The application of Generalized Linear Mixed Models in the combined analysis of clinical trials

Zichen Xu
zichenxu407@gmail.com

Advisor: Dr. Mengxi Yi
School of Statistics, Beijing Normal University
Co-advisor: Dr. Yang Wang
Medical Research & Biometrics Center, National Center for Cardiovascular Diseases

School of Statistics
Beijing Normal University

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Overall Directory

Section Directory

Review

The average investment cost before a drug reaches the market is 1,335.9 million dollars[1], with clinical trials being the most time-consuming and expensive phase.[2]

According to ICH E8[3], the new drug development period is generally divided into four phases, where similarities often exist between phases and trials.

Question: If a similar design already exists, can we borrow information from it?

Related topics: Combining analysis between:

1. Randomized Control Trials(RCTs)
2. Current RCT and observational data

Review

Main Goals

- Gather more information to support our effect evaluations.
- Avoid compromising statistical properties.

Main Questions

- Can we utilize information from historical trials? (Criteria)
- How should we utilize it? (Methods)
- How much information should/can we utilize? (Quantitative evaluations)

Innovations

Methodology

- Reformulate the relevant methods within the theoretical framework of the Generalized Linear Mixed Model (GLMM).
- Comprehensive comparison between frequentist and Bayesian combination methodologies.

Application

- Evidence for the combination in "drop-the-loser" dose-finding trials.
- A comprehensive to-do list and recommendations for historical combinations.

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Framework: Generalized Linear Mixed Model

Typically, GLMMs can be written as the formula shown below.

$$E\,(y|\eta) = \mu$$

$$g\,(\mu) = X\beta + Z\gamma$$

Likelihood function:

$$L\,(\beta, D) = \prod_i \int f(y_{ik}|\gamma_k) f(\gamma_k) d\gamma_k$$

Specifically, in the context of Bernoulli distribution, we have the probability density function as shown below.

$$P\,(y_{ki} = 1|\beta, \gamma_k) = \frac{exp(\gamma_k + X_{ki}\beta)}{1 + exp(\gamma_k + X_{ki}\beta)}$$

Question: How to deal with the complex likelihood function and estimate the parameter we are interested in?

Frequentist methods

1. (Two-stage) Meta analysis
2. MLE with Laplace approximation(LA)
3. MLE with Panelized Quasi Likelihood(PQL)

Bayesian Hierarchical Modeling(BHM)

1. Standard BHM
2. BHM with Power Prior(PP)
3. BHM with Normalized Power Prior(NPP)
4. BHM with Commensurate Priors(CPs)

(Two-stage) Meta analysis

The first stage: Estimate β_k and $var(\beta_k)$

$$y_{ik} \sim \textbf{Bernoulli}\,(p_{ik})$$

$$logit\,(p_{ik}) = ln\left(\frac{p_{ik}}{1-p_{ik}}\right) = \gamma_k + \beta_k x_{ki}$$

The second stage: Estimate β and τ_β

1. For the fixed effectβ: Inverse variance weighted average

$$\hat{\beta} = \frac{\sum_{k=1}^{N} \widehat{\beta_k} w_k}{\sum_{k=1}^{N} w_k}, \text{where } w_k = \frac{1}{var\left(\widehat{\beta_k}\right)}$$

2. For the random effect: REsidual Maximum Likelihood method(REML)

$$\widehat{\beta_k} \sim \mathcal{N}\left(\beta, \tau_\beta^2 + var\left(\widehat{\beta_k}\right)\right)$$

MLE with Laplace Approximation

For the likelihood:

$$\int f(y_k|\beta,\gamma_k)f(\gamma_k)\,d\gamma_k = \int e^{\log(a(\gamma_k|y_k,\beta,\Sigma))}\,d\gamma_k := \int e^{l(t)}\,dt$$

