HeKA Staff Meeting

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Lights: a generalized joint model for high-dimensional multivariate longitudinal data and censored durations

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I. Introduction

Overview

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

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- 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 Proximal Quasi-Newton Expectation Maximization algorithm

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

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Real-time decision support

- Medical context $\rightarrow$ event of interest: survival time, re-hospitalization, relapse or disease progression ; longitudinal data: biomarkers or vital parameters measurements

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Real-time decision support

- Medical context $\rightarrow$ event of interest: survival time, re-hospitalization, relapse or disease progression ; longitudinal data: biomarkers or vital parameters measurements
- Customer's satisfaction monitoring context $\rightarrow$ 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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- Survival analysis

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

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

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

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

II. Model

Submodels

Group-specific marker trajectories

- $h_l\Big(\mathbb{E}[Y^l(t)|b^l, G = k]\Big) = m_k^l(t) = u^l(t)^\top \beta_k^l + v^l(t)^\top b^l$
  with fixed effect parameters $\beta_k^l \in \mathbb{R}^{q_l}$ and subject-and-longitudinal outcome specific random effects $b^l \in \mathbb{R}^{r_l} \sim \mathcal{N}(0, D_{ll})$

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- $\mathrm{Cov}[b^l, b^{l'}] = D_{ll'}$ 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

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Group-specific risk of event

- $$\lambda(t|\mathcal{Y}(t), G=k) = \lambda_0(t) \exp\Bigg\{ \underbrace{\sum_{l=1}^{L} \sum_{a=1}^{\mathcal{A}} \gamma_{k,a}^l \Psi_a^l(t)}_{\gamma_k^\top \Psi(t)} \Bigg\}$$

  with $\mathcal{Y}(t) = \{Y(u), 0 \leq u < t\}$ and for each l-th longitudinal outcome, we consider $\mathcal{A} \in \mathbb{N}_+$ known functionals Ψ_a^l extracted from $\mathcal{Y}^l(t)$ through a given representation mapping

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- $\Psi(t) \in \mathbb{R}^{L\mathcal{A}}$: high-dim representation features vector, highly flexible and independent of any modeling assumption !

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- Usual functionals would be

Description	$\tilde{\Psi}_a^l(t, \beta_k^l, b^l)$	Reference
Linear predictor	$m_k^l(t)$	Chi and Ibrahim [2]
Random effects	b^l	Hatfield et al. [3]
Time-dependent slope	$\frac{\mathrm{d}}{\mathrm{d}t} m_k^l(t)$	Rizopoulos and Ghosh [6]
Cumulative effect	$\int_0^t m_k^l(s)\mathrm{d}s$	Andrinopoulou et al. [1]

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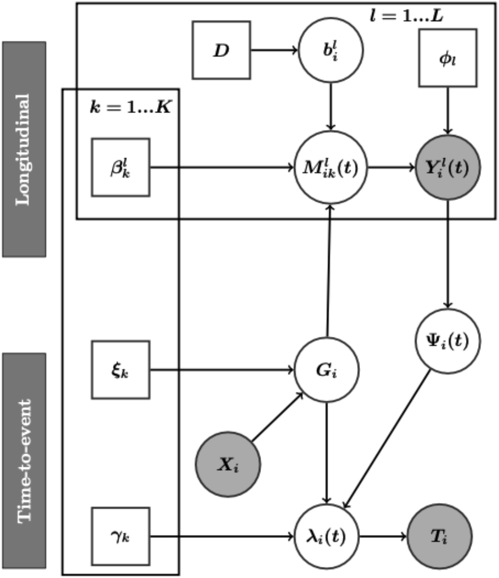
- Depend on β_k (then on k) which leads to complicated updates, and on b which leads to untracktable integrals that requires approximation methods : computationally intensive and not scalable

Graphical model



Notations

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

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- 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 $l = 1, \ldots, L$, one writes

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

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

Likelihood

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

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

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- Survival part:

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

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- Then, the log-likelihood (JLCMs type) writes

$$\ell_n(\theta) = n^{-1}\sum_{i=1}^n \log \sum_{k=0}^{K-1} \pi_{\xi_k}(x_i) f_\theta(t_i, \delta_i | G_i = k) f_\theta(y_i | G_i = k)\mathrm{d}b_i$$

III. Inference

Penalization

- Penalized objective

$$\ell_n^{\text{pen}}(\theta) = -\ell_n(\theta) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en},\eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sg}l_1,\tilde{\eta}}$$

with the elasticnet penalty

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

and the sparse group lasso penalty

$$\|z\|_{\text{sg}l_1,\tilde{\eta}} = (1-\tilde{\eta})\|z\|_1 + \tilde{\eta} \sum_{l=1}^{L} \|z^l\|_2$$

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- Resulting optimization problem

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

prox-QNEM algorithm (1/2)

