

I. Introduction

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Overview

- Deal with the problem of joint modeling of longitudinal data and censored durations

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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

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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

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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 Expectation Maximization algorithm

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- ▶ 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

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- ▶ 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

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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

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- ▶ 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

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

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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 $p \gg n$

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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

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

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

- Heterogeneity of the population: latent subgroups

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

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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 $b^l \in \mathbb{R}^{r_l} \sim \mathcal{N}(0, D_{ll})$

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

Submodels

Group-specific risk of event

► $\lambda(t|\Psi, G = k) = \lambda_0(t) \exp \left\{ \gamma_k^\top \Psi \right\}$

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Group-specific risk of event

- ▶ $\lambda(t|\Psi, G = k) = \lambda_0(t) \exp \{ \gamma_k^\top \Psi \}$
- ▶ Features Ψ are extracted from Y by the Python library `tsfresh`
- ▶ **TODO: Add descriptions**

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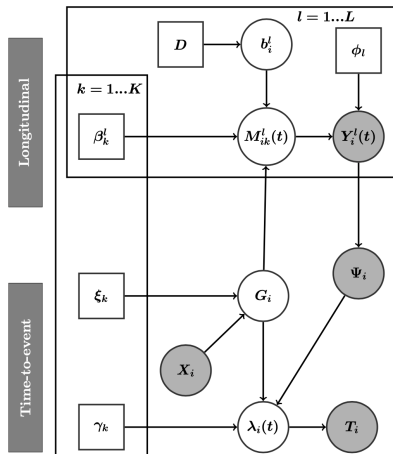
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Submodels

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



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- $\mathcal{D}_n = \{(x_1, y_1^1, \dots, y_1^L, t_1, \delta_1, \Psi_1), \dots, (x_n, y_n^1, \dots, y_n^L, t_n, \delta_n, \Psi_n)\}$
with $y_i^l = (y_{i1}^l, \dots, y_{in_i^l}^l)^\top \in \mathbb{R}^{n_i^l}$ and $y_{ij}^l = Y_i^l(t_{ij}^l)$

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with $y_i^l = (y_{i1}^l, \dots, y_{in_i^l}^l)^\top \in \mathbb{R}^{n_i^l}$ and $y_{ij}^l = Y_i^l(t_{ij}^l)$
- ▶ $y_i = (y_i^{1^\top} \cdots y_i^{L^\top})^\top \in \mathbb{R}^{n_i}$ with $n_i = \sum_{l=1}^L n_i^l$

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- ▶ $y_i = (y_i^{1^\top} \cdots y_i^{L^\top})^\top \in \mathbb{R}^{n_i}$ with $n_i = \sum_{l=1}^L n_i^l$
- ▶ $b_i = (b_i^{1^\top} \cdots b_i^{r^\top})^\top \in \mathbb{R}^r$ with $r = \sum_{l=1}^L r_l$

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with $y_i^l = (y_{i1}^l, \dots, y_{i n_i^l}^l)^\top \in \mathbb{R}^{n_i^l}$ and $y_{ij}^l = Y_i^l(t_{ij}^l)$
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- ▶ $b_i = (b_i^{1\top} \cdots b_i^{r\top})^\top \in \mathbb{R}^r$ with $r = \sum_{l=1}^L r_l$
- ▶ Design matrices

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

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

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

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with $y_i^l = (y_{i1}^l, \dots, y_{i n_i^l}^l)^\top \in \mathbb{R}^{n_i^l}$ 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 $n_i = \sum_{l=1}^L n_i^l$
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- ▶ $\beta_k = (\beta_k^{1^\top} \dots \beta_k^{L^\top})^\top \in \mathbb{R}^q$

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- ▶ $y_i = (y_i^{1^\top} \dots y_i^{L^\top})^\top \in \mathbb{R}^{n_i}$ with $n_i = \sum_{l=1}^L n_i^l$
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$$U_i = \begin{bmatrix} U_{i1} & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & U_{iL} \end{bmatrix} \in \mathbb{R}^{n_i \times q} \text{ and } V_i = \begin{bmatrix} V_{i1} & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & V_{iL} \end{bmatrix} \in \mathbb{R}^{n_i \times r}$$

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

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

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Likelihood

$$\blacktriangleright \theta = (\xi_0^\top \cdots \xi_{K-1}^\top, \beta_0^\top \cdots \beta_{K-1}^\top, \phi^\top, \text{vech}(D), \lambda_0^\top, \gamma_0^\top \cdots \gamma_{K-1}^\top) \in \mathbb{R}^{\vartheta}$$

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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 $\Phi_i = (\phi_1^{-1} \mathbf{1}_{n_i^1}^\top \cdots \phi_L^{-1} \mathbf{1}_{n_i^L}^\top)^\top \in \mathbb{R}^{n_i}$

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- ▶ $f(y_i|b_i, G_i = k) = \exp \left\{ (y_i \odot \Phi_i)^\top M_{ik} - c_\phi(M_{ik}) + d_\phi(y_i) \right\}$ 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:

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

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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:

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

- ▶ Then, the likelihood writes

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

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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

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

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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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QNEM algorithm (1/2)

