다지역임상시험을 위한 계층적 일반화 선형 모형

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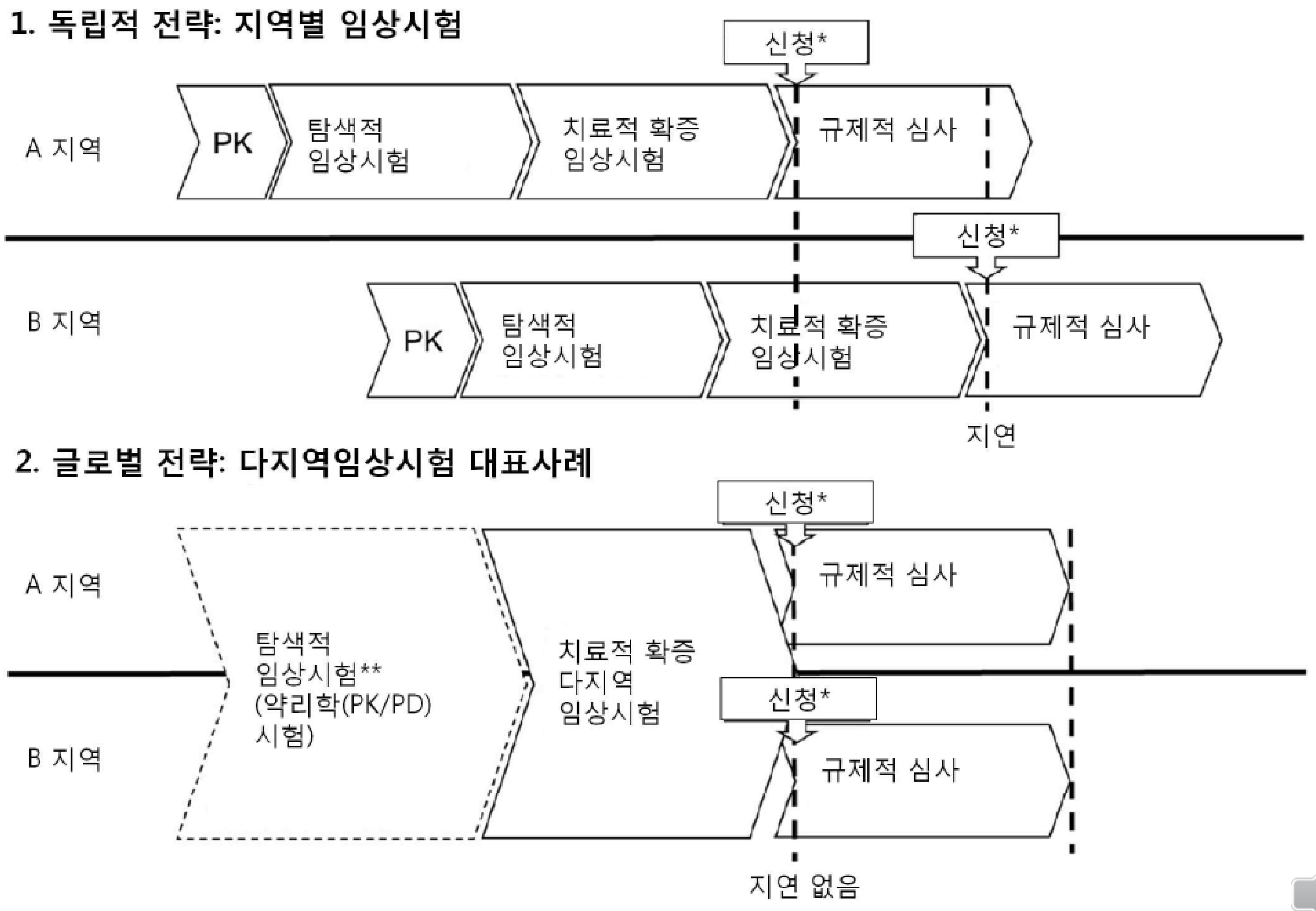
목차

I. 서론

- 다지역임상시험?