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

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Monte Carlo E-step

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

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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

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

for different functions g, where we denote

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

prox-QNEM algorithm (2/2)

Proximal Quasi-Newton M-step

- $\theta^{(w+1)} \in \text{argmin}_{\theta \in \mathbb{R}^{\vartheta}} \; \mathcal{Q}_n(\theta, \theta^{(w)}) + \sum_{k=0}^{K-1} \zeta_{1,k} \|\xi_k\|_{\text{en},\eta} + \zeta_{2,k} \|\gamma_k\|_{\text{sg}l_1, \tilde{\eta}}$

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- $D^{(w+1)} = n^{-1} \sum_{i=1}^{n} \hat{\mathbb{E}}_{\theta^{(w)}}[b_i b_i^\top | t_i, \delta_i, y_i]$
- $P_{n,k}^{(w)}(\xi_k) = -n^{-1} \sum_{i=1}^{n} \hat{\pi}_{ik}^{\theta^{(w)}} \log \pi_{\xi_k}(x_i)$

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prox-QNEM algorithm (2/2)

Proximal Quasi-Newton M-step

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$$
\begin{aligned}
\text{minimize} \quad & P_{n,k}^{(w)}(\xi_k^+ - \xi_k^-) + \zeta_{1,k}\Big((1-\eta)\sum_{j=1}^{p}(\xi_{k,j}^+ + \xi_{k,j}^-) + \frac{\eta}{2}\|\xi_k{}^+ - \xi_k{}^-\|_2^2\Big) \\
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Real-time prediction paradigm

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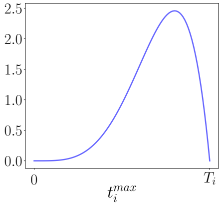

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- $\mathbb{P}_{\hat{\theta}}[G_i = k | T_i > t_i^{max}, \tilde{y}_i] = \dfrac{\pi_{\hat{\xi}_k}(x_i) f_{\hat{\theta}}(t_i^{max}, \delta_i = 0, \tilde{y}_i | G_i = k)}{\sum_{k=0}^{K-1} \pi_{\hat{\xi}_k}(x_i) f_{\hat{\theta}}(t_i^{max}, \delta_i = 0, \tilde{y}_i | G_i = k)}$

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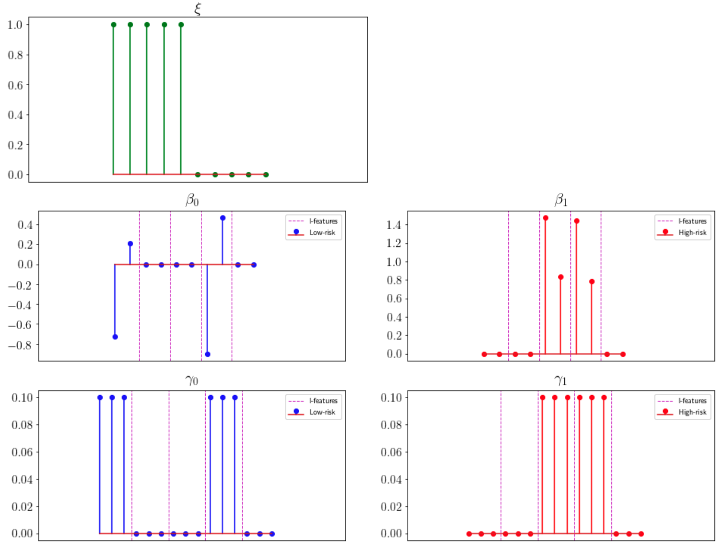
- Gompertz baseline $\lambda_0(t) = \kappa_1 \kappa_2 \exp(\kappa_2 t)$

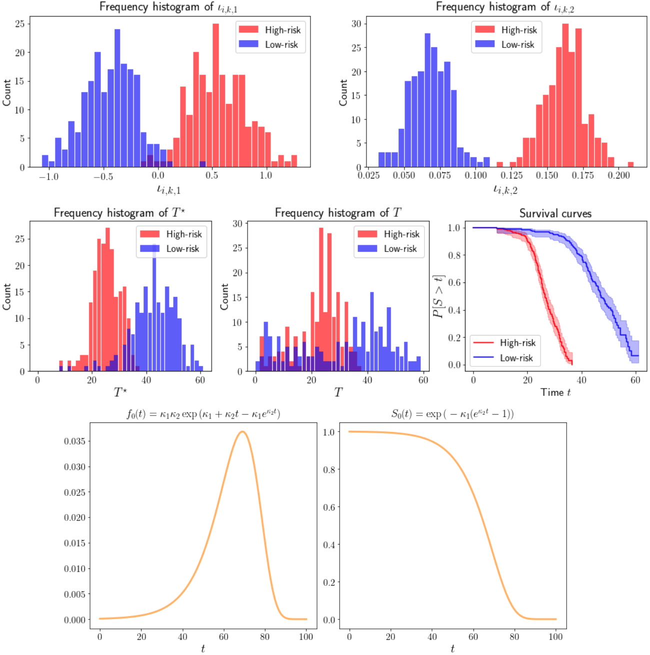
High-dimensional simulation study (1/2)

