Individual dynamic predictions using landmarking and joint modelling: validation of estimators and robustness assessment

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Abstract: After the diagnosis of a disease, one major objective is to predict cumulative probabilities of events such as clinical relapse or death from the individual information collected up to a prediction time, including usually biomarker repeated measurements. Several competing estimators have been proposed to calculate these individual dynamic predictions, mainly from two approaches: joint modelling and landmarking. These approaches differ by the information used, the model assumptions and the complexity of the computational procedures. It is essential to properly validate the estimators derived from joint models and landmark models, quantify their variability and compare them in order to provide key elements for the development and use of individual dynamic predictions in clinical follow-up of patients. Motivated by the prediction of two competing causes of progression of prostate cancer from the history of prostate-specific antigen, we conducted an in-depth simulation study to validate and compare the dynamic predictions derived from these two methods. Specifically, we formally defined the quantity to estimate and its estimators, proposed techniques to assess the uncertainty around predictions and validated them. We also compared the individual dynamic predictions derived from joint models and landmark models in terms of prediction error, discriminatory power, efficiency and robustness to model assumptions. We show that these prediction tools should be handled with care, in particular by properly specifying models and estimators.

Keywords: Competing risks; Dynamic Prediction; Landmarking; Joint modelling; Prediction accuracy; Robustness.
1 Introduction

After diagnosis and subsequent treatment of cancer, patients are typically monitored via repeated measurements of biomarkers. For example, in patients with prostate cancer treated by radiotherapy, the Prostate Specific Antigen (PSA) is measured routinely. Precisely predicting the individualized probabilities of events such as clinical relapse for these patients from their individual information collected until the prediction time has become a central issue (Goldstein et al., 2017; Proust-Lima and Taylor, 2009). Personalized treatment strategies can indeed be proposed according to the updated individual probabilities (Sène et al., 2016), or the planning of the next biomarker measurement can be optimized (Rizopoulos et al., 2015).

Two main approaches have been proposed to compute individual dynamic predictions: joint modelling and landmarking. These differ in the used information, the model assumptions and the complexity of computational procedures.

The joint modelling (JM) approach simultaneously models the repeated measurements of the biomarker (e.g., using a linear mixed model in standard JM) and the time-to-event data (e.g., using a proportional hazards model in standard JM) by linking them using a function of shared random effects (Tsiatis and Davidian, 2004). This approach has the advantage of taking into account the endogenous nature of biomarkers (Kalbfleisch and Prentice, 2011), of only requiring one model estimation for any prediction time, and of modelling the progression of the disease as a whole, which makes it very popular. But it is often based on simplifying assumptions (e.g., proportional hazards, number of random effects) and may be complex to estimate, so that it should be handled carefully and can remain difficult to apply in practice.

The landmarking approach consists of adjusting standard survival models considering only the subsample of subjects still at risk at the prediction time and the longitudinal information collected up to the prediction time (Van Houwelingen, 2007). These models induce significantly less numerical problems and reduce the possible estimation bias related to the proportional hazards assumption. However, as they do not fully explore the collected information during the follow-up and the correlation between the marker and the time of event, they can produce sub-efficient estimators (Huang et al., 2016) and are only an approximation of the (correct) joint estimator. Indeed, as supported in Suresh et al. (2017) they do not satisfy the consistency condition introduced by Jewell and Nielsen (1993) which stipulates that the hazard function and the marker dynamics must be linked at all time points to give consistent dynamic predictions. In the presence of longitudinal biomarkers, the landmark approach can result in several models. Most of the time a survival model (cause-specific proportional hazards) is adjusted on the last observed value of the biomarker. In addition to truncation at the prediction time, censoring is administered at the end of the prediction window to reduce possible bias related to the proportionality of hazards. But this approach does not take into account fluctuations of the biomarker, its observation at discrete times and measurement errors. To circumvent this problem, the last observed value of the biomarker may be replaced by its predicted value at the prediction time (obtained from a linear mixed model) (Rizopoulos et al., 2017; Sweeting et al., 2016). This two-step model considers the same method of truncation and administrative censoring. It takes into account all the collected information of the biomarker until the prediction time for the subjects at risk. But the event probabilities must be deduced by approximation and the model is not completely freed of the proportional hazards assumption. In the context of competing risks, rather than using a cause-specific proportional hazards model, the conditional probabilities of event can be directly estimated by a dynamic pseudo-observations approach (Nicolaie et al., 2013). This approach directly models the conditional probabilities of event and is freed from the proportionality hazards assumption. By considering the predicted value of the biomarker at
the prediction time as a covariate, it also takes into account the trajectory of the biomarker. But this approach requires the specification of a link function and can still provide less efficient estimators than the joint model. Note that, in these landmark models as well as in joint models, any function of the biomarker trajectory parameters can be used instead of the biomarker predicted value at the prediction time.