Using the second-order truncated Taylor Expansion at $\hat{t}$:

$$\int e^{l(t)}\,dt \approx \int e^{l(\hat{t})+\frac{1}{2}\left(t-\hat{t}\right)^T l''\left(\hat{t}\right)\left(t-\hat{t}\right)}\,dt = (2\pi)^{\frac{K}{2}}\left|-\hat{l}''\left(\hat{t}\right)\right|^{-\frac{1}{2}} e^{l\left(\hat{t}\right)}$$

$$L_k(\beta,\Sigma|y_k) \approx (2\pi)^{\frac{K}{2}}\left|\widehat{\Omega_k}\right|^{\frac{1}{2}} f(y_k|\beta,\widehat{\gamma_k})f(\widehat{\gamma_k}|0,\Sigma)$$

MLE with PQL

Based on the first-order Taylor expension of y_k:

$$
\begin{aligned}
y_{ki} \approx\ & b(X_{ki}\hat{\beta} + Z_{ki}\widehat{\gamma_k}) + b'(X_{ki}\hat{\beta} + Z_{ki}\widehat{\gamma_k})X_{ki}(\beta - \hat{\beta}) \\
& + b'(X_{ki}\hat{\beta} + Z_{ki}\widehat{\gamma_k})Z_{ki}(\gamma_k - \widehat{\gamma_k}) + \epsilon_{ki}
\end{aligned}
$$

, where $b(\cdot)$ denotes the inverse of the link function $g(\cdot)$.
The goal function:

$$
\sum_{k=1}^{K}\left(\log(f(y_k|\beta,\gamma_k)) - \frac{1}{2}\gamma_k^T\Sigma^{-1}\gamma_k\right)
$$

Standard Bayesian Hierarchical Models(BHM)

Based on Carvalho et al.(2021)[6] and Peter F. Thall et al.(2003)[7], we present the standard BHM model as shown below.

$$Y_{gi} \sim \textbf{Bernoulli}(\theta_i)$$

$$logit(\theta_i) = \gamma_g + \beta_g x_{gi}$$

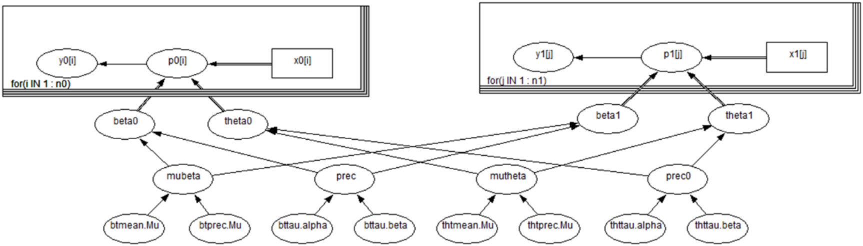
$$\gamma_g \sim \mathcal{N}(\mu_\gamma, \sigma_\gamma^2), \beta_g \sim \mathcal{N}(\mu_\beta, \sigma_\beta^2)$$

$$\sigma_\gamma^2 \sim \textbf{IGamma}(a_\gamma, b_\gamma), \sigma_\beta^2 \sim \textbf{IGamma}(a_\beta, b_\beta)$$

$$q(\beta|D_0, D) \propto \pi_0(\beta) L(D_0|\beta) L(D|\beta)$$

Standard Bayesian Hierarchical Models(BHM)

The graphical representation is shown below.



BHM with Power Prior(Ibrahim and Chen, 2000)

Based on Ibrahim et al.(2000)[8] and Carvalho et al.(2021), we can incorporate a power prior into our model, as shown below.

$$Y_{gi} \sim \text{Bernoulli}\left(\theta_i\right)$$

$$\text{logit}\left(\theta_i\right) = \gamma + \beta x_{gi}$$

$$\pi\left(\beta | D_0, a_0\right) \propto L\left(D_0 | \beta\right)^{a_0} \pi\left(\beta\right)$$

$$q(\beta, \alpha_0 | D_0, D) \propto L(D|\beta)\pi\left(\beta | D_0, a_0\right)\pi_A(\alpha_0)$$

BHM with Normalized Power Prior(Duan et al., 2006)

Based on Duan et al.(2006) [9], we can incorporate a normalized power prior into our model as shown below.

