Meta–Analysis of Clinical Trials with Ordinal Outcome using Random Cut-Points Theory

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Outline

1. Methods for a single trial
2. Meta-Analytic Methods
3. Simulation
4. Final Remarks
5. Outlook

Notation in a single trial

usual $2 \times k$ - table

	Category			
	1	2		k
Treatment (Y_1)	p_{11}	p_{12}	$\cdots$	p_{1k}
Control (Y_2)	p_{21}	p_{22}	$\cdots$	p_{2k}

Category 1 = *"best", ..., Category k* = *"worst"*

$$\text{Usually } Y_i \sim \mathcal{M}\left(p_{i1}, p_{i2}, \ldots, p_{ik}\right), \qquad i = 1, 2$$

Situation

Assumption

$$Y_1 \sim H_1 \qquad \text{and} \qquad Y_2 \sim H_2$$

- H_1, H_2 continuous cumulative density functions (cdf)

Problem: How to divide observations from H_1 resp H_2 in sensible categories?

Random Cut-Point Model

Let

$$\Theta = \{\theta_i\}_{i=1}^{k-1}$$

be a random sample with cdf F, taken without replacement

Make use of the order statistic

$$\theta_{(1)} < \theta_{(2)} < \cdots < \theta_{(k-1)}$$

and add

$$\theta_{(0)} = -\infty \quad \text{and} \quad \theta_{(k)} = \infty$$

Random Cut-Point Model

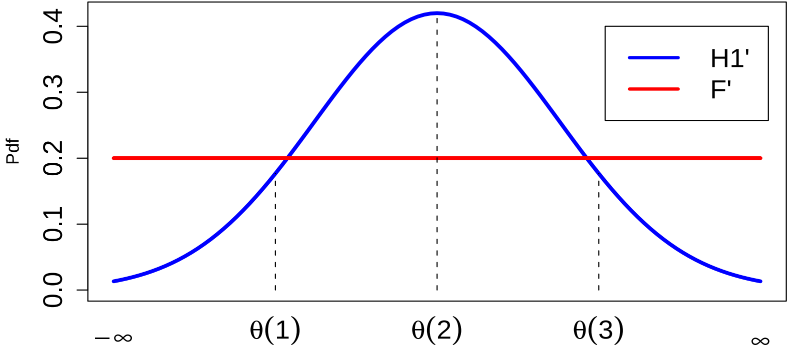
Let x be an unobservable realisation of a random sample of n_i values with cdf H_i, $i = 1, 2$.

Then n_{ij} is the number of observations where

$$\theta_{(j-1)} < x < \theta_{(j)}, \qquad j = 1, ..., k.$$

$\Longrightarrow$ realisation in category j

Example



Random Cut-Point Model

Assumption: n_1, n_2 and k known a priori

Then

$$p_{ij} = \int_{\theta_{(j-1)}}^{\theta_{(j)}} dH_i(x) = H_i\left(\theta_{(j)}\right) - H_i\left(\theta_{(j-1)}\right)$$

is a random variable

Random Cut-Point	$Y_i \sim \mathcal{M}\left(P_i\right)$	$P_i = \{p_{ij}\}$	random $i = 1, 2$
Conventional Approach	$Y_i \sim \mathcal{M}\left(\Pi_i\right)$	Π_i	fixed $i = 1, 2$

Mann-Whitney-Test

Test of no difference in Treatment or Placebo

- Mann-Whitney-Statistic (Edwardes 1997)

$$\hat{U} = n_1 \, n_2 \left(\sum_j \sum_{\ell<j} \hat{p}_{1\ell} \, \hat{p}_{2j} + \sum_j \hat{p}_{1j} \, \hat{p}_{2j}/2 - 1/2 \right)$$

- $\text{Var}_{MW(U|H_1=H_2)} = \dfrac{n_1 \; n_2 \, (n+1)}{12} - \dfrac{n_1 \; n_2}{12} \dfrac{\sum_{j=1}^{k} (n_{+j}^3 - n_{+j})}{n(n-1)}$

- $\text{Var}_{(U|F=H_1=H_2)} = \text{E}\left[\text{Var}_{MW(U|H_1=H_2)}\right]$

$$= \frac{n_1 \; n_2 \, (n+1)}{12} - \frac{n_1 \; n_2 \, (k+n)}{2\,(k+1)\,(k+2)}$$

Test decision

Asymptotic MW

$$\frac{\hat{U}}{\sqrt{\mathrm{Var}_{MW}(U|H_1 = H_2)}} \overset{H_0}{\sim} \mathcal{N}(0,\ 1)$$

Edwardes (2000) RC

$$\frac{\hat{U}}{\sqrt{\mathrm{Var}(U|F = H_1 = H_2)}} \overset{H_0}{\sim} R_k,$$

R_k known exact for $k = 2$

and by simulation for $k > 2$

Meta-Analytic Methods

Let $\hat{y}_i$ be an estimator for the treatment effect of study i, $i = 1, ..., L$

