Comparison of approaches for dynamic predictions in competing risks

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Résumé. Dans les études cliniques les patients sont généralement surveillés par des biomarqueurs mesurés de façon répétée. Dans cette population, il est souvent intéressant de prédire des probabilités cumulées individuelles d'événements tels que la rechute clinique ou la mort, à partir des informations individuelles collectées jusqu'au temps de prédiction. Pour calculer ces prédictions dynamiques individuelles, deux principales approches ont été proposées. L'approche de modélisation conjointe modélise simultanément le processus longitudinal (mesures répétées de biomarqueurs) et le processus de survie (données de temps d'événement) en les reliant à l'aide d'une fonction d'une structure latente commune. En revanche, l'approche landmarking cherche à ajuster des modèles de survie standards tenant compte des fonctions des prédictions de biomarqueurs, en ne considérant que le sous-échantillon des patients à risque au moment de la prédiction. Ces approches diffèrent notamment dans l'information utilisée, les hypothèses du modèle et la complexité des procédures computationnelles. Motivés par l'exemple de la prédiction de deux causes concurrentes de progression du cancer de la prostate à partir de l'histoire des PSA, nous avons mené une étude de simulation approfondie permettant d'évaluer et de comparer ces deux approches. Les prédictions dynamiques individuelles dérivées des modèles conjoints et des modèles landmarks ont été spécifiquement comparées en termes de précision de prédiction et de robustesse aux hypothèses du modèle.

Mots-clés. Prédictions dynamiques, Modélisation conjointe, Landmarking, Risques proportionnels, Pseudo-observations

Abstract. In clinical studies patients are usually monitored by repeatedly measuring biomarkers. In this population it is often of interest to predict subject-specific cumulative probabilities of event such as clinical recurrence or death from the individual information collected until the time of prediction. To compute these individual dynamic predictions, two main approaches have been proposed. The joint modelling approach simultaneously models the longitudinal process (repeated measures of biomarkers) and the survival process (time-to-event data) by linking them using a function of a common latent structure. In contrast, the landmarking approach fits standard survival models adjusted for functions of the biomarkers predictions by considering only the subsample of patients at risk

at the time of prediction. These approaches notably differ in the used information, the model assumptions and the complexity of the computational procedures. Motivated by the example of the prediction of two competing causes of prostate cancer progression from the PSA history, we conducted an extensive simulation study to assess and compare these two approaches. The individual dynamic predictions derived from joint models and landmark models were specifically compared in terms of accuracy of prediction and robustness to the model hypotheses.

Keywords. Dynamic predictions, Joint modelling, Landmarking, Proportional hazards, Pseudo-observations.

1 Context

In patients with localized prostate cancer and treated by radiotherapy, the Prostate-Specific Antigen (PSA) is measured routinely, and we are interested in two causes of events: disease recurrence and death. For each subject, strategies of treatment can be adapted according to his up-to-date individualized dynamic predictions of each type of progression.

In this manuscript, we consider the prostate cancer example with for each subject i, X_i the covariates measured at baseline, $\mathcal{Y}_i$ the repeated measurements of the longitudinal marker (PSA), and $K = 2$ possible causes of competing risk events.

To compute individualized dynamic predictions, two notions of time are of interest: the horizon time w, which is the prediction window, and the landmark time s, that denotes the time from which the prediction is made. For each subject i, we observe two processes: $\mathcal{Y}_i(s)$, the history of the marker until the landmark time s, and (T_i, δ_i) the couple of observed time-to-event and cause of event respectively. In practice, we are interested in the individual cumulative probability of the event of cause k between the times s and $s + w$. This is referred to as the landmark specific cumulative incidence of cause k:

$$\pi_i^k(s, w) = \Pr(T_i^* \leq s + w, \delta_i = k | T_i^* > s, \mathcal{Y}_i(s), X_i),$$

where $T_i^* = \min(\{T_{i,k}^*\}_k)$ is the true earlier event time for subject i, with $k = 1, \ldots, K$.

2 Dynamic prediction models

2.1 Joint modelling

The idea of the joint modelling is to link the longitudinal and survival processes according to a function of a shared latent structure. In our case, the latent structure is the random effects, and the joint model is then decomposed into two sub-models: a linear mixed model (for the repeated measures of PSA) and a cause-specific proportional hazard (CS

PH) model (for the competing event times). The function of the shared random effects, which is possibly multivariate and called dependence function, is included in the CS PH model as prognostic factor(s). Examples of functions are the true current level and/or the true current slope of the marker.

The likelihood function exploits the independence between the longitudinal process and the survival process conditionally to the random effects. The inference thus requires the computation of an integral over the random effects (in addition to the integrals over time) for which hard computational numerical integrations are needed.

Once the model is estimated on a learning sample, the vector of parameters $\hat{\theta}$ is deduced, and we are able to compute the estimated cumulative incidences for any new subject. Note that the computation of these conditional probabilities is also complex because it involves integrals over the random effects and integrals over time for which numerical integrations are also required.

2.2 Landmarking

To avoid the hard computational procedures of the joint modelling and reduce the possible bias linked to the proportional hazards assumption of the CS PH model, the landmark approach has been proposed. The idea is to fit standard survival models on the subsample of subjects at risk at the landmark time s.

These survival models are adjusted for the standard prognostic factors X_i and dynamics of the marker such as the last observed value of the marker (one talks about "naive" landmark model) or predictions from the mixed model at the landmark time s (one talks about "two-stage" landmark model). These predictions may include any function of the marker at the landmark time s, for example the predicted value or/and slope of the marker.