In addition, although of central interest in many recent works, estimators of dynamic predictions and of their uncertainty were never formally validated while there exist several competing proposals in the joint modelling framework (Maziarz et al., 2017; Rizopoulos, 2011; Sène et al., 2016). In the landmarking approach with longitudinal biomarkers, some estimators were also proposed but not validated, and no concept of uncertainty was introduced (Proust-Lima and Taylor, 2009; Rizopoulos et al., 2017; Sweeting et al., 2016).

Motivated by the prediction of competing progressions of prostate cancer from the PSA history, we first proposed estimators of individual dynamic predictions and of their uncertainty with 95% confidence intervals for the joint and the landmark approaches, and we validated them in a simulation study. We then compared the predictive accuracy of the models under several scenarios to explore their robustness to misspecification.

The rest of the paper is organized as follows. Section 2 introduces the prediction models and the derived estimators of dynamic predictions and of their uncertainty. Section 3 briefly describes the motivating data. The simulation studies are carried out in Section 4 for validating the proposed estimators and comparing them in terms of prediction accuracy. The paper ends with a discussion in Section 5.

2 Prediction models

Let us consider the competing risks setting where the subjects are at risk to experience $K$ competing events. For each subject $i$ ($i = 1, ..., N$), we denote $T_i$ the earliest time-to-event and $\delta_i = k$ the cause of event, with $k \in 1, ..., K$. In the presence of censoring, we observe the event time $T_i^\dagger = \min(T_i, C_i)$ with $C_i$ the censoring time, and the indicator of event becomes $\Delta_i = \delta_i \cdot 1\{T_i \leq C_i\}$ with $1$ the indicator function. We also observe $X_i$ the (possibly exogenous time-dependent) covariates collected until the event time, and $Y_i$ an endogenous longitudinal marker measured repeatedly with $Y_i(t_{ij})$ the observed measure at time $t_{ij}$ for $j = 1, ..., n_i$ and $t_{i0} \leq T_i^\dagger$. In the following, $X_i(s)$ denotes the history of $X_i$ until time $s$, $Y_i(s) = \{Y_i(t_{ij}) : 0 \leq t_{ij} \leq s, j = 1, ..., n_i(s)\}$ denotes the history of the marker until $s$, and the model formulations assume a longitudinal marker with Gaussian distribution.

2.1 Definition of individual dynamic prediction

In this paper we are interested in the individual cumulative probability of the event of cause $k$ between times $s$ and $s+w$ for a new subject $\star$, with $s$ the landmark time (or prediction time) and $w$ the horizon. This probability, also called landmark specific cumulative incidence of cause $k$ is defined as

$$\pi^k_\star(s, w) = \Pr(s < T_\star \leq s+w, \delta_\star = k|T_\star > s, Y_\star(s), X_\star(s)).$$

(1)

We focus on several parametric models that express this quantity of interest as a function of a vector of parameters $\theta$:

$$\pi^k_\star(s, w; \theta) = \Pr(s < T_\star \leq s+w, \delta_\star = k|T_\star > s, Y_\star(s), X_\star(s); \theta).$$

(2)

In practice, $\theta$ is unknown and is replaced by $\hat{\theta}$, its estimate from the considered observed data in the learning sample $I$. In the remainder of the manuscript, this subscript is omitted for the sake of simplicity, and the estimated quantity of interest is denoted $\hat{\pi}^k_\star(s, w; \hat{\theta})$. 

Two kinds of variability of $\hat{\pi}_k^\star(s, w; \hat{\theta})$ can be defined to quantify the uncertainty of this estimator. The first one consists in considering the variance of $\hat{\pi}_k^\star(s, w; \hat{\theta})$ conditional to $T_\star > s$, $Y_\star(s)$ and $X_\star(s)$, with respect to the estimated parameters $\hat{\theta}$ (Król et al., 2016; Maziarz et al., 2017; Proust-Lima and Taylor, 2009; Taylor et al., 2013). The second one consists in considering the variance as only conditional to $T_\star > s$ and $X_\star(s)$ by taking into account both the variability of the estimated parameters $\hat{\theta}$ and the variability of $Y_\star(s)$ due to measurement errors in the marker’s observations (Rizopoulos, 2011; Yu et al., 2008). In this contribution, we propose techniques to quantify both sources of uncertainty although simulations focus only on the former.

