Comparison of Shared Parameter Model and Latent Class Model for Joint Modeling of Longitudinal and Time-to-Event Data

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Introduction

- In practice, longitudinal data and survival data occur together mostly.
- joint models combine all information simultaneously and provide valid and efficient results.
- joint models include a sub-model for the
  - longitudinal measurements process, usually **a mixed effects model**
  - time-to-event process, usually **a proportional hazard model,** and a association structure
- **shared parameter model** and **joint latent class model** are used.

Notation

- consider a longitudinal study with n subjects
- $y_{ij} = y_i(s_{ij})$, $i = 1, 2, ..., n$, $j = 1, 2, ..., n_i$ denotes longitudinal measurements
- T_i^* is the true survival time of subject i
- C_i is the randomly censoring time for the ith subject
- $T_i = min(T_i^*, C_i)$ is the observed failure time for the ith subject
- δ_i is the event indicator,

$$\delta_i = \begin{cases} 1 & T_i^* \leq C_i \\ \cdot & T_i^* > C_i \end{cases}$$

Shared Parameter Model(SPM)

a linear mixed effects model for the longitudinal measurements

$$y_{ij} = \boldsymbol{x}'_{\boldsymbol{ij}}(\boldsymbol{s_{ij}})\boldsymbol{\beta_1} + \boldsymbol{z}'_{\boldsymbol{ij}}(\boldsymbol{s_{ij}})\boldsymbol{b_i} + \epsilon_{ij},\ i = 1, 2, ..., n, j = 1, 2, ..., n_i, \quad (1)$$

- $\boldsymbol{b_i} \sim N_q(0, \boldsymbol{D}),\ \epsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2_\epsilon).$

a proportional hazard model is considered for the time-to-event process

$$h_i(t) = h_0(t)\, exp\{\boldsymbol{X^{(2)}}'\boldsymbol{\beta_2} + \alpha\omega_i(t)\}, \quad (2)$$

With the true unobserved value for $\omega_i(t)$:

$$h_i(t) = h_0(t)\, exp\{\boldsymbol{X}^{(2)'}\boldsymbol{\beta}_2 + \alpha(\boldsymbol{x}'_{\boldsymbol{ij}}(\boldsymbol{s_{ij}})\boldsymbol{\beta}_1 + \boldsymbol{z}'_{\boldsymbol{ij}}(\boldsymbol{s_{ij}})\boldsymbol{b_i})\}, \quad (3)$$

Joint Latent Class Model(JLCM)

- G is the number of sub-population
- $c_i = g$, $g = 1, ..., G$ is the unobserved (latent) class indicator.
- The conditional independence assumptions:

$$
\begin{aligned}
f(T_i, \delta_i, \boldsymbol{y}_i | c_i = g, \boldsymbol{b}_i; \boldsymbol{\theta}) &= f(T_i, \delta_i | c_i = g; \boldsymbol{\theta}) \times f(\boldsymbol{y}_i | c_i = g, \boldsymbol{b}_i; \boldsymbol{\theta}), \\
f(\boldsymbol{y}_i | c_i = g, \boldsymbol{b}_i; \boldsymbol{\theta}) &= \prod_j f\{y_i(s_{ij}) | c_i = g, \boldsymbol{b}_i; \boldsymbol{\theta}\}. \qquad (4)
\end{aligned}
$$

The sub-models of the joint latent class model

$$\begin{cases} (\boldsymbol{Y}_i(s)|c_i = g) = X_i'(s)\boldsymbol{\beta}_g + Z_i'(s)\boldsymbol{b}_{ig} + \epsilon_i(s), \\ \qquad \epsilon_i(s) \sim N(0, \sigma^2) \\ \\ h_i(t|c_i = g) = h_{0g}(t) exp(\boldsymbol{w}_i{}'\boldsymbol{\gamma}_g) \\ \pi_{ig} = P(c_i = g) = \frac{exp(\boldsymbol{u}_i{}'\boldsymbol{\lambda}_g)}{\sum_{L=1}^{G} exp(\boldsymbol{u}_i{}'\boldsymbol{\lambda}_g)}. \end{cases} \tag{5}$$

- $\boldsymbol{b}_{ig} = \boldsymbol{b}_i|_{c_i=g} \sim N_q(\boldsymbol{\mu}_g, D_g)$, in which $D_g = \sigma_g^2 D$,
- i.e, $\boldsymbol{b}_i \sim \sum_{g=1}^{G} \pi_{ig} N_q(\boldsymbol{\mu}_g, D_g)$,
- $\sigma_G = 1$ & $\boldsymbol{\lambda}_G = 0$ for identifiability.

Applications: AIDS dataset

$n = 467$ patients with advanced (HIV) infection are randomly assigned to receive the drugs didanosine (ddI) and zalcitabine (ddC). **repeated measures of $CD4$ cell counts** were recorded every 2 months from the beginning to 20 months. **time to death** outcome was considered.