$$c\left(a_0\right) := \int L\left(D_0|\beta\right)^{a_0} \pi\left(\beta\right) d\beta$$

$$p\left(\beta, a_0|D_0, D\right) \propto \frac{1}{c\left(a_0\right)} L\left(D|\beta\right) L\left(D_0|\beta\right)^{a_0} \pi\left(\beta\right) \pi_A\left(a_0\right)$$

$$\begin{aligned} p\left(a_0|D_0, D\right) &= \int p\left(\beta, a_0|D_0, D\right) d\beta \\ &\propto \frac{\pi_A\left(a_0\right)}{c\left(a_0\right)} \int L\left(D|\beta\right) L\left(D_0|\beta\right)^{a_0} \pi\left(\beta\right) d\beta \end{aligned}$$

BHM with Commensurate Priors

Hobbs et al.(2011&2012)[10][11] introduced an advanced approach by measuring commensuration across trials. The commensurate power prior:

$$\gamma_1 \sim \mathcal{N}\left(\gamma_0, \tau^2\right), \beta_1 \sim \mathcal{N}\left(\beta_0, \tau^2\right)$$

$$\gamma_0 \sim \mathcal{N}(0, 1000), \beta_0 \sim \mathcal{N}(0, 1000)$$

$$q\left(\beta, \beta_0, a_0 | D_0, D, \tau^2\right) \propto \mathcal{N}\left(\beta | \beta_0, \tau^2\right) L\left(\beta_0 | D_0\right)^{\alpha_0} L(\beta | D) \pi_A\left(a_0 | \tau^2\right) \pi(\beta) \pi\left(\beta_0\right)$$

According to Scott Berry et al.(2010)[12], we adopt $Beta\left(\frac{a\sigma^2}{\tau^2}, 1\right)$ as the prior distribution for α_0.

Section Directory

Basic settings

- We simulated three scenarios with varying heterogeneity: complete homogeneity, moderate homogeneity, and significant heterogeneity.
- The current treatment response (true value) was varied to assess the statistical power and Type-I error characteristics of each method.

Simulation scenario dictionary

		Historical Control	Historical Treatment	Concurrent Control	Concurrent Treatment
Scenario 1	Response rate	0.6	0.72	0.6	Grids
	Sample size	21		228	
Scenario 2	Response rate	0.7	0.82	0.6	Grids
	Sample size	21		228	
Scenario 3	Response rate	0.8	0.92	0.6	Grids
	Sample size	21		228	

Type-I error and Power analysis

Scenario 1: Complete homogeneity

Simulation study results for scenario 1

Methods	Effect size					
	Type-I error	Power				
	0	0.05	0.1	0.12	0.15	0.2
Chi-sq test	0.05(set)	0.124	0.350	0.474	0.656	0.884
Two-stage Meta	0.112	0.326	0.576	0.659	0.714	0.732
PQL	0.051	0.144	0.390	0.515	0.690	0.870
Std BHM(High borrowing)	0.04	0.165	0.395	0.495	0.710	0.935
Std BHM(Moderate borrowing)	0.04	0.125	0.365	0.470	0.655	0.920
Std BHM(Low borrowing)	0.05	0.080	0.390	0.540	0.680	0.935
BHM with Power Prior	0.03	0.145	0.300	0.500	0.720	0.905
BHM with NPP approximate a_0	0.075	0.135	0.420	0.520	0.735	0.905
BHM with CP	0.04	0.165	0.405	0.495	0.650	0.940
BHM with CPP(w/out cov)	0.055	0.115	0.330	0.555	0.645	0.930

