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APPLYING THE LAW OF ITERATED LOGARITHM TO CUMULATIVE META-ANALYSIS OF A CONTINUOUS ENDPOINT

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Abstract: Cumulative meta-analysis typically involves performing an updated meta-analysis every time a new trial is added to a series of similar trials, which by definition involves multiple inspections. Since the studies are often conducted at different times with different protocols, the heterogeneity among studies is generally not ignorable and the estimation of the between-study variation poses the biggest challenge in cumulative meta-analyses because the testing process generally starts with a small number of studies. This is one of the major reasons why the conventional group sequential methods do not perform well in controlling the overall type I error. This paper presents an approach − motivated by the Law of Iterated Logarithm − that "penalizes" the Z-value of the test statistic to account for multiple tests. It also can account for estimation of heterogeneity in treatment effects across studies and for the unpredictable nature of information from trials in a cumulative meta-analysis. Our extensive simulation studies show that this method controls the overall type I error for a very broad range of practical situations for up to 25 inspections. An example based on data from the Stroke Unit Trialists' Collaboration is used to illustrate the method.

Key words and phrases: Cumulative meta-analysis, fixed effects model, law of iterated logarithm, multiple inspections, random effects model, sequential analysis, type I error.

1. Introduction

Cumulative meta-analysis of clinical trials has been proposed as a statistical tool that may facilitate the determination of clinical efficacy or harm and may be helpful in fostering clinical recommendations for therapy (Lau, Antman, Jimenez-Silva, Kupelnick, Mosteller and Chalmers (1992) and Antman, Lau, Kupelnick, Mosteller and Chalmers (1992)). When trials are chronologically ordered, this involves performing a new or updated meta-analysis every time one or more new trials are added to a series of similar trials. The accumulation may proceed according to the year of study completion or publication, and also according to study size, the event rate in the control group, some quality score assigned to each study, or other covariates such as drug dosage or trial duration (Lau, Schmid

and Chalmers (1995)). When trials are chronologically ordered, the implied goal of this process is to decide on the earliest time in which there is clinically and statistically significant evidence of benefit or harm of a new intervention to warrant its adoption or rejection.

Because it revises information in light of new information, cumulative meta-analysis is naturally amenable to a Bayesian analysis (Lau, Schmid and Chalmers (1995) and Stangl and Berry (2000)). From a classical (frequentist) perspective, however, it suffers from the problem of repeated testing and an inflated overall type I error (Berkey, Mosteller, Lau and Antman (1996), Pogue and Yusuf (1997), Whitehead (1997), Todd (1997) and Sutton, Abrams, Jones, Sheldon and Song (2000)). By definition, the technique involves multiple looks at accumulating evidence. Without appropriate adjustments, even if there is no genuine treatment effect, the process of adding trials and multiple testing will eventually lead to statistical significance and produce a false conclusion that there is a treatment effect.

In this manuscript, we suggest an approach − motivated by the Law of Iterated Logarithm (Robbins (1970) and Breiman (1992, Chap. 13)) − that "penalizes" the Z-value of the test statistic to account for multiple tests (say, across time) in a cumulative meta-analysis of a continuous endpoint, planned prospectively or examined retrospectively. When applied to a random-effects model, it also can account for estimation of heterogeneity in treatment effects across studies. Furthermore, the methodology implicitly accounts for the unpredictable nature of information from trials. In doing so, the method is intended to be flexible enough to allow inspections to occur at variable times and leave the maximum amount of information unspecified.

2. Sequential Aspects

Even though interest lies mainly in two-sample comparisons we start with the one-sample case for simplicity, and then generalize it to the two-sample case. Let $X_1, \ldots, X_n$ be n i.i.d. observations from a normal distribution $N(\mu, \sigma^2)$. Consider a one-tailed test: $H_0 : \mu = 0$ versus $H_1 : \mu > 0$. For the moment, assume $\sigma^2 = 1$. Under H_0, the standardized test statistic $Z_n = S_n/\sqrt{n} \sim N(0,1)$, where $S_n = \sum X_i$. We have $P\{Z_n \geq C \text{ for some } n = 1, 2, \ldots.\} = 1$ for any positive C. Hence, if Z_n is monitored sequentially and H_o is rejected when $Z_n \geq C$, the probability of eventually rejecting the null hypothesis is 1.