### 2.2 Joint model

#### 2.2.1 Model formulation

The joint model considers the full collected information $I = \{(T_i^1, \Delta_i, Y_i(T_i^1), X_i(T_i^1));$ $i = 1, \ldots, N\}$. It is decomposed into two sub-models linked by a function of a shared latent structure. The most popular joint model (Rizopoulos, 2012) links a linear mixed model for the repeated measurements of the marker and a cause-specific proportional hazards model for the specific hazard of each cause of event $k$ using a function of shared random effects:

$$
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= X_i^f(t)^\top \beta + Z_i(t)^\top b_i + \epsilon_i(t), \\
\lambda_i^k(t) &= \lambda_{i,0}(t) \exp \left\{ X_i^E(t)^\top \gamma_k + W_i(t)b_i; \beta \right\} \eta_k,
\end{align*}
$$

where $t > 0$ and $\lambda_i^k(t)$ denotes the hazard function of cause $k$ at time $t$, with $k = 1, \ldots, K$. In the longitudinal sub-part, $X_i^f(t)$ and $Z_i(t)$ denote vectors of covariates (possibly time-dependent) associated respectively with the vector of fixed effects $\beta$ and the vector of random effects $b_i, b_i \sim N_d(0, D)$. The error term is $\epsilon_i(t) \sim N(0, \sigma^2)$: the random effects and error terms are independent. In the survival sub-part, $\lambda_{i,0}(t)$ denotes the parametric baseline hazard of cause $k$ at time $t$. The vector of covariates $X_i^E(t)$ is associated with the vector of coefficients $\gamma_k$. Note that for simplicity, we do not consider any exogenous time-dependent prognostic variable although this is not a requirement. The (possibly multivariate) function $W_i, (t;b_i; \beta)$ denotes the function of dependence between the longitudinal process and the hazard of event of cause $k$, such as for example the unbiased current level of the marker $m_i(t)$, the unbiased current slope $\partial m_i(t) / \partial t$, or both ($m_i(t), \partial m_i(t) / \partial t)^\top$.

The joint model assumes proportional hazards (PH) between levels of covariates.

It can be estimated in the maximum likelihood framework by using the independence between the longitudinal process $Y_i(T_i^1)$ and the survival process $(T_i^1, \Delta_i)$ conditionally on the random effects $b_i$. The likelihood involves integrals over the random effects and time that have to be numerically solved, usually using Gaussian quadratures. Note that the number of quadrature points has to be chosen carefully to provide correct inference (Ferrer et al., 2016).

#### 2.2.2 Cumulative incidence estimator

Once the model is estimated, the vector of parameters $\hat{\theta}$ and its variance matrix $\hat{V(\hat{\theta})}$ are obtained and we are able to compute for each new subject $\bar{s}$ the predicted conditional cumulative incidence of cause
\( k \) for all the possible horizons \( w \) and landmark times \( s \):

\[
\hat{\pi}_k^*(s, w; \hat{\theta}) = \int_{\mathbb{R}^q} \Pr(s < T^* \leq s + w, \delta^* = k | T^* > s, Y_*(s), X_*(s); \hat{\theta}) f(b_* | T^* > s, Y_*(s), X_*(s); \hat{\theta}) \, db_*.
\] (3)

Another estimator of (2) (faster but less accurate) can be obtained by approximating the integral over the random effect distribution by the integrand computed at the modal point. This Laplace approximation of (3) will be called conditional estimator. The complete formulas of the marginal and conditional estimators are detailed in Section 1.1 of the Supplementary Material.

To validate our estimator in the simulation study, we mainly considered its variance as conditional to \( T^* > s \) and \( Y_*(s) \). The corresponding 95\% confidence interval of (3) can be obtained using parametric bootstrap techniques. The procedure is realized as follows:

Consider a large \( L \); for each \( l = 1, \ldots, L \),

1. generate \( \hat{\theta}^{(l)} \sim \mathcal{N}(\hat{\theta}, \sqrt{\hat{\sigma}}) \);

2. compute

\[
\hat{\pi}^{k(l)}_*(s, w; \hat{\theta}^{(l)}) = \int_{\mathbb{R}^q} \Pr(s < T^* \leq s + w, \delta^* = k | T^* > s, Y_*(s), X_*(s); \hat{\theta}^{(l)}) f(b_* | T^* > s, Y_*(s), X_*(s); \hat{\theta}^{(l)}) \, db_*.
\]

Compute the 95\% confidence interval from the 2.5th and 97.5th percentiles of \( \left( \hat{\pi}^{k(l)}_*(s, w; \hat{\theta}^{(l)}) \right) \) for each \( l \).

The same procedure can be used with the conditional estimator of the probability by replacing the expression in step 2.