Multi-Regional Clinical Trials, MRCT

(Quan et al. 2013, 2017; ICH 2017)



(출처: ICH E17 (2017. 11))

I. 서론

- 현재 MRCT 결과 분석에 있어 주로 사용하는 방법은 메타분석의 fixed effects model (e.g., Quan et al. 2013) 및 random effects model임 (e.g., Hung et al. 2010).
- 최근 Kim and Kang (2020)에서 MRCT의 연속형 결과변수에 대하여 정규분포를 가정한 two-level hierarchical linear model을 제안.
- 다지역 임상시험(Multi-Regional Clinical Trials, MRCT)에서 자료의 계층적 구조와 지수족 분포들을 다룰 수 있는 **계층적 일반화 선형 모형(hierarchical generalized linear models)**을 제안.
- Morton et al. (2018)의 MRCT 예에서 제안한 HGLM에 활용될 수 있는 region-level covariate의 예를 고려.

I. 서론

- Morton et al. (2018) “A Randomized, **Multinational,** Noninferiority, Phase III Trial to Evaluate the Safety and Efficacy of BF200 Aminolaevulinic Acid Gel vs. Methyl Aminolaevulinate Cream in the Treatment of **Nonaggressive Basal Cell Carcinoma** With Photodynamic Therapy”, *British Journal of Dermatology*, 179, 309–319.
  - 자외선 (UV): 피부암의 알려진 위험인자
  - 자외선 지수 (UV index) (e.g., Fioletov, Kerr, and Fergusson 2010)
  - 자외선 조사량: 독일 vs 영국

II. 모형

1. 베르누이 분포

\# of regions: $j = 1, \cdots, J$,
\# of patients: $i = 1, \cdots, n_j$.
Randomization ratio
1:1

1st region

Test: n_{T1} patients
Placebo: n_{P1} patients
$n_1 = n_{T1} + n_{P1}$

$\vdots$

Test: n_{Tj} patients
Placebo: n_{Pj} patients
$n_j = n_{Tj} + n_{Pj}$

Jth region

Test: n_{TJ} patients
Placebo: n_{PJ} patients
$n_J = n_{TJ} + n_{PJ}$

II. 모형

1.1 환자공변량, 지역공변량이 없는 단순한 모형:

$$Y_{ij} | u_{1j} \sim \text{independently } B(1, \mu_{ij}),$$

$$\eta_{ij} = g(\mu_{ij}) = \beta_{0j} + \beta_{1j} x_{1ij},$$

$$\beta_{0j} = \gamma_{00}, \quad \beta_{1j} = \gamma_{10} + u_{1j}, \quad u_{1j} \sim N(0, \tau^2), \quad \text{for } i = 1, \cdots, n_j, \text{and } j = 1, \cdots, J.$$

$$x_{1ij} = \begin{cases} 1, & \text{if } i = 1, \cdots, n_{Tj}, \\ 0, & \text{if } i = n_{Tj} + 1, \cdots, n_j, \end{cases} \qquad \text{for all } j = 1, \cdots, J.$$

II. 모형

1.1.1 기존 모형과의 관계

Test group in the jth region

$(Y_{T_j} = \Sigma_{i=1}^{n_{T_j}} Y_{ij})$

$$Y_{T_j} | u_{1j} \sim B\left(n_{T_j}, \mu_{T_j}\right),$$

$$\log\left(\frac{\mu_{T_j}}{1-\mu_{T_j}}\right) = \beta_{0j} + \beta_{1j},$$

$$\beta_{0j} = \gamma_{00}, \beta_{1j} = \gamma_{10} + u_{1j}, u_{1j} \sim N(0, \tau^2).$$

$$(\mu_{Tj} = \mu_{1j} = \cdots = \mu_{n_{Tj}j})$$

Placebo group in the jth region

$(Y_{P_j} = \Sigma_{i=n_{T_j}+1}^{n_j} Y_{ij})$

$$Y_{P_j} | u_{1j} \sim B\left(n_{P_j}, \mu_{P_j}\right),$$

$$\log\left(\frac{\mu_{P_j}}{1-\mu_{P_j}}\right) = \beta_{0j},$$

$$\beta_{0j} = \gamma_{00}.$$

$$(\mu_{Pj} = \mu_{n_{Tj}+1\ j} = \cdots = \mu_{n_j j})$$

II. 모형

Let $\hat{\mu}_{Tj} = Y_{Tj}/n_{Tj}$, $\hat{\mu}_{Pj} = Y_{Pj}/n_{Pj}$,

By normal approximation of the binomial distribution,

$$\hat{\mu}_{Tj} \approx N\big(\mu_{Tj}, \mu_{Tj}(1-\mu_{Tj})/n_{Tj}\big),\ \ \hat{\mu}_{Pj} \approx N\big(\mu_{Pj}, \mu_{Pj}(1-\mu_{Pj})/n_{Pj}\big).$$