We modify the testing sequence $\{Z_1, \ldots, Z_n, \ldots\}$ to create a new sequence $\{Z_1^*, \ldots, Z_n^*, \ldots\}$ so that the overall type I error rate can be maintained at the desired level for the sequential testing process. This modification is possible by the Law of Iterated Logarithm (LIL) which states that, under $H_o : \mu = 0$,

$$P\left(\limsup_{n\to\infty} \frac{S_n}{\sqrt{n \ln(\ln(n))}} = \sqrt{2}\right) = 1. \tag{1}$$

Note that $S_n/\sqrt{n\ln(\ln(n))} = Z_n/\sqrt{\ln(\ln(n))}$, and (1) can be restated as

$$P\left(\limsup_{n\to\infty} \frac{Z_n}{\sqrt{\ln(\ln(n))}} = \sqrt{2}\right) = 1. \tag{2}$$

If we introduce a penalty and create an adjusted test statistic $Z_n^* = Z_n/\sqrt{\ln(\ln(n))}$, the sequence $\{Z_n^*\}$ is a bounded sequence with probability 1.

When σ^2 is unknown, Z_n^* needs to be normalized by an estimate $\hat{\sigma}$ of σ.

3. Applying Z^* Sequentially to Cumulative Meta-Analysis

In a cumulative meta-analysis, one tests $\mu = 0$ repeatedly after each trial, ordered sequentially by year of publication. Suppose there are n_k additional subjects observed between the $(k-1)$th and the kth inspection $(k = 1, \ldots, K)$. The maximum number of inspections K can be large in practice and is, in principle, unbounded. Let $Z(k)$ be the Z-statistic of the kth inspection based on $n_1 + n_2 + \cdots + n_k (= n_{ck})$ observations up to the kth inspection. We define a new sequence $\{Z^*(k)\}$ to control the overall type I error.

3.1. The fixed effects model

The fixed effects model assumes a constant treatment effect across studies and considers only within-study variability of treatment effect. Reconsider the one-sample case with $\sigma^2 = 1$. Equation (1) based on LIL can be modified to arrive at the cumulative test statistic at the kth inspection:

$$S^*(k) = \frac{S(k)}{\sqrt{\lambda(n_{ck})\ln(\ln(n_{ck}))}}, \tag{3}$$

where $S(k)$ is the sum of all n_{ck} observations and λ is an adjustment factor. The value of λ will be determined through simulation to control the α (significance) level under different practical scenarios.

From this point on, we focus on the more common two-sample case. Suppose that, in the jth study, $X_1, \ldots, X_{n_{1j}}$ are n_{1j} i.i.d. $N(\mu_1, \sigma_{1j}^2)$ observations from the treatment group and $Y_1, \ldots, Y_{n_{2j}}$ are n_{2j} i.i.d. $N(\mu_2, \sigma_{2j}^2)$ observations from the control group. Let $\bar{X}_j$ and $\bar{Y}_j$ be the sample means, respectively, for treatment and control in the jth study. In the two-sample case, we test the hypothesis $H_0 : \delta = \mu_1 - \mu_2 = 0$ against the one-sided alternative $H_1 : \delta > 0$.

In the context of sequential analysis with two groups, (3) can be refined to obtain the cumulative test statistic at the kth inspection:

$$Z^*(k) = \frac{S(k)}{\sqrt{\lambda I_{ck}\ln(\ln(I_{ck}))}} = \frac{Z(k)}{\sqrt{\lambda\ln(\ln(I_{ck}))}}, \tag{4}$$

where $I_{ck} = \sum_{j=1}^{k} I_j = \sum_{j=1}^{k}[(\sigma_{1j}^2/n_{1j}) + (\sigma_{2j}^2/n_{2j})]^{-1}$ is the cumulative amount of information up to the kth inspection, and $S(k)$ is the weighted sum: $S(k) = \sum_{j=1}^{k} I_j(\bar{X}_j - \bar{Y}_j)$. These notations represent one study per inspection. Equation (4), though, is also valid for multiple studies per inspection by simply modifying the weighted sum $S(k)$ and the cumulative information I_{ck} accordingly using double sub-indices. The number of studies per inspection need not be constant.