The additional variability due to measurement errors in the observations \( Y_*(s) \) can be easily taken into account by adding a step to this algorithm which draws marker measurements from their estimated distribution:

1bis. generate \( Y_*^{(l)}(s) = \{ Y_*^{(l)}(t_{*j}) : 0 \leq t_{*j} \leq s, j = 1, \ldots, n_*(s) \} \)

with \( Y_*^{(l)}(t_{*j}) \sim \mathcal{N}(X_*^{(l)}(t_{*j}) \hat{\beta} + Z_*^{(l)}(t_{*j}) \hat{b}_*, \hat{\sigma}^2) \); \( \hat{b}_* = \mathbb{E}(b_* | Y_*(s), X_*(s); \hat{\theta}), \hat{\beta} \) and \( \hat{\sigma} \) subsets of \( \hat{\theta} \).

The l-th bootstrapped estimator is then obtained by replacing \( Y_*(s) \) by \( Y_*^{(l)}(s) \) in step 2.

2.3 Landmark cause-specific proportional hazards model

An alternative to joint models is landmark models which only consider subjects at risk at a landmark time \( s \) and the longitudinal information \( \{ Y(s), X(s) \} \) collected until \( s \). When considering PH landmark models, administrative censoring is applied at the end of the prediction window \( s + w \) in order to reduce the possible bias entailed by a violation of the PH assumption. The considered information becomes \( I = \{ (\xi_i(s, w), \Psi_i(s, w), Y_i(s), X_i(s)) : i = 1, \ldots, N \} \), with \( \xi_i(s, w) = \min(T_i^+, s + w) \), \( \Psi_i(s, w) = \Delta_i \cdot 1 \{ s < T_i \leq s + w \} \) and \( N^i(s) = \sum_{i=1}^N 1 \{ T_i^+ > s \} \).

2.3.1 Model formulation

The landmark cause-specific (CS) proportional hazards (PH) model is defined by
\[ \lambda^*_k(t) = \lambda_{k,0}(t) \exp \{ X^E_{i,t} \gamma_k + W_{k,i}(s)^T \eta_k \}, \]

where \( t > s \), \( \lambda_{k,0}(\cdot) \) is an unspecified cause-specific baseline hazard function and \( W_{k,i}(s) \) is a multivariate function that depicts the dynamics of the marker extrapolated at time \( s \). The model is estimated by maximizing the Cox partial likelihood (Cox, 1972) for each considered pair of landmark and horizon times. Note that for the sake of clarity, we did not use a subscript \( s, w \) for the model parameters although they are different for each \( (s, w) \).

To take into account the information of the marker before the landmark time \( s \), one can consider the last observed value only, i.e. \( W_{k,i}(s) = Y_i(t_{m.(s)}) \). However, this technique, called “naive landmark model” assumes that the marker is measured without error and considers neither the whole trajectory of the marker until \( s \) nor the subject-specific gap between \( t_{m.(s)} \) and \( s \).

A better alternative is to deduce the value of \( W_{k,i}(s) \) at time \( s \) from a linear mixed model estimated on the marker measurements collected until \( s \) in subjects at risk at \( s \). This technique, called the “two-stage landmark model” considers \( W_{k,i}(s) = \hat{W}_{k,i}(s)\hat{b}; \hat{\beta} \), where \( \hat{\beta} \) is the vector of estimated fixed effects and \( \hat{b}_i = \mathbb{E}(b_i|Y_i(s), X_i; \hat{\theta}) = \hat{D}_i^T \hat{V}_i^{-1}(Y_i - X_i^T \hat{\beta}) \) is the vector of empirical Bayes estimates of the individual random effects, with \( \hat{V}_i = Z_i \hat{D}_i^T + \sigma^2 I_{n_i(s)} \). Here \( X_i^T \) and \( Z_i \) are the matrices of covariates with respectively the row vectors \( X^T_{i,j}(t_{i}) \) and \( Z_{i,j}(t_{i}) \), and the column vector \( Y_i \) is with elements \( Y_{ij} \), for \( j = 1, \ldots, n_i(s) \). \( I \) is the identity matrix.

### 2.3.2 Cumulative incidence estimator

With the two-stage approach, the predicted conditional cumulative incidence of cause \( k \) for subject \( \ast \) is

\[
\hat{\Lambda}^*_k(s, w; \hat{\theta}) = \Pr(s < T_\ast \leq s + w, \delta_\ast = k|T_\ast > s, X_\ast(s), \hat{b}_\ast; \hat{\theta}),
\]

where \( \hat{\theta} \) is the vector of estimated parameters (with associated estimated variance \( \hat{V}(\hat{\theta}) \)), and \( \hat{b}_\ast = \mathbb{E}(b_\ast|Y_\ast(s), X_\ast(s); \hat{\theta}) \).