By delta-method with $h(t) = \log(t/(1-t))$,

$$h\big(\hat{\mu}_{Tj}\big) \approx N\left(\log\left(\frac{\mu_{Tj}}{1-\mu_{Tj}}\right), \frac{1}{n_{Tj}\mu_{Tj}} + \frac{1}{n_{Tj}(1-\mu_{Tj})}\right),\ \ h\big(\hat{\mu}_{Pj}\big) \approx N\left(\log\left(\frac{\mu_{Pj}}{1-\mu_{Pj}}\right), \frac{1}{n_{Pj}\mu_{Pj}} + \frac{1}{n_{Pj}(1-\mu_{Pj})}\right).$$

Approximate conditional distribution of the observed difference of log odds in the jth region $\hat{\delta}_j$:

$$\hat{\delta}_j \approx \gamma_{10} + u_{1j} + \sigma_j \epsilon_j,\quad u_{1j} \sim N(0, \tau^2),\quad \epsilon_j \sim N(0,1).$$

$$\left(\begin{array}{l} \sigma_j^2 = \frac{1}{n_{Tj}\mu_{Tj}} + \frac{1}{n_{Tj}(1-\mu_{Tj})} + \frac{1}{n_{Pj}\mu_{Pj}} + \frac{1}{n_{Pj}(1-\mu_{Pj})} \\ \hat{\sigma}_j^2 = \frac{1}{Y_{Tj}} + \frac{1}{n_{Tj}-Y_{Tj}} + \frac{1}{Y_{Pj}} + \frac{1}{n_{Pj}-Y_{Pj}} \end{array}\right).$$

II. 모형

1.1.2 일반화 선형 혼합 모형으로서의 측면:

$$Y_{ij} \big| u_{1j} \sim \text{independently } B(1, \mu_{ij}),$$

$$\eta_{ij} = g(\mu_{ij}) = \gamma_{00} + \gamma_{10} x_{1ij} + u_{1j} x_{1ij}, \quad u_{1j} \sim N(0, \tau^2), \quad \text{for } i = 1, \cdots, n_j, \text{and } j = 1, \cdots, J.$$

- 랜덤효과로 인한 결과 ($x_{1ij} = 1$ case).

$$E[Y_{ij}] = E[g^{-1}(\gamma_{00} + \gamma_{10} + u_{1j})],$$

$$Var[Y_{ij}] = E[g^{-1}(\gamma_{00} + \gamma_{10} + u_{1j})](1 - E[g^{-1}(\gamma_{00} + \gamma_{10} + u_{1j})]),$$

$$Cov[Y_{ij}, Y_{kj}] = Var[g^{-1}(\gamma_{00} + \gamma_{10} + u_{1j})].$$

II. 모형

1.2 환자 공변량, 지역 공변량이 있는 모형:

$$Y_{ij}|u_{1j} \sim \text{independently } B(1,\mu_{ij}),$$

$$\eta_{ij} = g(\mu_{ij}) = \gamma_{00} + \gamma_{01}w_j + \gamma_{10}x_{1ij} + u_{1j}x_{1ij} + \gamma_{20}x_{2ij},\ u_{1j} \sim N(0,\tau^2),\ \text{for } i = 1,\cdots,n_j, \text{and } j = 1,\cdots,J.$$

$$x_{1ij} = \begin{cases} 1, & \text{if } \ i = 1,\cdots,n_{Tj}, \\ 0, & \text{if } \ i = n_{Tj}+1,\cdots,n_j, \end{cases} \qquad \text{for all } \ j = 1,\cdots,J.$$

