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Overview

- ▶ Deal with the problem of joint modeling of longitudinal data and censored durations
- ▶ Large number of both longitudinal and time-independent features are available
- ▶ Flexibility in modeling the dependency between the longitudinal features and the event time with appropriate penalties
- ▶ Inference achieved using an efficient and novel Quasi-Newton Monte Carlo Expectation Maximization algorithm

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Use cases

- ▶ Predict the risk for an event of interest to occur quickly, taking into account simultaneously a huge number of longitudinal signals in a high-dimensional context
- ▶ Provides powerful interpretability by automatically pinpointing significant time-dependent and time-independent features

Real-time decision support

- ▶ Medical context → event of interest: survival time, re-hospitalization, relapse or disease progression ; longitudinal data: biomarkers or vital parameters measurements
- ▶ Customer's satisfaction monitoring context → event of interest: time when a client churns ; longitudinal data: the client's activity recorded from account opening throughout the duration of the business relationship

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High-dimensional framework

- Survival analysis

$$T = T^* \wedge C \quad \text{and} \quad \Delta = \mathbb{1}_{\{T^* \leq C\}}$$

- Time-independent features $X \in \mathbb{R}^p$ with $p \gg n$

- L longitudinal outcomes such that $L \gg n$ and

$$Y(t) = (Y^1(t), \dots, Y^L(t))^T \in \mathbb{R}^L$$

- Heterogeneity of the population: latent subgroups

$$G \in \{0, \dots, K-1\}$$

- Softmax link function for the latent class membership probability given time-independent features

$$\pi_{\xi_k}(x) = \mathbb{P}[G = k | X = x] = \frac{e^{x^T \xi_k}}{\sum_{k=0}^{K-1} e^{x^T \xi_k}}$$

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Group-specific marker trajectories

- ▶ $h_l(\mathbb{E}[Y^l(t)|b^l, G = k]) = m_k^l(t) = u^l(t)^\top \beta_k^l + v^l(t)^\top b^l$
with fixed effect parameters $\beta_k^l \in \mathbb{R}^{q_l}$ and subject-and-longitudinal outcome specific random effects $b^l \in \mathbb{R}^{r_l} \sim \mathcal{N}(0, D_{ll})$
- ▶ $\text{Cov}[b^l, b^{l'}] = D_{ll'}$ and

$$D = \begin{bmatrix} D_{11} & \cdots & D_{1L} \\ \vdots & \ddots & \vdots \\ D_{1L}^\top & \cdots & D_{LL} \end{bmatrix}$$

the global variance-covariance matrix

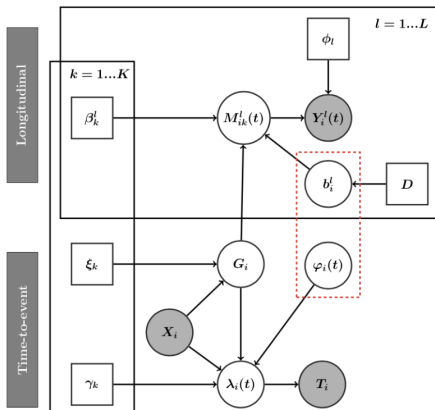
Group-specific risk of event

- ▶ $\lambda(t|G = k) = \lambda_0(t) \exp \left\{ \sum_{l=1}^L \sum_{a=1}^{\mathcal{A}} \gamma'_{k,a}{}^\top \varphi_{k,a}(t, b') \right\}$
- ▶ Functionals $(\varphi_a)_{a \in \mathcal{A}}$

Description	$\varphi_{k,a}(t, b')$	z_a	Reference
Linear predictor	$m'_k(t)$	1	Chi and Ibrahim [2]
Random effects	b'	r_l	Hatfield et al. [3]
Time-dependent slope	$\frac{d}{dt} m'_k(t)$	1	Rizopoulos and Ghosh [4]
Cumulative effect	$\int_0^t m'_k(s) ds$	1	Andrinopoulou et al. [1]

Submodels

- Graphical representation of a joint model of a time-to-event submodel and K-multivariate longitudinal outcomes submodel