To estimate valid 95\% confidence intervals, it is necessary to take into account the variability due to the parameter and baseline hazard estimates. The same parametric bootstrap technique as described for the joint model can be used for the parameter estimates but it can’t be applied for the baseline hazard estimates. The unspecified cumulative baseline hazard \( \Lambda_{k,0}(t) = \int_s^t \lambda_{k,0}(u) \, du \) is estimated using the Breslow’s estimator (Breslow, 1972),

\[
\hat{\Lambda}_{k,0}(t) = \int_s^t \hat{\Pi}_k(\hat{\theta}, u)^{-1} \, dJ_k(u) \quad \text{where} \quad \hat{\Pi}_k(\hat{\theta}, u) = \frac{1}{N^k(s)} \sum_{i=1}^{N^k(s)} \mathbbm{1}(\xi_{i}(s, w) \geq u) \exp \{ X^E_{i,s} \gamma_k + \hat{W}_{k,i}(s)^T \hat{\eta}_k \} \text{ and } J_k(u) = \frac{1}{N^k(s)} \sum_{i=1}^{N^k(s)} \mathbbm{1}(\xi_{i}(s, w) \leq u, \Psi_{i}(s, w) = k). \]

We propose a procedure that combines parametric bootstrap to take into account the variability associated to \( \hat{\theta} \) and perturbation-resampling methods, inspired by Sinnott and Cai (2016), to take into account the variability associated to \( \hat{\Lambda}_{k,0}(\cdot) \).

This technique, which also avoids hard computational cost, is validated in the simulation study in Section 4.1. The full procedure is realized as follows:
For each bootstrap sample $l = 1, \ldots, L$, where $L$ is large enough:

1. generate $\tilde{\theta}(l) \sim N(\hat{\theta}, V(\hat{\theta}))$ and deduce $\tilde{b}(l) = \mathbb{E}(b|Y_i(s), X_i(s); \tilde{\theta}(l))$;

2. for each subject $i \in 1, \ldots, N^l(s)$ of the learning sample, generate $v_i(l) \sim 4 \cdot \text{Beta}(1/2, 3/2)$;

3. compute $\tilde{\Lambda}_{k,i}^{(l)}(t) = \int_s^t \tilde{\Pi}_k^{(l)}(\tilde{\theta}(l), u)^{-1} \mathbf{1}\{\xi_i(s, w) \geq u\} \exp\{X_i^E \tau_k + \tilde{W}_{k,i}(s; \tilde{\theta}(l), \tilde{b}(l)) \tau_k \} \text{d}u$ with $\tilde{\Pi}_k^{(l)}(\tilde{\theta}(l), u) = \frac{1}{N^l(s)} \sum_{i=1}^{N^l(s)} v_i(l) \mathbf{1}\{\xi_i(s, w) \geq u\} \exp\{X_i^E \tau_k + \tilde{W}_{k,i}(s; \tilde{\theta}(l), \tilde{b}(l)) \tau_k \}$ and $\tilde{F}_k(l) = \frac{1}{N^l(s)} \sum_{i=1}^{N^l(s)} v_i(l) \mathbf{1}\{\xi_i(s, w) \leq u\}$, $\Psi_i(s, w) = k$;

4. for each subject $\star$ of the validation sample, deduce $\tilde{\pi}_k^{(l)}(s, w; \tilde{\theta}(l)) = f(\{\tilde{\Lambda}_{k,i}^{(l)}(u), s < u \leq s + w; k = 1, \ldots, K\}, \tilde{\theta}(l), \tilde{b}(l))$, where $f(\cdot)$ is a function specified in Section 1.4 of the Supplementary Material.

Compute the 95% confidence interval from the 2.5th and 97.5th percentiles of $\{\tilde{\pi}_k^{(l)}(s, w; \tilde{\theta}(l)); l = 1, \ldots, L\}$.

Similarly as in joint models, additional uncertainty on the individual marker measurements can be considered by adding a step 1.bis to perturb the individual marker’s observations.

Using a naive approach, the predicted conditional cumulative incidence of cause $k$ for subject $\star$ is

$$\tilde{\pi}_k(s, w; \hat{\theta}) = \Pr(s < T_\star \leq s + w, \delta_\star = k | T_\star > s, \{X_{E,i,k}^E; k = 1, \ldots, K\}, Y_i(t_{n_i(s)}; \hat{\theta}),$$

and the same technique combining parametric bootstrap and perturbation-resampling can be used to obtain 95% confidence intervals. Note however that using the naive approach, the variance of $\tilde{\pi}_k(s, w; \hat{\theta})$ necessarily neglects the variability due to the measurement errors in the marker measurements.