- MRCT 자료의 가능도 함수:

$$L = \prod_{j=1}^{J} \int_{-\infty}^{\infty} \prod_{i=1}^{n_j} \mu_{ij}^{y_{ij}} (1-\mu_{ij})^{1-y_{ij}} \frac{1}{\sqrt{2\pi\tau^2}} \exp\left(-\frac{u_{1j}^2}{2\tau^2}\right) du_{1j}\,.$$

- 최대 가능도 추정량 $\widehat{\boldsymbol{\theta}}$:

$$\boldsymbol{\theta} = [\gamma_{00},\gamma_{01},\gamma_{10},\gamma_{20},\tau^2]', \qquad \frac{\partial}{\partial\boldsymbol{\theta}} \log L(\widehat{\boldsymbol{\theta}}) = \mathbf{0}.$$

II. 모형

2. 포아송 분포

$$Y_{ij}|u_{1j} \sim \text{independently } Pois(\mu_{ij}),$$

$$\eta_{ij} = g(\mu_{ij}) = \gamma_{00} + \gamma_{10}x_{1ij} + u_{1j}x_{1ij}, \quad u_{1j} \sim N(0, \tau^2), \quad \text{for } i = 1, \cdots, n_j, \text{ and } j = 1, \cdots, J.$$

- 랜덤효과로 인한 결과 ($x_{1ij} = 1$ case).

$$E[Y_{ij}] = \exp(\gamma_{00} + \gamma_{10} + \tau^2/2),$$

$$Var[Y_{ij}] = \exp(\gamma_{00} + \gamma_{10} + \tau^2/2)\,(1 - \exp(\gamma_{00} + \gamma_{10} + \tau^2/2)),$$

$$Cov[Y_{ij}, Y_{kj}] = (\exp(\tau^2) - 1)\exp(2(\gamma_{00} + \gamma_{10}) + \tau^2).$$

II. 모형

- 환자 공변량, 지역 공변량이 있는 모형:

$$Y_{ij} | u_{1j} \sim \text{independently } Pois(\mu_{ij}),$$

$$\eta_{ij} = g(\mu_{ij}) = \gamma_{00} + \gamma_{01} w_j + \gamma_{10} x_{1ij} + u_{1j} x_{1ij} + \gamma_{20} x_{2ij},\ u_{1j} \sim N(0, \tau^2),\ \text{ for } i = 1, \cdots, n_j, \text{and } j = 1, \cdots, J.$$

$$x_{1ij} = \begin{cases} 1, & \text{if } \ i = 1, \cdots, n_{Tj}, \\ 0, & \text{if } \ i = n_{Tj} + 1, \cdots, n_j, \end{cases} \qquad \text{for all } \ j = 1, \cdots, J.$$

- 가능도 함수:

$$L = \prod_{j=1}^{J} \int_{-\infty}^{\infty} \prod_{i=1}^{n_j} \frac{\mu_{ij}^{y_{ij}} e^{-\mu_{ij}}}{y_{ij}!} \frac{1}{\sqrt{2\pi\tau^2}} \exp\left(-\frac{u_{1j}^2}{2\tau^2}\right) du_{1j}\,.$$

- 최대 가능도 추정량 $\hat{\boldsymbol{\theta}}$:

$$\boldsymbol{\theta} = [\gamma_{00}, \gamma_{01}, \gamma_{10}, \gamma_{20}, \tau^2]', \qquad \frac{\partial}{\partial \boldsymbol{\theta}} \log L(\hat{\boldsymbol{\theta}}) = \mathbf{0}.$$

II. 모형

1. 지수족:

$$f(y_{ij}|\mathbf{u_j}) = \exp\left[\frac{y_{ij}\eta_{ij} - b(\phi)}{a(\phi)} + c(y_{ij}, \phi)\right],$$

$$\mathbf{u_j} \sim N(\mathbf{0}, \mathbf{T}), \quad \text{for } i = 1, \cdots, n_j, \text{ and } j = 1, \cdots, J.$$