3.2. The random effects model

The random effects model allows each study to have its own treatment effect and the central value around which these individual study effects vary becomes the overall treatment effect. Suppose that, in the jth study, the sample mean difference $D_j = \bar{X}_j - \bar{Y}_j$ follows a normal distribution $N(\Delta_j, \sigma_{1j}^2/n_{1j} + \sigma_{2j}^2/n_{2j})$, where Δ_j is a random variable normally distributed as $N(0, \tau^2)$, in which τ^2 is the population between-study variance component of treatment effects. Unconditionally, under the null hypothesis, D_j has mean of 0 and variance of $(\sigma_{1j}^2/n_{1j}) + (\sigma_{2j}^2/n_{2j}) + \tau^2$. The revised test statistic, which incorporates τ^2, is

$$Z^*(k) = \frac{S^+(k)}{\sqrt{\lambda I_{ck}^+ \ln(\ln(I_{ck}))}} = \frac{Z^+(k)}{\sqrt{\lambda \ln(\ln(I_{ck}))}}, \tag{5}$$

where $S^+(k) = \sum_{j=1}^{k} I_j^+(\bar{X}_j - \bar{Y}_j)$ is again the weighted estimator of the treatment difference and $I_{ck}^+ = \sum_{j=1}^{k} I_j^+ = \sum_{j=1}^{k}[(\sigma_{1j}^2/n_{1j}) + (\sigma_{2j}^2/n_{2j}) + \tau^2]^{-1}$ is the cumulative information through the kth inspection. It should be noted that $I_{ck} = \sum_{j=1}^{k} I_j = \sum_{j=1}^{k}(\sigma_{1j}^2/n_{1j} + \sigma_{2j}^2/n_{2j})^{-1}$ is used instead of the corresponding cumulative information I_{ck}^+ for the log-log penalty in the denominator of (5). The reason for this is that the penalty using $\ln(\ln(I_{ck}^+))$ will be too small for large n_{1j} and n_{2j}, in which case the between-study variance τ^2 is likely to dominate in I_j^+. In addition, in (4) and (5), the penalty $\ln(\ln(I_{ck}))$ is set to 1 if it is smaller than 1 (to be conservative).

3.3. Estimation of between-study variance in random effects models

The most commonly used estimator of τ^2 is the moment estimator (see, e.g., Shadish and Haddock (1994, Chap. 18)). For the kth inspection, the between-study variance is estimated by

$$\hat{\tau}_k^2 = \frac{Q_k - (k-1)}{\sum_{j=1}^{k} \hat{I}_j - \left[\left(\sum_{i=1}^{k} \hat{I}_j^2\right) / \sum_{i=1}^{k} \hat{I}_j\right]}, \tag{6}$$

where $Q_k = \sum_{j=1}^{k} \hat{I}_j(D_j - \bar{D}_w^{(k)})^2$ and $\bar{D}_w^{(k)}$ is the weighted average of $D_1, \ldots, D_k$ with weights $\hat{I}_j$. However, the estimate in (6) can be unstable and negative, with

negative variance estimates customarily treated as zero. These shortcomings may make the estimator in (6) biased (Brockwell and Gordon (2001)); moreover, in our simulation, we found this estimator anti-conservative by often inflating type I error rates. We propose to use the simple variance estimator

$$\hat{\tau}_k^2 = \frac{1}{(k-1)} \sum_{j=1}^{k} (D_j - \bar{D}^{(k)})^2 \tag{7}$$

when there are five or fewer studies, or whenever the estimate in (6) is non-positive. The quantity $\bar{D}^{(k)}$ in (7) is the simple or unweighted average of $D_1, \ldots, D_k$.

Equation (7) is an unbiased estimate for the total variance and therefore overestimates the between-study variance. Yet it may be preferred to be conservative when the estimate (6) is wrong (non-positive) or unreliable especially when based on a small number of studies. Actually, in some situations, this conservative estimator of τ^2 may still need to be inflated to control overall type I error (see Sections 4 and 5 for details).