### 2.4 Landmark model based on pseudo-observations

Cause-specific hazard models rely on the PH assumption and require the computation of integrals over time in the individual cumulative incidences. To avoid these issues, some authors have focused on the direct modelling of the individual cumulative incidences with for example the Fine-Gray model (Fine and Gray, 1999), the binomial regression models (Scheike et al., 2008) or the pseudo-value approach (Andersen and Pohar Perme, 2010). The latter is developed here. The pseudo-observation approach does not require the PH assumption, hence the considered information is $I = \{(T_i^\top, \Delta_i, Y_i(s), X_i(s)); i = 1, \ldots, N^l(s)\}$.

#### 2.4.1 Model formulation

For subjects at risk at time $s$, we are interested in the expectation of $\mu_i^*(s, w) = \mathbb{I}(T_i \leq s + w, \delta_i = k)$. In presence of censoring, this quantity is not always observable. Thus the idea is to define the dynamic jackknife pseudo-observation (Nicolaie et al., 2013) of the non-parametric estimator of $\tilde{\pi}_k(s, w)$:

$$\tilde{\mu}_k(s, w) = N^l(s) \tilde{F}_k(s, w) - (N^l(s) - 1) \tilde{F}_{k,l}(s, w),$$

where $N^l(s)$ is the number of subjects at risk at $s$ and $\tilde{F}_{k,l}(s, w)$ is the Aalen-Johansen estimate of $\pi_k(s, w)$ (Andersen et al., 1993).

To include the dynamic information on the marker until $s$, the same two-stage approach as defined in Section 2.3 can be used to deduce $\tilde{W}_{k,i}(s; \tilde{\theta}; \hat{\beta})$ in those still at risk in $s$. The pseudo-observation and
the prognostic factors are then linked through a generalized linear model with link function $g$:
\[ g\left(\mathbb{E}[\hat{\mu}_i(s,w) | \mathcal{I}_i^+ > s]\right) = \gamma_{0,k} + X_{L,k}^\top \gamma_{1,k} + \tilde{W}_{k,i}(s,i;b;\tilde{\beta})^\top \eta_k. \]
The model is thus estimated using generalized estimating equations (GEE) (Andersen and Pohar Perme, 2010).

### 2.4.2 Cumulative incidence estimator

The predicted conditional cumulative incidence can directly be expressed as
\[ \tilde{\pi}^k_i(s,w;\tilde{\theta}) = \Pr(s < T_* \leq s + w, \delta_* = k|T_* > s, \mathcal{X}_*(s), \tilde{b}^*; \tilde{\theta}), \]
with $\tilde{b}^* = \mathbb{E}(b_* | \mathcal{Y}_*(s), \mathcal{X}_*(s); \tilde{\theta})$, where $\tilde{\theta}$ is the vector of estimated parameters (with associated estimated variance matrix $V(\tilde{\theta})$). For example with the clog link function $g(x) = \text{cloglog}(x) = \log(-\log(1-x))$, it can be expressed as:
\[ \tilde{\pi}^k_i(s,w;\tilde{\theta}) = 1 - \exp\left[-\exp\{\gamma_{0,k} + X_{L,k}^\top \gamma_{1,k} + \tilde{W}_{k,i}(s,i;b;\tilde{\beta})^\top \eta_k\}\right]. \]

The 95% confidence intervals of (6) may be calculated using parametric bootstrap:

Consider a large $L$; for each $l = 1, \ldots, L$,

1. generate $\tilde{\theta}^{(l)} \sim N(\tilde{\theta}, V(\tilde{\theta}))$ and deduce $\tilde{b}^{(l)}_* = \mathbb{E}(b_* | \mathcal{Y}_*(s), \mathcal{X}_*(s); \tilde{\theta}^{(l)})$;
2. compute $\tilde{b}^{(l)}_{1,i}(s,w;\tilde{\theta}^{(l)}) = \tilde{b}^{(l)}_*(s,w;\tilde{\theta}^{(l)}), \tilde{\theta}^{(l)}).

Compute the 95% confidence interval from the 2.5th and 97.5th percentiles of $[\tilde{\pi}^{k,l}_i(s,w;\tilde{\theta}^{(l)}); l = 1, \ldots, L]$.

Uncertainty from $\mathcal{Y}_*(s)$ in the variance of $\tilde{\pi}^k_i(s,w;\tilde{\theta})$ can again be accounted for by perturbing the observations $\mathcal{Y}_*(s)$ in an additional 1.bis step, as described in Section 2.3.2.