2. 연결 함수:

$$\boldsymbol{\eta_j} = g(\boldsymbol{\mu_j}) = \mathbf{X_j}\boldsymbol{\beta_j},$$

$$\boldsymbol{\beta_j} = \mathbf{W_j}\boldsymbol{\gamma} + \mathbf{u_j}, \quad \text{for } j = 1, \cdots, J.$$

III. 결과

- 통계적 가설검정

$$H_0: \gamma_{10} = 0 \ \text{ versus } \ H_A: \gamma_{10} \neq 0,$$

- 시뮬레이션
  1. 적절한 지역 및 지역 내 표본 수를 선정: (J, n_j).
  2. 각 조합 (J, n_j) 내에서 모수들을 선정: $(\gamma_{00}, \gamma_{10}, \gamma_{20}, \gamma_{01}, \tau)$.
  3. $\psi \in \{1, \cdots, 2000\}$에서, 다음을 반복:
     a. 선정한 모형에서 랜덤 표본을 생성.
     b. 치료 효과 γ_{10}의 최대 가능도 추정량을 고정 효과 모형, 랜덤 효과 모형, 계층적 일반화 선형 모형 하에서 추정.
     c. 가설검정 수행 e.g. SAS의 PROC GLIMMIX로 모수 추정 시 모형내의 fixed effect 모수들은 Wald-type 가설검정이 가능함.
  4. 3.에서 얻은 결과로 기각 비율을 기록.

Table 1. 이분형 주평가변수에서의 경험적 1종 오류 (α = 5%).

$(\gamma_{00}, \gamma_{10}, \gamma_{20}, \gamma_{01}) = (0,0,-1,-1)$

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
3	200	0.20	0.10	0.05	13.80
		0.10	0.00	0.00	7.50
		0.02	0.00	0.00	5.25
		0.00	0.00	0.00	4.60
	500	0.20	0.50	0.05	23.85
		0.10	0.00	0.00	10.90
		0.02	0.00	0.00	5.30
		0.00	0.00	0.00	4.75

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
6	200	0.20	3.25	0.75	13.95
		0.10	1.65	0.35	7.25
		0.02	0.95	0.15	5.20
		0.00	0.50	0.10	4.95
	500	0.20	4.25	0.65	22.65
		0.10	1.85	0.00	10.35
		0.02	0.45	0.00	10.35
		0.00	0.50	0.00	4.35

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
10	200	0.20	4.45	0.80	14.40
		0.10	3.25	0.40	7.40
		0.02	2.35	0.40	5.55
		0.00	1.45	0.10	4.20
	500	0.20	5.00	0.50	25.55
		0.10	3.75	0.00	11.10
		0.02	1.80	0.00	4.95
		0.00	1.70	0.00	4.75

Table 2. 이분형 주평가변수에서의 경험적 1종 오류 ($\alpha = 5\%$).

$(\gamma_{00}, \gamma_{10}, \gamma_{20}, \gamma_{01}) = (0,0,-1,-0.5)$

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
3	200	0.20	0.20	0.15	15.00
		0.10	0.00	0.00	8.75
		0.02	0.00	0.00	6.35
		0.00	0.00	0.00	4.65
	500	0.20	0.65	0.35	24.70
		0.10	0.00	0.00	10.65
		0.02	0.00	0.00	4.95
		0.00	0.00	0.00	4.50

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
6	200	0.20	3.80	2.40	15.80
		0.10	1.95	1.20	7.80
		0.02	1.00	0.65	5.25
		0.00	0.50	0.35	5.40
	500	0.20	4.95	2.35	25.00
		0.10	2.75	0.65	11.10
		0.02	0.90	0.20	4.90
		0.00	0.35	0.05	4.20

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
10	200	0.20	4.85	2.70	16.50
		0.10	3.05	1.80	7.50
		0.02	2.20	1.35	5.15
		0.00	1.95	1.10	4.50
	500	0.20	5.05	2.50	27.95
		0.10	3.80	0.75	11.75
		0.02	2.20	0.50	4.70
		0.00	4.70	0.55	4.75

Table 3. 이분형 주평가변수에서의 경험적 1종 오류 ($\alpha = 5\%$).

