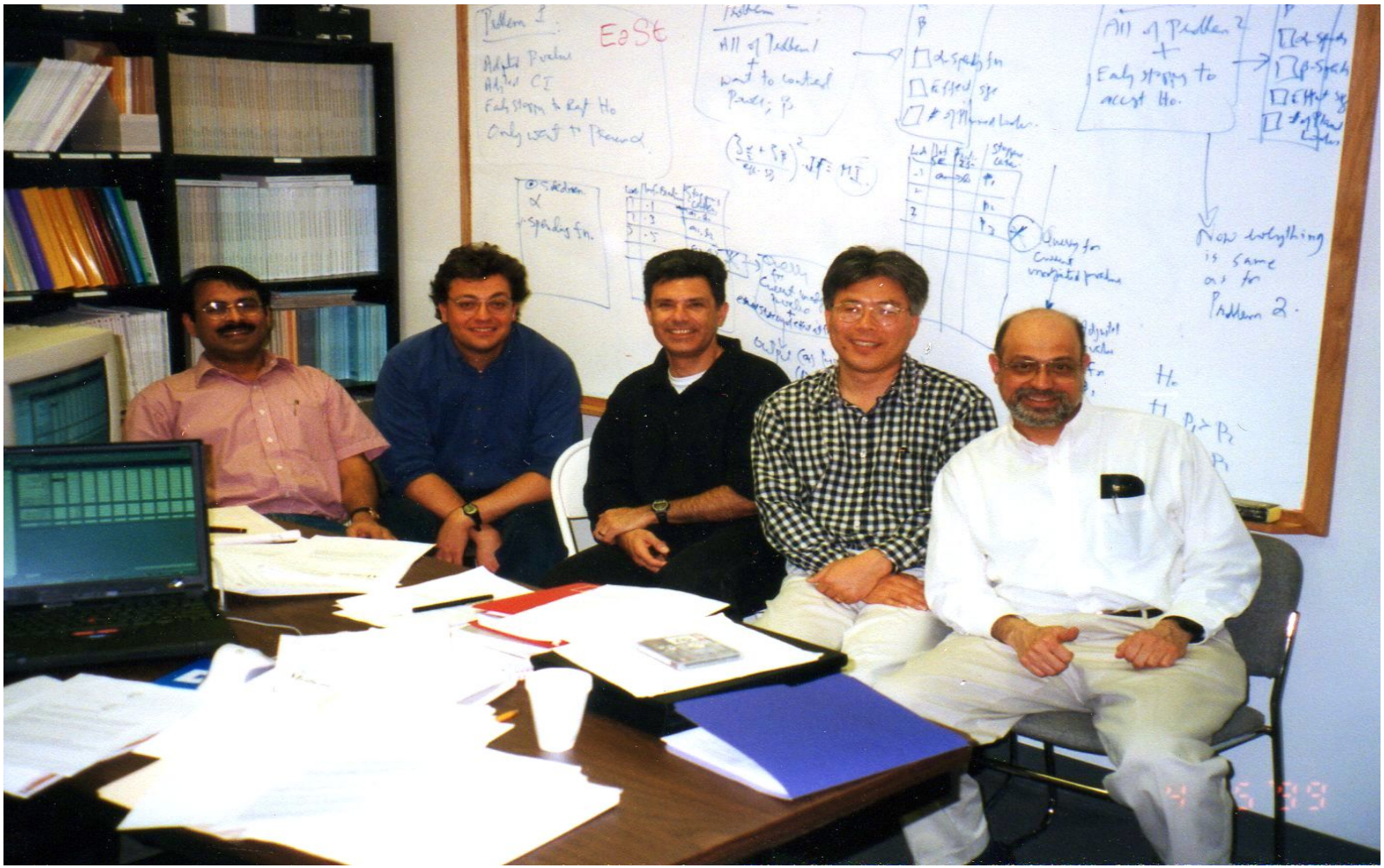
Tsiatis (1982)

- Generalization of the results in Tsiatis (1981) to a general class of nonparametric test statistics characterized by
  - Tarone and Ware (1977)
  - Prentice and Marek (1979)
- The asymptotic joint distribution of the sequentially computed test statistics, within this general class of nonparametrict ests, is derived, showing independent increments
- Again this allows group sequential methods to be based on this general class of nonparametric tests in clinical trials with time to event outcome subject to random censoring

Kim & Tsiatis (1990)

- The first in a series of joint publications on group sequential methods
- Based on Tsiatis (1981)
  - Propose a unified design procedure for group sequential clinical trials with time to event outcom subject to random censoring and staggered patient entry
  - Provide a foundation for the launch of the commercial product EaSt by Cytel Corp.
- Kim, Boucher & Tsiatis (1995)
  - Maximum information vs duration designs

At Cytel Corp. for EaSt Version 2 in April 1996



Tsiatis, Boucher & Kim (1995)

- Joint distribution of sequentially computed score and Wald tests for a general parametric model for time to event outcome, including a cure rate model
- In particular, score and Wald tests for a parameter of interest in the presence of nuisance paramters have independent increments
- Seed for group sequential methods based on semiparametric efficient test statistics by Scharfstein, Tsiatis & Robins (1997)

Lee, Kim & Tsiatis (1996)

- An independent increments structure of sequentially computed test statistics based on the generalised estimating equations of Liang & Zeger (1986) for longitudinal data
- The limiting distribution has uncorrelated increments when the “working variances” are equal to or consistently estimate the true variances
- This simplifies the computational procedure for group sequential boundaries to one involving recursive univariate integrations and allows the use of standard group sequential methods

Scharfstein, Tsiatis & Robins (1997)

- Joint distributions of many group sequential statistics used to analyze data arising from clinical trials with time to event and longitudinal outcomes are multivariate normal with an independent increments covariance structure
- This limiting distribution arises naturally when one uses an efficient test statistic to test a single parameter in a semiparametric or parametric model
- Most general results based on semiparametric efficienct tests
- Jennison & Turnbull (1997) for general regression models

Conclusion

- Congratulations to Butch!
  - A very prolific run from 1981 to 1997 and beyond
  - Established many important results for group sequential methods for clinical trials
  - Set the standards for pratice of group sequential methods for clinical trials
- Many thanks to Butch and former students
  - Sandro Pampallona
  - Hélène Boucher
  - Sandra Lee