MODEL-BASED CLUSTERING OF RIGHT-CENSORED LIFETIME DATA WITH FRAILTIES AND RANDOM COVARIATES

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ABSTRACT: We introduce a new parametric approach for clustering multilevel survival data that accounts for the heterogeneity at baseline and random distributions of the explanatory variables. The proposed method aims to identify clusters of patients with different survival patterns and uncover the impact of the known hierarchy on survival within each cluster. The objective function is maximized using a stochastic EM algorithm tailored to right-censored lifetime data. The proposed methodology can be seen as a generalization of multilevel cluster-weighted modeling for time-to-event outcomes. Promising results are showcased on synthetic data.

KEYWORDS: model-based clustering, survival data, frailty models, EM algorithm, cluster-weighted models

1 Introduction and model formulation

The paper proposes an approach for clustering survival data in which the procedure takes advantage of cluster-wise different random covariates. Additionally, the heterogeneity at the baseline due to a known hierarchy present in the sample (e.g., patients within hospitals) is accounted for in the time-to-event outcome by means of a parametric frailty model. In details, in our proposal a statistical unit is identified by the triplet \((y_{ij}, \delta_{ij}, x_{ij})\) where:

- \(y_{ij}\) is the minimum between the survival time \(t_{ij}\) and censoring time \(c_{ij}\) for subject \(i\) in hospital \(j\),
- \(\delta_{ij} = I(t_{ij} \leq c_{ij})\) is the event indicator,
- \(x_{ij} = (u_{ij}, v_{ij})\) denotes the vector of covariates with \(u_{ij}\) and \(v_{ij}\) respectively indicating the subset of continuous and categorical predictors for the \(ij\)-th unit.
The entire sample is therefore composed by \( N = \sum_{j=1}^{J} n_j \) observations among the \( J \) hospitals. We further assume that the observed data can be partitioned into \( G \) latent clusters independently of the known \( J \) groups. The resulting log-likelihood for the considered model reads as follows:

\[
\ell \left( \left\{ \tau_g, \beta_g, \mu_g, \Sigma_g, \lambda_g, \theta_g \right\}_{g=1}^{G} \right) = \\
\sum_{g=1}^{G} \left\{ \sum_{j=1}^{J} \log \tau_g + \sum_{j=1}^{J} \left[ \sum_{i \in R_{jg}} \delta_{ij} \left( \log h_0(y_{ij}) + x_{ij}' \beta_g \right) \right] \right. \\
+ \log \left[ (-1)^{d_{jg}} L^{(d_{jg})} \left( \sum_{i \in R_{jg}} H_0(y_{ij}) \exp \left( x_{ij}' \beta_g ; \theta_g \right) \right) \right] \\
+ \sum_{j=1}^{J} \sum_{i \in R_{jg}} \log \phi(u_{ij} ; \mu_g, \Sigma_g) + \sum_{j=1}^{J} \sum_{i \in R_{jg}} \log \psi(v_{ij} ; \lambda_g) \right\} ,
\]

The quantities \( h_0(\cdot) \) and \( H_0(\cdot) \) denote the baseline hazard and cumulative hazard functions, and \( L^{(q)} \) is the \( q \)-th derivative of the Laplace transform of the frailty distribution. Depending on the chosen baseline and/or frailty term, the formulation in (1) encompasses a general family of parametric mixture frailty models. With \( \phi(\cdot) \) and \( \psi(\cdot) \) we respectively identify the densities of a multivariate Gaussian and independent multinomial distributions (one for each categorical variable), needed to incorporate the cluster-wise different contribution of the covariates. Further, \( d_{jg} \) is the total number of observed events assigned to cluster \( g \) belonging to hospital \( j \), and \( R_{jg} \) contains the indexes of the observations in cluster \( g \) and hospital \( j \). The remaining terms are model parameters that need to be estimated from the sample. In details, \( \tau_g \) represents the mixing proportion for cluster \( g \), with \( \tau_g \geq 0 \) for all \( g \) and \( \sum_{g=1}^{G} \tau_g = 1 \). The vector of regression coefficients is denoted with \( \beta_g \), while \( \theta_g \) is the heterogeneity parameter for \( g = 1, \ldots, G \). Lastly, parameters for the conditionally independent multinomial distributions within each cluster are compactly identified with \( \lambda_g \), and \( \mu_g, \Sigma_g \) denote the mean vector and the covariance matrix of the continuous covariates.

Maximization of (1) is carried out by means of a stochastic EM algorithm tailored to right-censored lifetime data (Bordes & Chauveau, 2016). The proposed methodology extends the work in Berta & Vinciotti, 2019 by considering a time-to-event outcome, leveraging on recent advances in the efficient estimation of parametric frailty models (Munda et al., 2012). To this extent, the goal of the proposed procedure is twofold. On the one hand, we aim to identify \( G \) clusters of patients with different survival patterns. On the other hand, within
each cluster we wish to uncover the different impact the known hierarchy has on the survival. Promising results are reported for synthetic data, as described in the next section.

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2 Results on simulated data

We assess the performance of the proposed procedure on a two components ($G = 2$) synthetic population simulated with the genfrail function of the frailtySurv R package (Monaco et al., 2018). The data generating process includes $n_j = 40$ for all $j = 1, \ldots, J$ and $J = 10$, resulting in a sample whose size is equal to $N = 400$. The baseline hazard has a parametric Weibull distribution, while a Gamma density is used to simulate the frailty term in the equally sized clusters. The survival time depends on two continuous covariates, whose distribution is multivariate Gaussian with cluster-wise different mean vectors and equal covariance matrix. Model results are reported in Table 1 in which several specifications for the baseline and frailty densities are considered. The comparison includes also an option with fixed effects only, denoted with Frailty equals to None in the table. We observe that the model with Weibull baseline, Gamma frailty and true number of clusters outperforms the competing methods in both goodness of fit and clustering performance, showcasing higher values in both Bayesian Information Criterion and Adjusted Rand Index metrics.
3 Conclusion

The proposed approach provides a flexible method for analyzing right-censored lifetime data with random covariates and frailties, making it a valuable tool for applications in personalized medicine and hospitals evaluation. Some analyses are currently being accomplished on this regard and they will be the object of future work.

References