4. Simulation Study and Results

4.1. The fixed effects model: two groups

In the simulation, the maximum number of inspections, K, was evaluated at 5, 10, 15, 20 and 25. Testing stopped if there was significance at an interim inspection or if there was no statistical significance after all K inspections. The number of incremental subjects added to each study was simulated from $N(M, SD^2)$. We evaluated M at 20, 40, 100, 200, 300, 400, 500, 600, 700 and 800, with two SD values for each M, $SD = 1/3M$ or $2/3M$. At least 20 new subjects were required to be available for testing at each inspection.

We did not assume the variances in the two treatment groups were equal. We also allowed sample variances to vary from study to study, although we assumed the treatment effect was fixed. The sample standard deviation ratio σ_{2j}/σ_{1j} was simulated from a uniform distribution over $[1/2, 2]$, while σ_{1j}^2 for the jth study was simulated from $\chi^2(5)/5$. Furthermore, the sample size ratio n_{1j}/n_{2j} randomly varied over $[0.4, 0.6]$ uniformly.

For each simulation scenario, the objective was to determine the λ in (4) that gave an overall one-sided significance level of 0.025. All results were based on 100,000 simulation replications. In all cases, the adjustment factor $\lambda = 1.5$ was found to control the overall type I error at the desired level for a maximum number of inspections up to 25, which should cover most practical situations. As the size of the studies increases, this adjustment factor decreases. For large studies, that is when the combined average study size M was greater than 300,

no such adjustment was needed and $\lambda = 1$ works. As expected, more inspections required larger λ.

4.2. The random effects model: two groups

In addition to the common factors mentioned above for the fixed effects model, the random effects model allowed the treatment effect to vary from study to study. For the kth study, the treatment difference Δ_k between the two treatment groups was simulated from $N(0, \tau^2)$, where three values of τ were evaluated: $\tau = 0.2313$, 0.4314 and 0.6725. A random relationship was generated between within-study variation (σ_k) and cross-study variation (τ) : $\sigma_k = r_k \cdot \tau$ such that $E(\sigma_k^2) = 1$. Corresponding to the three τ values, the ratio r_k was simulated from three mixed uniform distributions: (1) mixer of $U(0.1, 1)$ and $U(1, 10)$; (2) mixer of $U(0.2, 1)$ and $U(1, 5)$; and (3) mixer of $U(0.3, 1)$ and $U(1, 3.333)$, with a probability of 0.5 for each uniform distribution in each mixer. The second mixed uniform distribution (corresponding to $\tau = 0.4314$) resulted in a 25-fold difference between the largest and the smallest within-study sample standard deviation, which was close to the example given in Section 5.

We evaluated scenarios both with one study per inspection and with multiple studies per inspection. For the latter, the number of studies per inspection was simulated from a Poisson (1.5) distribution; if 0 was generated, it was set to 1. With a random number of studies per inspection, the estimate of the between-study variance $\hat{\tau}_k^2$ needed to be multiplied by 10, 9, 8, ..., 2 and 1 when the total number of studies at an inspection was 2, 3, 4, ... and 11, respectively. With one study per inspection, these multipliers needed to be further doubled. This enlargement of $\hat{\tau}_k^2$ is thought of as an "extra penalty."

While our simulations were wide ranging, $\lambda = 2$ can basically control the overall type I error in the random effects model. Table 1 presents the overall type I error rates for several different scenarios.

Table 1. Type I error rates with $\lambda = 2$ in the two-sample continuous case with a random effects model based on 100,000 simulation replications.

τ	Range of σ/τ	Maximum Inspections	Maximum Type I Error Rate*
0.2313	[0.1, 10]	15	0.0219 (0.0261)
		25	0.0253 (0.0276)
0.4314	[0.2, 5]	15	0.0214 (0.0247)
		25	0.0235 (0.0253)
0.6725	[0.3, 3.3]	15	0.0214 (0.0246)
		25	0.0231 (0.0256)

* Main entries pertain to one study per inspection and entries in parentheses pertain to multiple studies per inspection. The main entries are smaller than the entries in parentheses because the extra penalty on estimates of between-study variance for the one study per inspection is double that of multiple studies per inspection.