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- ▶ $\mathcal{D}_n = \{(x_1, y_1^1, \dots, y_1^L, t_1, \delta_1), \dots, (x_n, y_n^1, \dots, y_n^L, t_n, \delta_n)\}$ with $y_i^l = (y_{i1}^l, \dots, y_{in_l}^l)^\top \in \mathbb{R}^{n_l^l}$ and $y_{ij}^l = Y_i^l(t_{ij}^l)$
- ▶ $y_i = (y_i^{1^\top} \dots y_i^{L^\top})^\top \in \mathbb{R}^{n_i}$ with $n_i = \sum_{l=1}^L n_l^l$
- ▶ $b_i = (b_i^{1^\top} \dots b_i^{L^\top})^\top \in \mathbb{R}^r$ with $r = \sum_{l=1}^L r_l$
- ▶ Design matrices

$$U_i = \begin{bmatrix} U_{i1} & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & U_{iL} \end{bmatrix} \in \mathbb{R}^{n_i \times q} \text{ and } V_i = \begin{bmatrix} V_{i1} & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & V_{iL} \end{bmatrix} \in \mathbb{R}^{n_i \times r}$$

with $q = \sum_{l=1}^L q_l$ and where for all $l = 1, \dots, L$, one writes

$$\begin{cases} U_{il} = (u_i^l(t_{i1}^l)^\top \dots u_i^l(t_{in_l}^l)^\top)^\top \in \mathbb{R}^{n_l^l \times q_l}, \\ V_{il} = (v_i^l(t_{i1}^l)^\top \dots v_i^l(t_{in_l}^l)^\top)^\top \in \mathbb{R}^{n_l^l \times r_l}. \end{cases}$$

- ▶ $\beta_k = (\beta_k^{1^\top} \dots \beta_k^{L^\top})^\top \in \mathbb{R}^q$
- ▶ $M_{ik} = U_i \beta_k + V_i b_i \in \mathbb{R}^{n_i}$

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Likelihood

- ▶ $\theta = (\xi_0^\top \cdots \xi_{K-1}^\top, \beta_0^\top \cdots \beta_{K-1}^\top, \phi^\top, \text{vech}(D), \lambda_0^\top, \gamma_0^\top \cdots \gamma_{K-1}^\top) \in \mathbb{R}^\vartheta$
- ▶ $f(y_i|b_i, G_i = k) = \exp \left\{ (y_i \odot \Phi_i)^\top M_{ik} - c_\phi(M_{ik}) + d_\phi(y_i) \right\}$ with $\Phi_i = (\phi_1^{-1} \mathbf{1}_{n_i^1}^\top \cdots \phi_L^{-1} \mathbf{1}_{n_i^L}^\top)^\top \in \mathbb{R}^{n_i}$
- ▶ Survival part:

$$f(t_i, \delta_i|b_i, G_i = k; \theta) = \left[\lambda(t_i|\mathcal{M}_k(t_i), G_i = k) \right]^{\delta_i} \\ \times \exp \left\{ - \int_0^{t_i} \lambda(s|\mathcal{M}_k(s), G_i = k) ds \right\}$$

- ▶ Then, the likelihood writes

$$\ell_n(\theta) = n^{-1} \sum_{i=1}^n \log \int_{\mathbb{R}^r} \sum_{k=0}^{K-1} \pi_{\xi_k}(x_i) f(t_i, \delta_i|b_i, G_i = k; \theta) \\ \times f(y_i|b_i, G_i = k; \theta) f(b_i; \theta) db_i$$

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Penalization

► Penalized objective

$$\ell_n^{\text{pen}}(\theta) = -\ell_n(\theta) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en},\eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sgl}_1,\tilde{\eta}}$$

with the elasticnet penalty

$$\|z\|_{\text{en},\eta} = (1 - \eta)\|z\|_1 + \frac{\eta}{2}\|z\|_2^2$$

and the sparse group lasso penalty

$$\|z\|_{\text{sgl}_1,\tilde{\eta}} = (1 - \tilde{\eta})\|z\|_1 + \tilde{\eta} \sum_{l=1}^L \|z^l\|_2$$

► Resulting optimization problem

$$\hat{\theta} \in \operatorname{argmin}_{\theta \in \mathbb{R}^{\vartheta}} \ell_n^{\text{pen}}(\theta)$$

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QNMCEM algorithm (1/2)

- ▶ $\ell_n^{\text{comp}}(\theta) = \ell_n^{\text{comp}}(\theta; \mathcal{D}_n, \mathbf{b}, \mathbf{G})$