### 2.5 Implementation

The estimation of the prediction models and the computation of the derived estimators were performed in R using standard packages and extensions coded by the authors, with the JM package for the joint model, the survival package for the landmark cause-specific proportional hazards models and the pseudo and geepack packages for the landmark model based on pseudo-values. Examples of codes used for the manuscript writing can be found in Section 5 of the Supplementary Material, and detailed examples can be found at https://github.com/LoicFerrer/ for practical use.

### 3 Motivating data

The paper relies on simulation studies inspired by the data analyzed in Ferrer et al. (2016). In this study, patients ($N = 1474$) had a clinically localized prostate cancer and were treated by external beam radiotherapy. After the end of the radiotherapy, repeated measurements of the Prostate Specific Antigen (PSA) were collected until the occurrence of a clinical event defined as the recurrence of the disease (local/distant recurrence, initiation of hormonal therapy or death due to the prostate cancer) or death due to an other cause. Post-treatment PSA trajectory was mostly biphasic with a short term drop followed by a stable or slight increase (Proust-Lima et al., 2008). Several authors (Proust-Lima and Taylor, 2009; Taylor et al., 2013) showed that including these post-treatment PSA dynamics in dynamic prediction tools of disease recurrence highly reduced the prediction error.
4 Simulation studies

Two simulation studies were performed, one for the validation of the estimators (Section 4.1), and a second for their comparison and the assessment of their robustness to misspecification (Section 4.2). Both simulation studies relied on the same following design.

\( R = 500 \) learning samples of \( N = 1000 \) subjects as well as a validation sample of \( N^{\text{new}}(0) = 500 \) subjects were generated from a joint model with parameter values \( \theta_0 \) (Crowther and Lambert, 2013; Ferrer et al., 2016). The models detailed in section 2 were estimated on each learning sample \( r (r = 1, ..., R) \) and the derived estimators of cumulative incidence were computed for a given horizon \( w \) on the \( N^{\text{new}}(s) \) subjects \( (\star = 1, ..., N^{\text{new}}(s)) \) of the validation sample who did not experience any event before landmark time \( s \). The simulation design was built to validate the estimator defined in (2) and its associated variance conditional to the full set of individual observations for prediction, so that we did not resample the observed markers in the prediction sample.

For each replicate \( r \), we then compared the true generated cumulative incidence \( \pi^{\star}_k(s, w; \theta_0) = \int_{\mathbb{R}_+} \pi^{\star}_k(s, w|b_\star; \theta_0) f(b_\star | T_\star > s, Y_\star(s), X_\star(s); \theta_0) \, db_\star \) with the estimators \( \hat{\pi}^{\star}_k(s, w; \hat{\theta}) \).

4.1 Simulation study I : Validation of the estimators \( \pi^{\star}_k(s, w; \theta_0) \)

To validate the proposed estimators, we checked the distributions over the individuals of the estimated relative bias and the estimated coverage rates for \( \pi^{\star}_k(s, w; \theta_0) \). We also investigated the efficiency of the estimators with the mean relative change in the confidence interval widths.

4.1.1 Model specification

For each subject \( i \) (learning or validation sample), data were generated according to the joint model:

\[
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= \left( \beta_0 + \beta_{0,X_i} X_i + b_0 \right) + \left( \beta_1 + \beta_{1,X_i} X_i + b_1 \right) t + \epsilon_i(t), \\
\lambda_{k,i}(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_k X_i + \eta_{1,k} m_i(t) + \eta_{2,k} \frac{\delta m_i(t)}{\delta t} \right\},
\end{align*}
\]

where \( \log(\lambda_{k,0}(t)) \) is a combination of cubic B-splines with one internal knot, \( k \) is the cause of event \( (\text{Recurrence} ; \text{Death}) \); \( X_i \) is a continuous variable. The coefficients and the distribution of the covariates used for the generation data correspond to those obtained on the motivating data with \( X_i \) the PSA level before treatment initiation. They are given in Section 3.1 of the Supplementary Material.

4.1.2 Results

Due to the duration of the procedures, the simulations were run for two landmark times \( s = 1, 5 \), one horizon time \( w = 3 \) and 200 subjects randomly selected from the validation sample. \( R = 499 \) and \( R = 486 \) replicates were considered for \( s = 1 \) and \( s = 5 \) respectively, due to convergence problems in the landmark model estimation.