- High-risk subjects proportion $\pi_1 \in [0, 1]$
- $\mathcal{H} = \big\{ \lfloor \pi_1 n \rfloor \text{ random samples without replacement} \big\}$
- $[x_{ij}] \in \mathbb{R}^{n \times p} \sim \mathcal{N}\big(0, \Sigma_1(\rho_1)\big)$
- $x_{ij} \leftarrow x_{ij} + (-1)^{\mathbb{1}_{\{i \notin \mathcal{H}\}}} gap$ for $j = 1, \ldots, s$
- $\xi = (\underbrace{\varsigma_1, \ldots, \varsigma_1}_{s}, 0, \ldots, 0) \in \mathbb{R}^p$
- $G_i \sim \mathcal{B}\big(\pi_\xi(x_i)\big)$
- $\mathcal{S}_k = \Big\{ k \big\lfloor \frac{L r_s}{K} \big\rfloor + 1, \ldots, (k+1) \big\lfloor \frac{L r_s}{K} \big\rfloor \Big\}$
- $\beta_k^l \sim \mathbb{1}_{\{l \in \mathcal{S}_k\}} \mathcal{N}\Big(\mu_k, \begin{bmatrix} \rho_3 & 0 \\ 0 & \rho_3 \end{bmatrix} \Big)$
- $Y_i^l(t) = \epsilon_i^l(t) + \mathbb{1}_{\{l \in \mathcal{S}_k\}} \sum_{k=0}^{K-1} \mathbb{1}_{\{G_i = k\}} \big((1, t)^\top \beta_k^l + (1, t)^\top b_i^l \big)$
- $\big(\tilde{\Psi}_{k,a}(t, \beta_k, b_i^l) \big)_{a \in \{1,2\}} = \big(\beta_{k,1}^l + \beta_{k,2}^l t + b_{i,1}^l + b_{i,2}^l t \ , {b_i^l}^\top \big)$
- $\tilde{\gamma}_{k,a}^l = \varsigma_2 \mathbb{1}_{\{l \in \mathcal{S}_k, \ a \in \{1,2\}\}}$
- $\lambda_i(t | G_i = k) = \lambda_0(t) \exp \big\{ \iota_{i,k,1} + \iota_{i,k,2} t \big\}$
- Gompertz baseline $\lambda_0(t) = \kappa_1 \kappa_2 \exp(\kappa_2 t)$
- $T_i^\star | G_i = k \sim \dfrac{1}{\iota_{i,k,2} + \kappa_2} \log \Big(1 - \dfrac{(\iota_{i,k,2} + \kappa_2) \log U_i}{\kappa_1 \kappa_2 \exp \iota_{i,k,1}} \Big)$

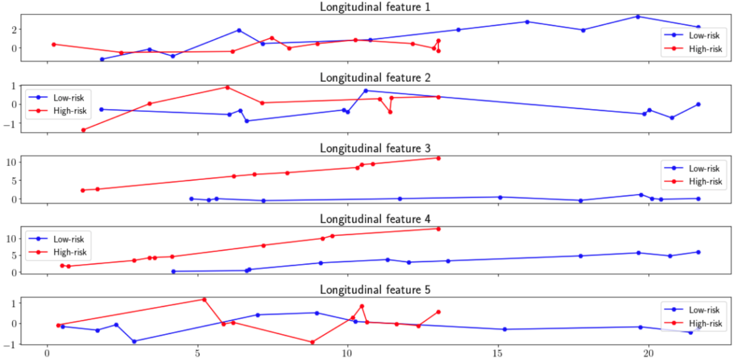
High-dimensional simulation study (2/2)



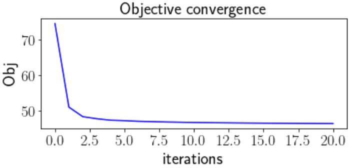
High-dimensional simulation study (2/2)

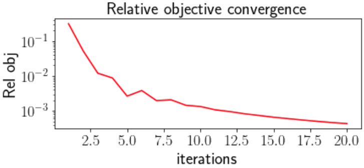


High-dimensional simulation study (2/2)



First results (1/2)





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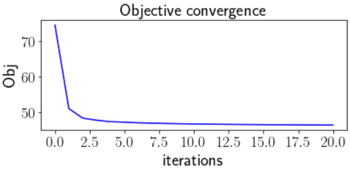