4.3. Statistical power

The inflation of type I error is the main concern in cumulative meta-analyses. Statistical power, on the other hand, may pose a lesser concern because sample sizes are often sufficiently large, especially at the later stages of the testing process. Our method is conservative and controls type I errors for a broad range of practical situations simultaneously and, therefore, may be less powerful than a method carefully calibrated for a specific situation. It is difficult to evaluate power for our method. Nonetheless, Table 2 includes some simulation results to impart some sense of power performance.

Table 2. Power evaluation of the LIL-based methods with $\lambda = 2$ and the traditional random-effects method in two-sample random-effects models with $\tau = 0.4314$ based on 100,000 simulation replications.

Treatment Difference	Average Study Size	Number of Inspections	Type I Error Rate or Power*	
			LIL Method	Traditional Method
0	500	15	0.0200 (0.0234)	0.2985 (0.2810)
		25	0.0217 (0.0234)	0.3183 (0.3016)
0.4	100	15	0.4869 (0.7004)	0.9615 (0.9906)
		25	0.7208 (0.9099)	0.9944 (0.9997)
	500	15	0.5154 (0.7511)	0.9724 (0.9956)
		25	0.7511 (0.9388)	0.9968 (0.9999)
0.6	100	15	0.8506 (0.9683)	0.9986 (0.9999)
		25	0.9778 (0.9989)	0.9999 (1.0000)
	500	15	0.8711 (0.9788)	0.9995 (1.0000)
		25	0.9824 (0.9994)	1.0000 (1.0000)

*For main entries, one study per inspection; for entries in parentheses, multiple studies per inspection.

5. Illustrative Example

A retrospective cumulative meta-analysis using LIL is illustrated with 18 randomized or quasi-randomized studies in which specialized organized inpatient stroke units were compared with conventional care after patients suffered a stroke (Stroke Unit Trialists' Collaboration (1999)). The outcome of interest was the mean (or median) length of stay (days) in a hospital or institution. Because of substantial heterogeneity in the outcome, a random effects model was applied to these data.

The adjusted Z values with and without the extra penalty (Table 3, columns 1 and 2, respectively) were similar for the first eleven studies (ten inspections) and identical for the remaining seven studies (seven inspections). Because of added

uncertainty imposed by the extra penalty, the standardized Z values with extra penalty were closer to the null hypothesis ($Z = 0$) than the standardized Z values without the extra penalty. In both situations statistical significance ($Z \leq -1.96$) was reached only after the last study in 1998, favoring the organized stroke unit in reducing mean length of stay. Figure 1 depicts the cumulative results with extra penalty. After 18 studies, relative to conventional care, the organized stroke unit resulted in a significant average reduction of approximately 7.5 hospital days (95% confidence interval, −15.0 to −0.015).

Table 3. Results of a random effects cumulative meta-analysis for stroke example (single study per inspection): standardized test statistics*.

		Column 1	Column 2	Column 3
Study	**(yr)**	**Extra Penalty**	**Without Extra Penalty**	**No Correction**
1	(1980)	—	—	—
2	(1982)	−0.08	−0.31	−0.44
3	(1984)	−0.07	−0.28	−0.35
4	(1984)	−0.10	−0.40	−0.61
5	(1984)	−0.11	−0.34	−0.58
6	(1985)	0.005	−0.31	−0.43
7	(1985)	−0.12	−0.70	−0.97
8	(1993)	−0.22	−0.64	−0.89
9	(1993)	−0.40	−0.76	−1.06
10	(1993)	−0.58	−1.30	−1.83
11	(1993)	−1.41	−1.88	**−2.65**
12	(1993)	−1.70	−1.70	**−2.38**
13	(1995)	−1.73	−1.73	**−2.44**
14	(1996)	−1.42	−1.42	**−1.99**
15	(1996)	−1.25	−1.25	−1.76
16	(1997)	−1.25	−1.25	−1.76
17	(1997)	−1.60	−1.60	**−2.26**
18	(1998)	**−1.97**	**−1.97**	**−2.80**

*Standardized test statistics without extra penalty used the correction factor $\lambda = 2$ (column 2). Standardized test statistics with no correction (column 3) made no adjustment. Standardized test statistics with extra penalty (column 1) not only used $\lambda = 2$ but also doubled our estimates of inter-study variability from the analysis without extra penalty. Bold-faced numbers indicate statistical significance ($Z \leq -1.96$).