$(\gamma_{00}, \gamma_{10}, \gamma_{20}, \gamma_{01}) = (0,0,-1,0)$

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
3	200	0.20	0.15	0.10	15.80
		0.10	0.05	0.00	8.80
		0.02	0.00	0.00	6.10
		0.00	0.00	0.00	4.90
	500	0.20	0.75	0.55	26.80
		0.10	0.00	0.10	11.95
		0.02	0.00	0.00	5.75
		0.00	0.00	0.00	4.25

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
6	200	0.20	3.45	3.15	16.40
		0.10	1.90	1.80	8.80
		0.02	1.15	1.10	5.45
		0.00	0.90	0.90	4.70
	500	0.20	4.25	3.70	26.55
		0.10	2.90	2.40	12.05
		0.02	0.80	0.75	5.25
		0.00	0.50	0.50	4.15

J	n_j	τ	Type I error (%)		
			HGLM	Random	Fixed
10	200	0.20	4.70	4.05	16.20
		0.10	3.25	3.15	7.40
		0.02	2.10	2.00	5.35
		0.00	1.90	1.95	4.60
	500	0.20	5.00	4.75	28.65
		0.10	4.05	3.75	12.45
		0.02	2.30	2.25	5.50
		0.00	2.15	2.15	4.85

Table 4. 이분형 주평가변수에서의 경험적 검정력 ($\alpha = 5\%$).

$(\gamma_{00}, \gamma_{20}, \gamma_{01}) = (0, -1, -1)$

J	n_j	τ	Power (%)					
			$\gamma_{10} = 0.2$		$\gamma_{10} = 0.4$		$\gamma_{10} = 0.6$	
			HGLM	Random	HGLM	Random	HGLM	Random
3	200	0.20	2.20	0.85	13.90	6.40	49.15	25.45
		0.10	0.90	0.45	13.60	4.95	60.40	28.25
		0.02	0.25	0.10	11.90	4.55	63.65	27.75
		0.00	0.45	0.20	11.35	4.95	65.00	30.05
	500	0.20	7.55	2.20	40.45	15.05	75.40	38.65
		0.10	4.70	0.90	61.05	16.50	96.15	45.20
		0.02	2.80	0.35	72.35	17.25	99.45	47.15
		0.00	3.25	0.60	71.75	17.20	99.60	47.80
6	200	0.20	26.40	9.75	79.45	49.65	99.15	88.25
		0.10	31.80	9.35	93.00	57.30	100.00	95.25
		0.02	33.70	8.60	96.55	62.50	100.00	97.85
		0.00	33.75	8.90	95.90	62.80	99.95	97.25
	500	0.20	40.40	11.00	93.55	61.00	100.00	94.90
		0.10	65.00	10.35	99.95	74.50	100.00	99.20
		0.02	78.65	10.25	100.00	81.05	100.00	99.90
		0.00	79.65	9.95	100.00	80.20	100.00	99.95
10	200	0.20	49.45	19.95	97.65	82.00	100.00	99.65
		0.10	64.95	21.95	99.90	91.80	100.00	100.00
		0.02	69.40	22.60	100.00	94.60	100.00	100.00
		0.00	69.60	22.15	100.00	95.40	100.00	100.00
	500	0.20	67.15	23.85	99.85	91.25	100.00	100.00
		0.10	92.60	28.75	100.00	98.90	100.00	100.00
		0.02	98.10	30.00	100.00	99.75	100.00	100.00
		0.00	97.95	28.90	100.00	99.80	100.00	100.00

Table 5. 이분형 주평가변수에서의 경험적 검정력 ($\alpha = 5\%$).