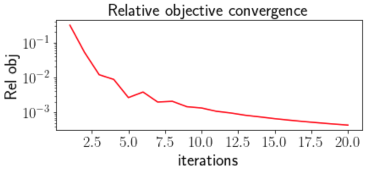

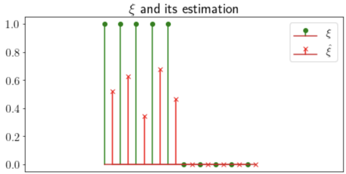

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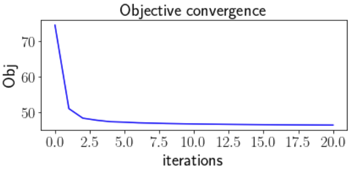
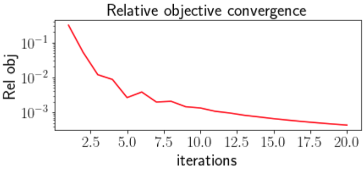
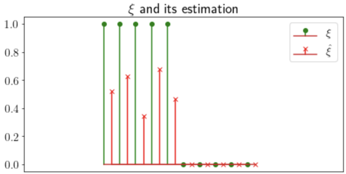
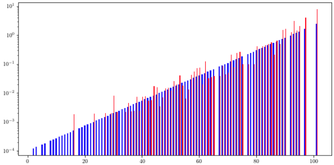
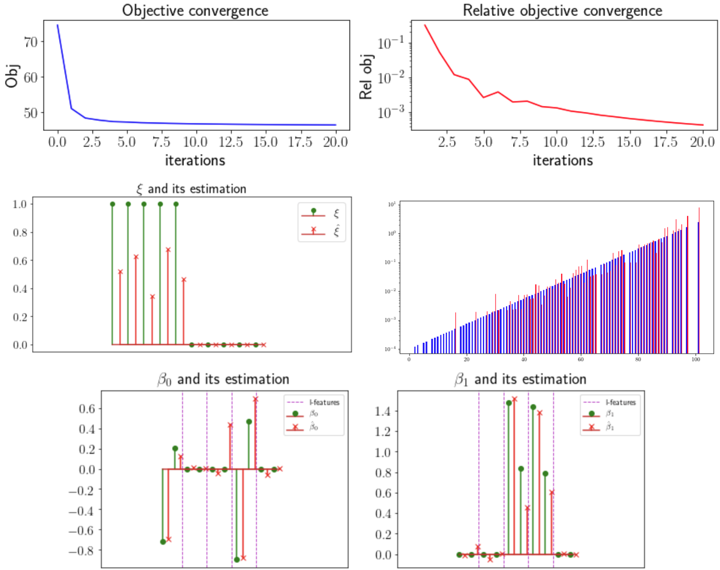




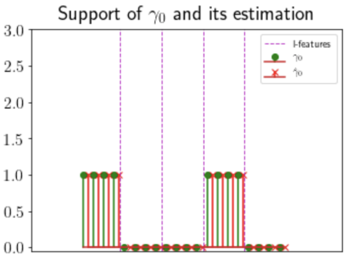


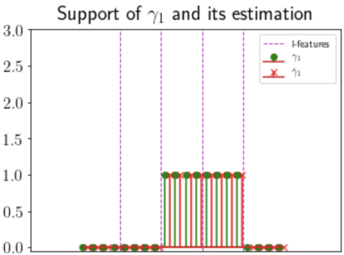


First results (1/2)

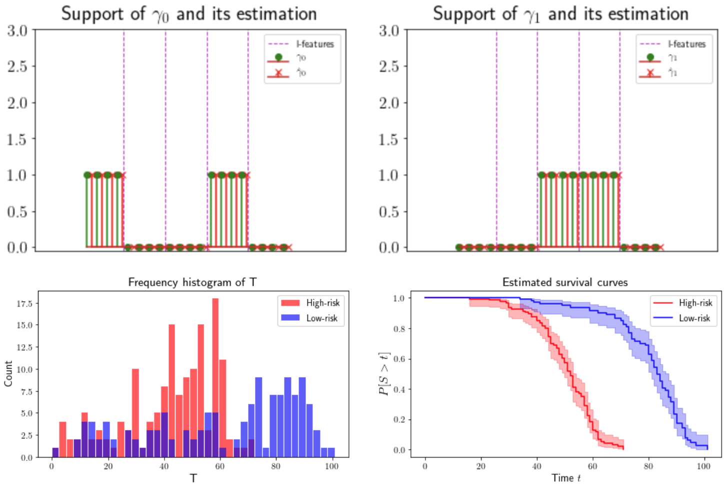


First results (2/2)





First results (2/2)



V. Conclusion

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Python 3 package

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Python 3 package

- Available at `https://github.com/Califrais/lights`
- Applications of the model available soon

Thank you!

References

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