Type-I error and Power analysis
Scenario 2: Partial homogeneity

Simulation study results for scenario 2

Methods	Effect size					
	Type-I error	Power				
	0	0.05	0.1	0.12	0.15	0.2
Chi-sq test	0.05(set)	0.124	0.350	0.474	0.656	0.884
Two-stage Meta	0.039	0.129	0.340	0.475	0.605	0.815
PQL	0.048	0.155	0.416	0.523	0.718	0.902
Std BHM(High borrowing)	0.04	0.170	0.365	0.500	0.680	0.910
Std BHM(Moderate borrowing)	0.035	0.120	0.320	0.515	0.660	0.935
Std BHM(Low borrowing)	0.05	0.080	0.335	0.490	0.735	0.920
BHM with Power Prior	0.1	0.095	0.410	0.480	0.660	0.885
BHM with NPP approximate a_0	0.02	0.140	0.405	0.490	0.715	0.925
BHM with CP	0.045	0.175	0.395	0.485	0.685	0.920
BHM with CPP(w/out cov)	0.03	0.115	0.345	0.495	0.680	0.945

Type-I error and Power analysis

Scenario 3: Large heterogeneity

Simulation study results for scenario 3

Methods	Effect size					
	Type-I error	Power				
	0	0.05	0.1	0.12	0.15	0.2
Chi-sq test	0.05(set)	0.124	0.350	0.474	0.656	0.884
Two-stage Meta	0.063	0.207	0.491	0.640	0.782	0.904
PQL	0.053	0.144	0.419	0.532	0.719	0.929
Std BHM(High borrowing)	0.04	0.170	0.375	0.520	0.680	0.910
Std BHM(Moderate borrowing)	0.035	0.125	0.325	0.485	0.660	0.935
Std BHM(Low borrowing)	0.055	0.105	0.515	0.485	0.680	0.935
BHM with Power Prior	0.05	0.155	0.390	0.515	0.755	0.910
BHM with NPP approximate a_0	0.03	0.170	0.390	0.515	0.700	0.920
BHM with CP	0.04	0.180	0.430	0.550	0.690	0.940
BHM with CPP(w/out cov)	0.04	0.135	0.370	0.570	0.675	0.865

Highlights

- Frequentist methods, particularly two-stage meta-analysis, are more prone to Type I error inflation.
- In cases of small effect sizes, historical trials become more influential, leading to inflated statistical power.
- Commensurate priors demonstrate the best overall performance in terms of Type I error rates and statistical power.(i.e., BHM with CP)

Section Directory

Profile of trials and their data

- Investigational product: rhM-tPA
- Comparator: rt-PA
- Purposes:
  1. Observe the efficacy and safety for patients with acute ST-segment elevation myocardial infarction.
  2. Select doses subsequently.
- Primary efficacy endpoint (**binary**):
  The proportion of TIMI 2+3 grade blood flow in the infarct-related artery at 90 minutes post-thrombolysis as determined by coronary angiography.

Profile of trials and their data

Historical trial: A Phase IIa trial for rhM-tPA

1. 5 doses
2. Sample size (design): 50 participants(10 for each dose)

Current trial: A Phase IIb trial for rhM-tPA

1. 3 doses (included in IIa)
2. Sample size (design): 360 participants(120 for each dose)

Commensuration

Same medicine, inclusive doses, same researchers, same baseline features, same control and treatments...

Baseline: analysis separately

Global comparison between methods

Doses	Methods	(b)Treatment Effect	(b)Std. Err	(b)2.5% Quantile	(b)97.5% Quantile	(b)P-value	(a)Treatment Effect	(a)Std. Err	(a)2.5% Quantile	(a)97.5% Quantile	(a)P-value
0.3mg/kg	Chi-sq test					0.442					0.8901
	Baseline: GLM Two-stage Meta Laplace Approximation Panelized Quasi-Likelihood	0.2107	0.2741	-0.3260	0.7505	0.442	0.1335	0.9667	-1.8157	2.0885	0.89
	Std BHM(High shrinkage) Std BHM(Moderate shrinkage) Std BHM(Low shrinkage) BHM with Power Prior BHM with NPP BHM with NPP BHM with NPP BHM with NPP approximate a_0 BHM with CP BHM with CPP(w/out cov)	0.2126	0.2743	-0.3242	0.7514		0.1753	0.9689	-1.7220	2.0940	
0.4mg/kg	Chi-sq test					0.051*					0.5254
	Baseline: GLM Two-stage Meta Laplace Approximation Panelized Quasi-Likelihood	0.5501	0.2826	-0.0005	1.1099	0.052*	0.6568	1.0427	-1.3807	2.8866	0.529
	Std BHM(High shrinkage) Std BHM(Moderate shrinkage) Std BHM(Low shrinkage) BHM with Power Prior BHM with NPP BHM with NPP BHM with NPP BHM with NPP approximate a_0 BHM with CP BHM with CPP(w/out cov)	0.5534	0.2830	0.0013	1.1110		0.7235	1.0540	-1.2870	2.8700	