$(\gamma_{00}, \gamma_{20}, \gamma_{01}) = (0, -1, -0.5)$

J	n_j	τ	Power (%)					
			$\gamma_{10} = 0.2$		$\gamma_{10} = 0.4$		$\gamma_{10} = 0.6$	
			HGLM	Random	HGLM	Random	HGLM	Random
3	200	0.20	2.25	1.85	16.35	11.95	52.70	39.85
		0.10	0.90	0.65	15.50	11.45	64.95	51.15
		0.02	0.35	0.25	14.25	10.80	70.85	57.95
		0.00	0.50	0.35	14.25	10.50	71.10	57.60
	500	0.20	8.10	4.30	42.85	29.25	75.85	61.40
		0.10	6.45	3.15	64.60	40.80	96.25	80.90
		0.02	4.45	2.05	78.95	48.90	99.80	90.20
		0.00	3.90	1.90	79.70	48.35	99.85	90.35
6	200	0.20	28.65	20.35	81.30	72.30	99.10	97.60
		0.10	35.75	25.25	94.75	87.10	100.00	99.90
		0.02	37.90	26.85	97.50	92.70	100.00	100.00
		0.00	38.15	26.55	98.05	93.70	100.00	100.00
	500	0.20	42.60	29.25	94.25	85.75	99.95	99.65
		0.10	68.95	44.65	99.95	98.65	100.00	100.00
		0.02	83.35	53.45	100.00	99.90	100.00	100.00
		0.00	84.90	53.00	100.00	100.00	100.00	100.00
10	200	0.20	52.05	41.40	98.05	96.10	100.00	99.95
		0.10	67.60	54.05	99.90	99.45	100.00	100.00
		0.02	72.60	59.70	100.00	99.85	100.00	100.00
		0.00	73.75	61.00	100.00	99.95	100.00	100.00
	500	0.20	68.45	54.95	99.90	99.45	100.00	100.00
		0.10	93.55	79.85	100.00	100.00	100.00	100.00
		0.02	99.20	90.65	100.00	100.00	100.00	100.00
		0.00	99.00	90.00	100.00	100.00	100.00	100.00

Table 6. 이분형 주평가변수에서의 경험적 검정력 ($\alpha = 5\%$).

$$(\gamma_{00}, \gamma_{20}, \gamma_{01}) = (0, -1, 0)$$

J	n_j	τ	Power (%)					
			$\gamma_{10} = 0.2$		$\gamma_{10} = 0.4$		$\gamma_{10} = 0.6$	
			HGLM	Random	HGLM	Random	HGLM	Random
3	200	0.20	2.40	2.05	17.10	14.40	55.30	50.15
		0.10	1.35	1.30	16.85	15.35	68.20	65.00
		0.02	0.45	0.45	15.25	15.15	74.65	73.00
		0.00	0.45	0.45	16.45	15.60	75.05	74.25
	500	0.20	9.05	6.75	42.80	37.90	76.50	72.35
		0.10	6.90	6.05	67.35	63.25	96.60	96.25
		0.02	4.55	4.45	81.40	80.55	99.80	99.85
		0.00	4.45	4.25	83.90	81.95	99.90	99.95
6	200	0.20	30.25	28.10	82.15	81.10	99.25	99.25
		0.10	37.20	36.15	95.45	95.25	99.95	99.95
		0.02	39.90	39.35	98.15	98.10	100.00	100.00
		0.00	39.60	39.25	98.45	98.25	100.00	100.00
	500	0.20	42.35	40.50	94.55	94.50	100.00	100.00
		0.10	71.85	69.90	100.00	100.00	100.00	100.00
		0.02	85.85	85.30	100.00	100.00	100.00	100.00
		0.00	87.85	87.85	100.00	100.00	100.00	100.00
10	200	0.20	51.95	51.50	98.40	98.20	100.00	100.00
		0.10	69.10	68.55	99.95	99.95	100.00	100.00
		0.02	75.60	75.45	100.00	100.00	100.00	100.00
		0.00	77.90	77.55	100.00	100.00	100.00	100.00
	500	0.20	69.55	68.65	99.95	99.95	100.00	100.00
		0.10	94.95	94.50	100.00	100.00	100.00	100.00
		0.02	99.35	99.30	100.00	100.00	100.00	100.00
		0.00	99.55	99.55	100.00	100.00	100.00	100.00

IV. 결론

- 다지역임상시험을 위한 계층적 일반화 선형 모형
  - 다지역임상시험의 모델링, 분석을 위한 2-수준의 계층적 일반화 선형 모형을 제안.
  - 지수족 분포들, 이분형 자료나 가산 자료 등을 다룰 수 있는 장점.
  - MRCT 자료의 계층적 구조를 잘 반영.
  - 기존 random effects model에 비하여 검정력 이점.

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- 감사합니다