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

E-step

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QNEM algorithm (1/2)

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

E-step

- ▶ $Q_n(\theta, \theta^{(w)}) = \mathbb{E}_{\theta^{(w)}}[\ell_n^{\text{comp}}(\theta) | \mathcal{D}_n]$

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QNEM algorithm (1/2)

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

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

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

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QNEM algorithm (2/2)

Quasi-Newton M-step

$$\blacktriangleright \theta^{(w+1)} \in \operatorname{argmin}_{\theta} \mathcal{Q}_n(\theta, \theta^{(w)}) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sgl}, \tilde{\eta}}$$

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QNEM algorithm (2/2)

Quasi-Newton M-step

- ▶ $\theta^{(w+1)} \in \operatorname{argmin}_{\theta} \mathcal{Q}_n(\theta, \theta^{(w)}) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sgl}_1, \tilde{\eta}}$
- ▶ $D^{(w+1)} = n^{-1} \sum_{i=1}^n \hat{\mathbb{E}}_{\theta^{(w)}}[b_i b_i^{\top} | t_i, \delta_i, y_i]$

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- ▶ $R_{n,k}^{(w)}(\beta_k) =$
 $-n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \left[(y_i \odot \Phi_i^{(w)})^\top \hat{\mathbb{E}}_{\theta^{(w)}} [M_{ik} | t_i, \delta_i, y_i] - \hat{\mathbb{E}}_{\theta^{(w)}} [c_{\phi^{(w)}}(M_{ik}) | t_i, \delta_i, y_i] \right]$

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- ▶ $\beta_k^{(w+1)} \in \operatorname{argmin}_{\beta_k \in \mathbb{R}^q} R_{n,k}^{(w)}(\beta_k)$

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- ▶ $P_{n,k}^{(w)}(\xi_k) = -n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \log \pi_{\xi_k}(x_i)$

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- ▶ $P_{n,k}^{(w)}(\xi_k) = -n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \log \pi_{\xi_k}(x_i)$
- ▶ $\xi_k^{(w+1)} \in \operatorname{argmin}_{\xi_k \in \mathbb{R}^p} P_{n,k}^{(w)}(\xi_k) + \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta}$

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- ▶ L-BFGS-B to solve the problem

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- ▶ $P_{n,k}^{(w)}(\xi_k) = -n^{-1} \sum_{i=1}^n \hat{\pi}_{ik}^{\theta^{(w)}} \log \pi_{\xi_k}(x_i)$
- ▶ $\xi_k^{(w+1)} \in \operatorname{argmin}_{\xi_k \in \mathbb{R}^p} P_{n,k}^{(w)}(\xi_k) + \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta}$
- ▶ L-BFGS-B to solve the problem
- ▶ Proximal gradient method to estimate $\gamma_k^{(w+1)}$

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- ▶ $\theta^{(w+1)} \in \operatorname{argmin}_{\theta} \mathcal{Q}_n(\theta, \theta^{(w)}) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sg}^1_1, \tilde{\eta}}$
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- ▶ $\xi_k^{(w+1)} \in \operatorname{argmin}_{\xi_k \in \mathbb{R}^p} P_{n,k}^{(w)}(\xi_k) + \zeta_{1,k} \|\xi_k\|_{\text{en}, \eta}$
- ▶ L-BFGS-B to solve the problem
- ▶ Proximal gradient method to estimate $\gamma_k^{(w+1)}$
- ▶ Predictive marker $\hat{\mathcal{R}}_{ik} = \frac{\pi_{\hat{\xi}_k}(x_i) \hat{f}(t_i^{\max}, y_i | G_i = k, \Psi_i; \hat{\theta})}{\sum_{k=0}^{K-1} \pi_{\hat{\xi}_k}(x_i) \hat{f}(t_i^{\max}, y_i | G_i = k, \Psi_i; \hat{\theta})}$, which is an estimate of $\mathbb{P}_{\theta}[G_i = k | T_i^* > t_i^{\max}, y_i]$

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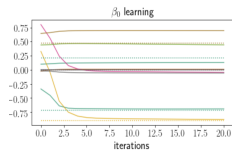
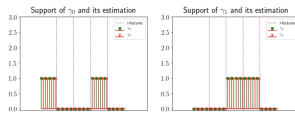
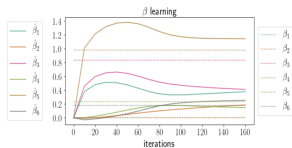
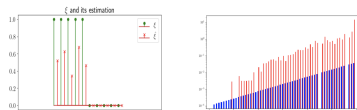
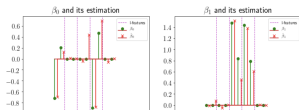
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- ▶ Prognostic method called lights introduced to deal with the problem of joint modeling of longitudinal data and censored durations, where a large number of longitudinal features are available

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- ▶ 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

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- ▶ 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 (QNEM) has been derived

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- ▶ 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 (QNEM) has been derived
- ▶ Automatically determines significant prognostic longitudinal features

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- ▶ 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
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Python 3 package

- ▶ Available at <https://github.com/Califrais/lights>

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- ▶ 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 (QNEM) 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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