Cause-specific proportional hazards models

The landmark CS PH models only consider the events that occurred between s and $s+w$ to reduce the possible bias linked to the PH assumption. The events after $s+w$ are censored in $s+w$. It is referred to as left truncation in s and administrative censoring in $s+w$.

Once the landmark CS PH model is estimated and the vector of parameters $\hat{\theta}$ is obtained on a learning sample, the cumulative incidences can be computed for any new subject. Note that these conditional probabilities require integrals over time. The Aalen-Johansen estimator may be used to avoid the numerical integration.

Dynamic pseudo-observations

The cause-specific proportional hazards models are based on the cause-specific hazards. Thus the computation of cumulative incidences require integrals over time. The idea of

the dynamic pseudo-observations approach is to directly model the conditional probability of event. One talks about direct estimation.

The idea is to select the subjects at risk at time s and regress the expectation of $\mu^k_{i,s,w} = \mathbf{1}(T_i^* \leq s + w, \delta_i = k)$ according to covariates using generalized linear models with a specified link function and a GEE approach. In practice, $\mu^k_{i,s,w}$ is not available for censored subjects. Thus, one uses the dynamic pseudo-observation $\widehat{\mu}^k_{i,s,w} = N_s \widehat{F}^k(s,w) - (N_s - 1)\widehat{F}^k_{(-i)}(s,w)$ where N_s is the number of subjects at risk at time s and $\widehat{F}^k(s,w)$ is the non-parametric estimator of $\pi^k(s,w)$.

After the estimation of the regression on a learning sample, the predicted conditional cumulative incidence can be directly computed for any new subject by handling the inverse of the link function.

3 Comparison

As previously described, the joint model, the landmark CS PH model and the dynamic pseudo-observations approach differ notably in the complexity of the estimation procedure and the information used. The objective of this work was to compare the predictive abilities of the joint modelling and the landmarking according to several landmark time points and horizons in an extensive simulation study. We considered a "well-specified" case (the term "well-specified" is only verified for the joint model) as well as scenarios in which data were generated according to several misspecifications of the joint model in order to verify the models robustness:

- Violation of the PH assumption,
- Misspecification of the dependence function,
- Misspecification of the longitudinal sub-model.

For each scenario and each learning sample $r = 1, \ldots, R$, we used the joint and landmark models. For a given landmark time s and a given horizon w, predictions were computed on the same subjects $i = 1, \ldots, N_s$, where N_s is the number of subjects at risk at time s. Because this is a simulation study, the true cumulative incidence $\pi_i^{k,r}(s,w;\theta)$ is known. It is also estimated for each method with $\widehat{\pi}_i^{k,r}(s,w;\widehat{\theta})$.

To compare the true and the predicted conditional probabilities, a first tool is the difference of mean absolute percentage error which directly compares the bias of prediction. It is defined as:

$$\text{MAPE}^{k,r}_{(1)}(s,w) - \text{MAPE}^{k,r}_{(2)}(s,w), \quad \text{where}$$

$$\text{MAPE}^{k,r}_{(1)}(s,w) = \sum_{i=1}^{N_s} \frac{1}{N_s} \frac{\left| \pi_i^{k,r}(s,w;\theta) - \widehat{\pi}_i^{k,r,(1)}(s,w;\widehat{\theta}^{(1)}) \right|}{\pi_i^{k,r}(s,w;\theta)}$$

for the r^{th} replicate. We are able to use graphical plots such as boxplots to see the distribution of this estimator over the R replicates.

A second tool for comparison considers the 95% coverage rate of cumulative incidence using a Monte-Carlo technique. Boxplots are also used to describe the estimator distribution over the R replicates.

4 Expected results

Individualized predictions may be difficult to compute when we are confronted to a dynamic information such as repeated measurements of biomarkers. Two main approaches have been developed to estimate these individualized dynamic predictions. The joint model explores the complete relationship between the longitudinal process and the survival process. However the PH assumption and the hard computational inference may be obstacles to the use of this model. The landmark CS PH models have been proposed in this sense, by selecting only the subjects at risk at the landmark time point and by censoring administratively the events at the end of the prediction window. Observed or predicted markers dynamics are introduced. Such models are easy to use in practice and reduce the possible bias linked to the PH assumption, but do not explore the complete correlation between markers and time-to-event data and may give less efficient estimators. The dynamic pseudo-observations are freed from the PH assumption, consider a more complete information and ensure a direct estimation of the probabilities. But they assume a specification of the link function, incorporate also a function of the biomarkers histories, and may give less efficient estimators than the joint model.

The simulation study performed over 500 replicates should bring major informations on the pros and cons of each method to provide dynamic individual predictions.

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References

[1] Fisher, L. D. and Lin, D. Y. (1999), Time-dependent covariates in the Cox proportional hazards regression model. *Annual Review of Public Health*, 20, 145-157.

[2] Nicolaie, M. A., van Houwelingen, J. C., de Witte, T. M., and Putter, H. (2013), Dynamic Pseudo-Observations: A Robust Approach to Dynamic Prediction in Competing Risks. *Biometrics*, 69(4), 1043-1052.
[3] Proust-Lima, C. and Blanche, P. (2015), Dynamic Predictions. In: */WileyStatsRef: Statistics Reference Online/*. John Wiley & Sons, Ltd.
[4] Rizopoulos, D. (2011), Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics*, 67(3), 819-29.
[5] van Houwelingen, H. and Putter, H. (2011), *Dynamic Prediction in Clinical Survival Analysis*. Monographs on Statistics & Applied Probab #123. Chapman & Hall/CRC, London.