

1 Model settings

The unrestricted linear mixed effect model for the i th subject in the k treatment group is:

$$\begin{aligned} \mathbf{y}_{ki} &= \mathbf{X}_i(\boldsymbol{\beta}_k + \sum_{j=1}^p \gamma_{kj} \mathbf{x}_{ij}) + \mathbf{X}_i \mathbf{b}_{ki} + \boldsymbol{\epsilon}_{ki} \\ &= \mathbf{X}_i \boldsymbol{\beta}_k + (\mathbf{X}_i \otimes \mathbf{x}_i') \boldsymbol{\gamma}_k + \mathbf{X}_i \mathbf{b}_{ki} + \boldsymbol{\epsilon}_{ki} \end{aligned} \quad (1)$$

where

- \mathbf{X}_i is the $n_t \times t$ dimension design matrix for subject i ;
- $\mathbf{x}_i = (x_{i1} \dots x_{ip})'$ is the $p \times 1$ vector of predictors for subject i ; x_{ij} presents the j th predictor for the i th subject;
- $\boldsymbol{\beta}_k$ is the fixed effect coefficient with dimension $t \times 1$;
- γ_{kj} is the $t \times 1$ fixed effect coefficient, which is correlated to the j th predictors;
- $\boldsymbol{\gamma}_k = (\gamma'_{k1} \dots \gamma'_{kp})'$ is the $pt \times 1$ vector.
- $\mathbf{b}_{ki} \sim N(0, \mathbf{D}_k)$, \mathbf{D}_k is a $t \times t$ matrix, with $\frac{t(t+1)}{2}$ parameters.
- $\boldsymbol{\epsilon}_{ki} \sim N(0, \sigma_k^2)$

which means that different predictors in different treatment groups have different coefficients for different degree of design matrix \mathbf{X} , e.g. when $t = 3$, \mathbf{X} is constructed with intercept, slope and concavity. the predictors have coefficient corresponding to the predictor \times intercept, predictor \times slope, and predictor \times concavity.

Therefore, the total number of parameters in equation 1 is

$$k \times (t + pt + \frac{t(t+1)}{2} + 1)$$

The GEM model under restriction can be modeled as:

$$\begin{aligned} \mathbf{y}_{ki} &= \mathbf{X}_i(\boldsymbol{\beta}_k + \mathbf{b}_{ki} + \boldsymbol{\Gamma}_k(\boldsymbol{\alpha}' \mathbf{x}_i)) + \boldsymbol{\epsilon}_{ki} \\ &= \mathbf{X}_i \boldsymbol{\beta}_k + (\mathbf{X}_i \otimes \mathbf{x}_i')(\boldsymbol{\Gamma}_k \otimes \boldsymbol{\alpha}) + \boldsymbol{\epsilon}_{ki} \end{aligned} \quad (2)$$

That is, in equation 2, we replace the $pt \times 1$ vector $\boldsymbol{\gamma}_k = (\gamma'_{k1} \dots \gamma'_{kp})'$ with another $pt \times 1$ vector $\boldsymbol{\Gamma}_k \otimes \boldsymbol{\alpha}$, which is with $p + t$ parameters.

Therefore, the total number of parameters in equation 2 is

$$k \times (t + p + t + \frac{t(t+1)}{2} + 1)$$

2 Likelihood ratio test

The assumption of the likelihood ratio test is set as

- H_0 : predictors share the same $\boldsymbol{\alpha}$, i.e. equation 2 is true
 H_1 : predictors do not share the same $\boldsymbol{\alpha}$

The degree of freedom of this test is

$$k \times (t + pt + \frac{t(t+1)}{2} + 1) - k \times (t + p + t + \frac{t(t+1)}{2} + 1) = k \times (pt - p - t)$$

The log-likelihood value can be calculated through the *lme4* package in R.
 Test statistics: $-2(\text{loglike}_2 - \text{loglike}_1)$

Simulation

Suppose we generate a data set as following:

```
##      subj      X1      X2 tt      w_drg      w_pbo      fd1      fd2
## 1      1 0.5768541 -0.2587745 0 0.2249162 0.2249162 2.891554 -0.3190356
## 2      1 0.5768541 -0.2587745 1 0.2249162 0.2249162 2.891554 -0.3190356
## 3      1 0.5768541 -0.2587745 2 0.2249162 0.2249162 2.891554 -0.3190356
## 4      1 0.5768541 -0.2587745 3 0.2249162 0.2249162 2.891554 -0.3190356
## 5      1 0.5768541 -0.2587745 4 0.2249162 0.2249162 2.891554 -0.3190356
## 6      1 0.5768541 -0.2587745 6 0.2249162 0.2249162 2.891554 -0.3190356
##      fd3      fp1      fp2      fp3      yi_drg      yi_pbo      y      int1
## 1 0.2665183 1.714478 -0.6931485 0.1199219 2.586166 1.698288 1.698288 0.5768541
## 2 0.2665183 1.714478 -0.6931485 0.1199219 4.350818 2.085088 2.085088 0.5768541
## 3 0.2665183 1.714478 -0.6931485 0.1199219 3.709400 1.629090 1.629090 0.5768541
## 4 0.2665183 1.714478 -0.6931485 0.1199219 3.711872 1.308231 1.308231 0.5768541
## 5 0.2665183 1.714478 -0.6931485 0.1199219 3.665005 1.779612 1.779612 0.5768541
## 6 0.2665183 1.714478 -0.6931485 0.1199219 11.696931 2.654913 2.654913 0.5768541
##      slop1      cov1      int2      slop2      cov2
## 1 0.0000000 0.0000000 -0.2587745 0.0000000 0.0000000
## 2 0.5768541 0.5768541 -0.2587745 -0.2587745 -0.2587745
## 3 1.1537082 2.3074164 -0.2587745 -0.5175490 -1.0350981
## 4 1.7305623 5.1916868 -0.2587745 -0.7763236 -2.3289707
## 5 2.3074164 9.2296654 -0.2587745 -1.0350981 -4.1403924
## 6 3.4611245 20.7667472 -0.2587745 -1.5526471 -9.3158828
```