Monte Carlo E-step

- ▶ $\mathcal{Q}_n(\theta, \theta^{(w)}) = \mathbb{E}_{\theta^{(w)}}[\ell_n^{\text{comp}}(\theta) | \mathcal{D}_n]$
- ▶ Requires to compute expectations of the form

$$\mathbb{E}_{\theta^{(w)}}[g(b_i, G_i) | t_i, \delta_i, y_i] = \sum_{k=0}^{K-1} \pi_{ik}^{\theta^{(w)}} \int_{\mathbb{R}^r} g(b_i, G_i) f(b_i | t_i, \delta_i, y_i; \theta^{(w)}) db_i$$

for different functions g , where we denote

$$\pi_{ik}^{\theta^{(w)}} = \mathbb{P}_{\theta^{(w)}}[G_i = k | t_i, \delta_i, y_i]$$

- ▶ Monte Carlo approximations used for untractable integrals

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QNMCEM algorithm (2/2)

Quasi-Newton M-step

- ▶ $\theta^{(w+1)} \in \operatorname{argmin}_{\theta} \mathcal{Q}_n(\theta, \theta^{(w)}) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sgl}_1, \tilde{\eta}}$
- ▶ $D^{(w+1)} = n^{-1} \sum_{i=1}^n \hat{\mathbb{E}}_{\theta^{(w)}}[b_i b_i^\top | t_i, \delta_i, y_i]$
- ▶ $R_{n,k}^{(w)}(\beta_k) = -n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \left[(y_i \odot \Phi_i^{(w)})^\top \hat{\mathbb{E}}_{\theta^{(w)}}[M_{ik} | t_i, \delta_i, y_i] - \hat{\mathbb{E}}_{\theta^{(w)}}[c_{\phi^{(w)}}(M_{ik}) | t_i, \delta_i, y_i] \right]$
- ▶ $\beta_k^{(w+1)} \in \operatorname{argmin}_{\beta_k \in \mathbb{R}^q} R_{n,k}^{(w)}(\beta_k)$
- ▶ $P_{n,k}^{(w)}(\xi_k) = -n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \log \pi_{\xi_k}(x_i)$
- ▶ $\xi_k^{(w+1)} \in \operatorname{argmin}_{\xi_k \in \mathbb{R}^p} P_{n,k}^{(w)}(\xi_k) + \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta}$
- ▶ L-BFGS-B to solve the problem
- ▶ Proximal gradient method to estimate $\gamma_k^{(w+1)}$
- ▶ Predictive marker $\hat{\mathcal{R}}_{ik} = \frac{\pi_{\hat{\xi}_k}(x_i) \hat{f}(t_i^{\max}, y_i | b_i, G_i = k; \hat{\theta})}{\sum_{k=0}^{K-1} \pi_{\hat{\xi}_k}(x_i) \hat{f}(t_i^{\max}, y_i | b_i, G_i = k; \hat{\theta})}$, which is an estimate of $\mathbb{P}_{\theta}[G_i = k | T_i^* > t_i^{\max}, y_i]$

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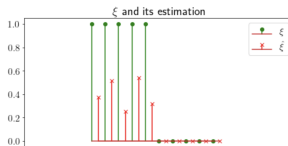
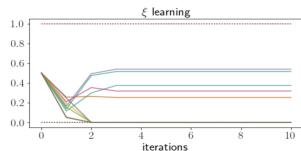
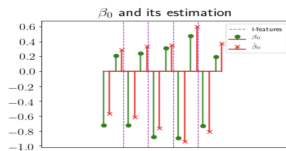
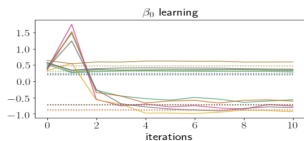
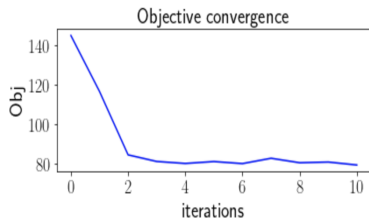
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Conclusion

- ▶ Prognostic method called lights introduced to deal with the problem of joint modeling of longitudinal data and censored durations, where a large number of longitudinal features are available
- ▶ Penalization of the likelihood in order to perform feature selection and to prevent overfitting
- ▶ New efficient estimation algorithm (QNMCEM) has been derived
- ▶ Automatically determines significant prognostic longitudinal features

Python 3 package

- ▶ Available at <https://github.com/Califrais/lights>
- ▶ Applications of the model available soon on an arXiv paper.

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Thank you!

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