SPM (implement by using **JM** function in package **JointModel**)

$$\begin{aligned} y_i(s) &= \omega_i(s) + \varepsilon_i(s) \\ &= \beta_0 + \beta_1 s + \beta_2 \{s \times ddI_i\} + b_{i0} + b_{i1} s + \varepsilon_i(s), \end{aligned} \tag{6}$$

$$h_i(t) = h_0(t) \exp\{\gamma ddI_i + \alpha\omega_i(t)\}. \tag{7}$$

$h_0(t)$ is assumed piecewise-constant with six knots.

JLCM (implement with package **lcmm**)

$$y_i(s)_{|c_i=g} = \beta_{0g} + \beta_{1g}s + \beta_{2g}\text{ddI}_i + b_{i0} + b_{i1}s + \varepsilon_i(s), \quad i = 1, ..., n, \quad g = 1, ..., G, \tag{8}$$

$$h_i\left(t \mid c_i = g\right) = h_{0g}(t)\exp\left(\gamma_g \ \text{ddI}_i\right), \tag{9}$$

$$\mathrm{P}\left(c_i = g\right) = \frac{\exp\left(\lambda_{0g} + \lambda_{1g} \ \text{ddI}_i\right)}{\sum_{l=1}^{G}\exp\left(\lambda_{0l} + \lambda_{1l}\text{ddI}_i\right)}. \tag{10}$$

The class-specific baseline risk functions with parameters $\boldsymbol{\nu}_g$ are assumed to be piecewise-constant with six knots

- Four joint models with 2, 3, 4 and 5 latent classes are fitted and choose the model with 3 latent classes and $BIC = 8650.44$

TABLE 1. Results of SPM for Aids dataset

Parameter	Value	S.Err	Z-value	P-value
		longitudinal process		
$\beta_0(Intercept)$	7.220	0.222	32.554	<0.0001
$\beta_1(time)$	-0.191	0.022	-8.836	<0.0001
$\beta_2(time * ddI)$	0.017	0.030	0.383	0.702
		event process		
$\gamma(ddI)$	0.335	0.157	2.139	0.032
$\alpha(association)$	-0.288	0.036	-8.014	<0.0001
$\log(x_i.1)$	-2.544	0.191	-13.295	-
$\log(x_i.2)$	-2.272	0.178	-12.734	-
$\log(x_i.3)$	-1.955	0.240	-8.136	-
$\log(x_i.4)$	-2.501	0.341	-7.330	-
$\log(x_i.5)$	-2.415	0.316	-7.654	-
$\log(x_i.6)$	-2.402	0.401	-5.995	-
$\log(x_i.7)$	-2.424	0.530	-4.573	-
Variance-covariance matrix of the random-effects & Residual standard error				
D_{11}	21.012	-	-	-
D_{12}	-0.039	-	-	-
D_{22}	0.033	-	-	-
σ	1.738	-	-	-
		Comparison criteria		
$log.lik$	-4328.260	-	-	
AIC	8688.520	-	-	
BIC	8754.862	-	-	

TABLE 3. Results of JLCM for AIDS dataset with $g = 3$

Parameter	class	Est.	S.E	Wald	p-value
fixed effects in the longitudinal model					
β_{01}	1	4.552	0.210	2.699	0.000
β_{02}	2	11.973	0.612	19.577	0.000
β_{03}	3	15.385	0.504	30.503	0.000
β_{11}	1	−0.135	0.017	−7.750	0.000
β_{12}	2	−0.334	0.044	−7.560	0.000
β_{13}	3	0.008	0.032	2.243	0.808
β_{21}	1	0.192	0.272	0.705	0.481
β_{22}	2	−0.364	0.903	−0.404	0.686
β_{23}	3	−1.034	0.570	−1.815	0.069
Parameters in the proportional hazard model					
ν_{11}	1	0.175	0.016	10.612	0.000
ν_{21}	1	0.178	0.017	10.628	0.000
ν_{31}	1	0.206	0.019	10.524	0.000
ν_{41}	1	0.284	0.026	10.106	0.000
ν_{51}	1	0.220	0.022	10.108	0.000
ν_{12}	2	0.075	0.043	1.768	0.077
ν_{22}	2	0.000	0.077	0.004	0.997
ν_{32}	2	0.000	0.065	0.006	0.995
ν_{42}	2	0.000	0.094	0.000	1.000
ν_{52}	2	0.178	0.053	3.333	0.001
ν_{13}	3	0.014	0.029	0.466	0.641
ν_{23}	3	−0.012	0.026	−0.459	0.646
ν_{33}	3	0.022	0.047	0.477	0.633
ν_{43}	3	0.000	0.014	0.000	1.000
ν_{53}	3	0.000	0.013	0.000	1.000
γ_1	1	0.281	0.159	1.769	0.077
γ_2	2	−0.393	0.951	−0.413	0.680
γ_3	3	3.603	4.206	0.857	0.392
Fixed effects in the class-membership model:					
λ_{01}	1	1.891	0.236	8.026	0.000
λ_{02}	2	0.378	0.312	1.210	0.226
λ_{11}	1	−0.617	0.304	−2.032	0.042
λ_{12}	2	−0.833	0.434	−1.921	0.055
Variance-covariance matrix of the random-effects					
D_{11}	-	4.998	-	-	-
D_{12}	-	−0.240	-	-	-
D_{22}	-	0.017	-	-	-
Residual standard error:					
σ	-	1.734	0.047	-	-

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