where

- X_1, X_2 shows the value of two predictors
- tt presents the time in the trial
- w_drg and w_pbo are the true $\alpha'_{drg}x, \alpha'_{pbo}x$ values.
- $(fd1, fd2, fd3)$ are the coefficients for the trajectory (intercept, slope, concavity) is the subject is in drug group.
- $(fp1, fp2, fp3)$ are the coefficients for the trajectory (intercept, slope, concavity) is the subject is in placebo group.
- yi_drg and yi_pbo are the outcomes for drug treatment and placebo treatment
- trt is the group assignment and y is the observed outcome.
- X is the design matrix $X = (1, t, t^2), t = 0, 1, 2, 3, 4, 6, 8$
- $int1$ is the value of $X_1 \times X[, 1]$, $slop1$ is the value of $X_1 \times X[, 2]$, $cov1$ is the value of $X_1 \times X[, 3]$.
- $int2$ is the value of $X_2 \times X[, 1]$, $slop2$ is the value of $X_2 \times X[, 2]$, $cov2$ is the value of $X_2 \times X[, 3]$.

To fit the unrestricted LME, we have the formula as

```
formula_full
```

```
## [1] "y~1+ tt + I(tt^2) + int1 + slop1 + cov1 + int2 + slop2 + cov2 + (1+ tt + I(tt^2) |subj)"
```

The LME

```
dat_pbo = data[data$trt == 1, ]; rownames(dat_pbo) = NULL
dat_drg = data[data$trt == 2, ]; rownames(dat_drg) = NULL
```

```
fit_pbo_est_full = lmer(formula_full, data = dat_pbo, REML = FALSE)
fit_drg_est_full = lmer(formula_full, data = dat_drg, REML = FALSE)
```

The loglikelihood in the models

```
summary(fit_pbo_est_full)$logLik
```

```
## 'log Lik.' -1539.87 (df=16)
```

```
summary(fit_drg_est_full)$logLik
```

```
## 'log Lik.' -1507.694 (df=16)
```

To fit the GEM LME, we have the function as

```
fit_pbo_est_si = lmer(y ~ tt + I(tt^2) + w_pbo + w_pbo * tt +
  w_pbo * I(tt^2) + (tt + I(tt^2) |subj),
  data = dat_pbo, REML = FALSE)
fit_drg_est_si = lmer(y ~ tt + I(tt^2) + w_drg + w_drg * tt +
  w_drg * I(tt^2) + (tt + I(tt^2) |subj),
  data = dat_drg, REML = FALSE)
```

The loglikelihood in the models

```
summary(fit_pbo_est_si)$logLik
```

```
## 'log Lik.' -1542.624 (df=13)
```

```
summary(fit_drg_est_si)$logLik
```

```
## 'log Lik.' -1507.912 (df=13)
```

Therefore the test statistics is

```
chis = as.numeric(summary(fit_pbo_est_full)$logLik + summary(fit_drg_est_full)$logLik -
  (summary(fit_pbo_est_si)$logLik + summary(fit_drg_est_si)$logLik))
chis = chis*2
chis
```

```
## [1] 5.943638
```

The p value is

```
1-pchisq(chis, df= (3*(p-1)-p)*2)
```

```
## [1] 0.05121008
```

For different dimension p , the likelihood ratio test can be conducted and we can get p values as

If we use $df = 2 \times (3p - p - 3)$,

p	2	3	4	5	6	7	8	9	10	11
p-value	0.051	0.071	0.033	0.002	0.006	0.025	0.684	0.048	0.001	0

p	12	13	14	15	16	17	18	19	20	21
p-value	0.008	0.055	0.008	0.033	0	0.025	0	0	0	0

p	22	23	24	25	26	27	28	29	30
p-value	0	0	0.006	0	0	0	0.002	0	0

Most of the p values are less than 0.05. Therefore, we tend to reject H_0 , that they do not share the same α . However, the true model is the GEM model. The results do not consistant with the true scenario.

If we use $df = 2 \times (3p - 3)$,

p	2	3	4	5	6	7	8	9	10	11
p-value	0.43	0.476	0.355	0.081	0.186	0.432	0.995	0.639	0.157	0.04

p	12	13	14	15	16	17	18	19	20	21
p-value	0.443	0.787	0.51	0.758	0.171	0.766	0.201	0.016	0.177	0.268

p	22	23	24	25	26	27	28	29	30
p-value	0.335	0.091	0.734	0.142	0.118	0.021	0.674	0.1	0.026

Most of the p values are larger than 0.05. Therefore, we tend to accept H_0 , that they share the same α .