Combining analysis: the global comparison

Global comparison between methods

Doses	Methods	(a+b)Treatment Effect	(a+b)Std. Err	(a+b)2.5% Quantile	(a+b)97.5% Quantile	α_0	(a+b)P-value
0.3mg/kg	Chi-sq test						0.43
	Two-stage Meta	0.204969	0.26373	-0.3119	0.7219		0.437
	Laplace Approximation	0.204972	0.26371	-0.4019	0.8143		0.437
	Panelized Quasi-Likelihood	0.204972	0.26372	-0.3145	0.7244		0.4405
	Std BHM(High borrowing)	0.208173	0.26510	-0.3117	0.7283	1.00	
	Std BHM(Moderate borrowing)	0.206323	0.26712	-0.3162	0.7306	1.00	
	Std BHM(Low borrowing)	0.205748	0.27193	-0.3276	0.7394	1.00	
	BHM with Power Prior	0.212986	0.27358	-0.3226	0.7504	0.08	
	BHM with NPP	0.210406	0.26366	-0.3070	0.7267	0.99(set)	
	BHM with NPP	0.211456	0.27044	-0.3162	0.7458	0.50(set)	
	BHM with NPP	0.213595	0.27647	-0.3290	0.7575	0.01(set)	
	BHM with NPP approximate a_0	0.210373	0.26713	-0.3098	0.7342	0.66	
	BHM with CP	0.210357	0.26545	-0.3087	0.7277	1.00	
	BHM with CPP(w/out cov)	0.212700	0.27569	-0.3260	0.7542	0.10	
0.4mg/kg	Chi-sq test						0.039⋆
	Two-stage Meta	0.557418	0.27280	0.0227	1.0921		0.041⋆
	Laplace Approximation	0.557460	0.27278	-0.0660	1.2414		0.041⋆
	Panelized Quasi-Likelihood	0.557460	0.27275	0.0202	1.0947		0.043⋆
	Std BHM(High borrowing)	0.563446	0.27649	0.0214	1.1135	1.00	
	Std BHM(Moderate borrowing)	0.558577	0.27680	0.0204	1.1034	1.00	
	Std BHM(Low borrowing)	0.554849	0.27971	0.0108	1.1063	1.00	
	BHM with Power Prior	0.555955	0.28235	0.0059	1.1120	0.08	
	BHM with NPP	0.564997	0.27386	0.0343	1.1074	0.99(set)	
	BHM with NPP	0.561970	0.27861	0.0201	1.1106	0.50(set)	
	BHM with NPP	0.557110	0.28397	0.0002	1.1169	0.01(set)	
	BHM with NPP approximate a_0	0.562603	0.27739	0.0227	1.1081	0.65	
	BHM with CP	0.564063	0.27584	0.0283	1.1098	1.00	
	BHM with CPP(w/out cov)	0.557105	0.28238	0.0068	1.1146	0.11	

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Discussions

- With only two clinical trials, particularly with small sample sizes in each, frequentist methods are at greater risk of inflating Type I errors and are less stable in estimating between-group heterogeneity.
- Commensuration evaluations based on covariates and baseline (intercept) significantly improve methodological stability against model misspecification.
- Frequentist methods consistently demonstrate better precision than Bayesian methods.
- Sensitivity testing is highly recommended due to the inherent arbitrariness in selecting Bayesian hyperparameters and conducting Bayesian hierarchical modeling.

Section Directory

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The End

Thanks!