On the other hand, the traditional cumulative meta-analysis gave reversal in terms of statistical significance ($Z \leq -1.96$). Statistical significance was reached at the eleventh study (1993) and continued through the fourteenth study (1996) (Table 3, column 3). Then the large amount of between-study heterogeneity

resulted in lack of statistical significance for the fifteenth and sixteenth studies (1996-1997) before statistical significance reemerged, this time in the last two studies (1997-1998). In summary, this example shows that the two modified approaches based on LIL appeared to instill prudence before convincingly demonstrating statistical significance, whereas the traditional approach gave unstable results on statistical significance.

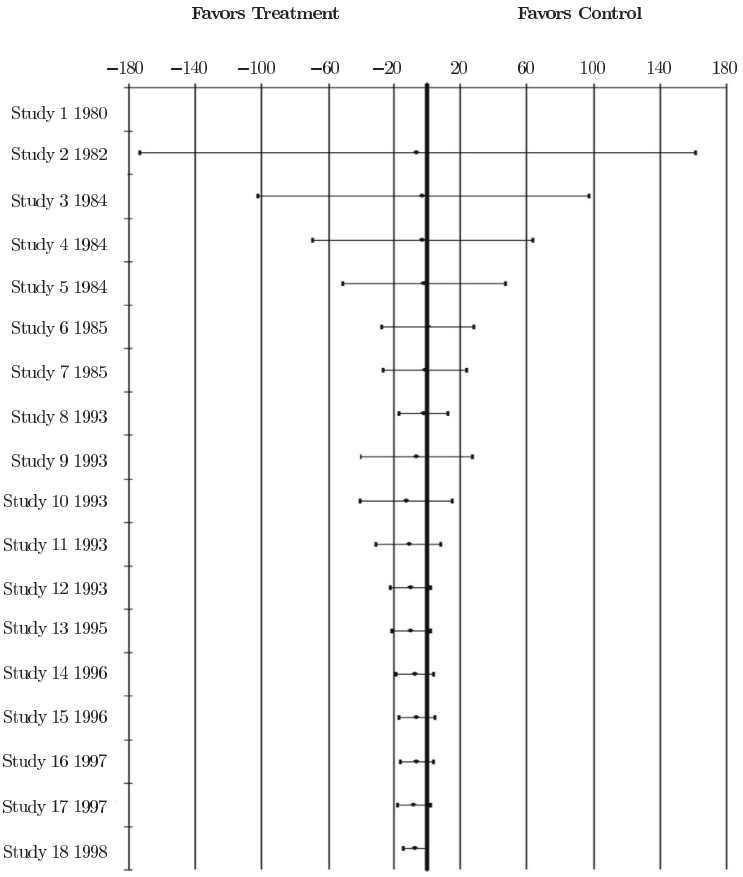

Figure 1. Applying law of iterated logarithm with extra penalty to cumulative meta-analysis: stroke example.

6. Discussion

One major concern in meta-analysis is the heterogeneity among different studies, since the studies may be conducted at different times with different protocols. The fixed effects model, which assumes that results from all the trials come from a hypothetically homogeneous population, may be too simple to be

realistic. The random effects model includes a between-study variance component τ^2 in the treatment effect evaluation, but it is a challenging problem to obtain a reliable estimate for τ^2. This variance component can be estimated accurately only if the number of studies is large. If testing in a cumulative meta-analysis starts with a small number of studies, inaccuracies may ensue as the estimate of τ^2 tends to be extremely unstable at the beginning of the process. This difficulty helps to explain why the overall type I error in the cumulative meta-analysis is so hard to control through conventional group sequential methods. As shown in another simulation study (Whitehead (1997)), the type I error rates of both the conventional random-effects analysis and the proposed method by Whitehead can quickly go over the pre-specified level of 0.025, even with only four inspections, when the between-study variation is high (e.g., $\tau = 0.847$).

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