General random-effects model of meta-analysis

$$\hat{y}_i \sim \mathcal{N}\left(\mu, \sigma_i^2 + \tau^2\right)$$

Note: Estimate of σ_i^2 is available from each trial

$\tau^2 = 0 \Longrightarrow$ Fixed effects model

Estimation of μ

In general: given some weights b_i with

$$\hat{\mu} = \sum_{i=1}^{L} b_i \hat{y}_i, \qquad \sum_{i=1}^{L} b_i = 1$$

Two possibilities for the choice of b_i

1. using sample sizes
2. using variances

Sample Size Weighting

Approach of Hartung / Böckenhoff / Knapp (2003)

- Scoring of the studies by weights λ_i with
- with $\lambda_i = T_{N_i} / \sum_{j=1}^{L} T_{N_j}$ with $T_{N_i} = n_{i1} n_{i2} / (n_{i1} + n_{i2})$
- Direct estimator of variance

$$\widehat{\text{Var}}(\hat{\mu}) = \frac{1}{1 + \sum_{j=1}^{L} \frac{\lambda_j^2}{1-2\lambda_j}} \sum_{j=1}^{L} \frac{\lambda_j^2}{1 - 2\lambda_j} \left(\hat{y}_i - \sum_{m=1}^{L} \lambda_m \hat{y}_m \right)^2$$

Variance Weighting

Fixed Effects Model

Let be $\nu_i = \frac{1}{\sigma_i^2}, \quad \nu = \sum_{i=1}^{L} \nu_i \quad \Longrightarrow \quad \hat{\mu}_{FE} = \sum_{i=1}^{L} \frac{\nu_i}{\nu} \hat{y}_i$

Random Effects Model

Let be $\omega_i = \frac{1}{\tau^2 + \sigma_i^2}, \quad \omega = \sum_{i=1}^{L} \omega_i \quad \Longrightarrow \quad \hat{\mu}_{RE} = \sum_{i=1}^{L} \frac{\omega_i}{\omega} \hat{y}_i$

Reject hypothesis of no treatment difference if

$$\psi_1 = \frac{|\hat{\mu}_{FE}|}{\sqrt{(1/\nu)}} > u_{1-\alpha/2} \quad \text{resp.} \quad \psi_2 = \frac{|\hat{\mu}_{RE}|}{\sqrt{(1/\omega)}} > u_{1-\alpha/2}$$

Variance Weighting

Direct estimator for the variance of μ is given by

$$q = \frac{1}{L-1} \sum_{i=1}^{L} \frac{\omega_i}{\omega} \left(\hat{y}_i - \hat{\mu}_{RE} \right)^2$$

Hartung, Knapp (2001): reject hypothesis of no treatment difference if

$$\psi_2 = \frac{|\hat{\mu}_{RE}|}{\sqrt{q}} > t_{L-1;\, 1-\alpha/2}$$

Some Simulation Results

- null hypothesis of no treatment differences
- $L = 6$ or $L = 12$ studies included
- analysis in conventional in random cut-point model
- prescribed level $\alpha = 0.05$
- 25.000 replications

Some Simulation Results

$L = 6$ trials	Conventional MW			Random Cutpoint MW			
τ^2	FE	RE	HK	FE	RE	HK	SSW
0.0	4.99	3.72	5.11	5.10	7.06	5.03	5.45
0.1	5.27	3.93	4.76	6.37	6.71	4.95	4.68
0.2	7.31	5.04	5.01	11.24	7.56	5.05	5.03
0.5	18.57	8.39	4.93	28.90	9.60	4.97	4.75
1.0	41.26	11.27	5.33	49.44	11.45	5.11	5.51
1.5	54.26	13.47	5.12	59.12	11.95	5.01	5.58

Some Simulation Results

$L = 12$ trials Conventional MW Random Cutpoint MW

τ^2	FE	RE	HK	FE	RE	HK	SSW
	Conventional MW			Random Cutpoint MW			
0.0	5.00	4.07	4.78	5.63	6.18	4.69	4.90
0.1	5.43	4.03	4.88	7.66	6.30	5.00	4.95
0.2	7.71	5.40	5.38	15.77	7.34	5.17	5.30
0.5	18.84	7.29	4.96	29.44	7.68	4.95	5.46
1.0	40.47	7.89	5.32	49.10	8.10	5.25	5.48
1.5	52.17	8.09	5.44	58.07	8.33	5.08	5.56

Some Simulation Results

Summary

- variance weighting by using fixed effects or conventional random effects do not hold prescribed level especially in model with random cut point
- variance weighting by Hartung / Knapp and assuming random cut-point theory hold prescribed level satisfactorily
- alternative approach (Hartung / Böckenhoff / Knapp) is to taken into account

Final Remarks

- random cut-point theory may be considered as a method in meta–analysis of trials with ordinal outcome
- approach by Hartung / Böckenhoff / Knapp (2003) yields good result without much complexity
- otherwise variance weighting by Hartung/Knapp (2001) should be considered

Outlook

- assign Agresti's α, generalized Risk Ratio and Risk Difference into random cut-point model
- analyse different link function between random cut-points and underlying continuum

References

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