Figures 1a and 1b depict respectively the distribution over the subjects of the relative bias of the estimator and the coverage rates of its 95\% confidence interval both for the joint and two-stage landmark CS PH models for landmark times \( s = 1 \) and \( s = 5 \) and one horizon time \( w = 3 \). The box plots highlight the correct estimation of \( \pi^{\star}_k(s, w; \theta_0) \), except for the conditional expression from the joint model in the
earlier landmark times \((s = 1)\). This confirms that considering the modes of the distributions a posteriori of the random effects (defined in Section 1.2 of the Supplementary Material) in the conditional estimator is valid only when there is enough longitudinal information. The coverage rates which are very close to 0.95 validate the proposed 95% confidence interval computations for both approaches. Finally the comparison of the widths of the 95% confidence intervals according to the joint and two-stage landmark CS PH models (Figure 1c) confirms that the joint model estimator is much more efficient than the landmark CS PH estimator. This result was expected because the included information in the landmark models is lower than the one in the joint model.

4.2 Simulation study II: Robustness to models hypotheses

The second simulation study aimed to compare the performances of the different approaches to provide individual dynamic predictions. We relied for that on predictive accuracy and explored their robustness to the models hypotheses.

Predictive accuracy was assessed through both the Mean Squared Error of Prediction (MSEP) popularized through the Brier Score (BS) (Gerds and Schumacher, 2006) and the Area Under the ROC curve (AUC) (Heagerty et al., 2000). The former assesses both calibration and discrimination abilities of the methods while the latter only focuses on discrimination ability and as such, neglects an important aspect of predictive accuracy (Blanche et al., 2015). As in a simulation setting, we directly used the true individual prediction rather than the event indicator for the BS and did not have to deal with censoring. This lead to the computation of a standard MSEP on the validation sample:

\[
\text{MSEP}_{s,w}^k = \frac{1}{N_{\text{new}}(s)} \times \sum_{s=1}^{N_{\text{new}}(s)} \left( \hat{\pi}_{s,j}(s,w; \theta) - \pi_{s,j}(s,w; \hat{\theta}) \right)^2.
\]

For the AUC, we applied the definition adapted to the competing risks setting (Blanche et al., 2015):

\[
\text{AUC}_{s,w}^k = \text{Pr}(\hat{\pi}_{s,j}(s,w; \hat{\theta}) > \pi_{s,j}(s,w; \hat{\theta}) | \Delta_{s,j}^k(s,w) = 1, T_i > s, \Delta_{s,j}^k(s,w) = 0, T_j > s),
\]

where \(\Delta_{s,j}^k(s,w) = 1 \{s < T_i \leq s + w, \delta_i = k\} \) with \(\delta_i = k\) the cause of event; \(i\) and \(j\) are here two subjects for prediction (see Section 2.2 of the Supplementary Material for details on the AUC formulation). Note that both AUC and MSEP estimators were intrinsically model free as we did not have to deal with censoring.

We considered four scenarios: correct specification of the joint model, misspecification of the dependence function, violation of the proportional hazards assumption, and misspecification of the longitudinal trajectory of the marker. The distribution of the covariates and the coefficients used for the generation data in the four cases can be found in Section 3 of the Supplementary Material. Under each scenario, prediction models were compared two by two using boxplots of the differences in the predictive accuracy measures over the \(R\) replicates.

In the main manuscript, we present the results on MSEP and refer to the results on AUC which are detailed in Supplementary Material. For a given replicate \(r\) and a given landmark time \(s\), only models that converged were considered.

4.2.1 Case 1: Correct specification of the joint model

For the well-specified case, data generation and specification of the joint and landmark models in the estimation and prediction steps were the same as in Section 4.1.

Figure 2 shows differences of MSEP for 8 pairs of landmark and horizon times \((s = 1, 3, 5, 8\) and \(w = 1.5, 3)\). As expected, the joint model performed better than the landmark models for all the pairs \((s, w)\). Once again, the conditional estimator of the predicted probability in the joint model was much
worse than its marginal alternative in the earliest landmark times, but gave similar performances from \( s = 5 \).

[Figure 2 about here.]

When considering discriminatory power only with AUC (Figure 3 in Supplementary Material), the joint model still performed better than landmark models, especially the naive landmark model. However, no difference was highlighted between the conditional and marginal estimators suggesting a problem of calibration rather than discrimination for the conditional estimator in the earliest times. It can be noted that the convergence problems in the model estimations usually arose from insufficient considered information in landmarking.

### 4.2.2 Case 2: Misspecification of the dependence function

To investigate a misspecification of the dependence structure, we used the same generated data as in case 1 but the prediction models neglected the slope of the marker in the estimation and prediction steps. Yet the latter had a strong impact on the risk of recurrence.

The distributions over the replicates of the differences of MSEP for all the selected pairs of landmark and horizon times are depicted in Figure 3. Relative to the marginal estimator from the joint model, the other estimators behave similarly as in case 1. Mainly, the joint model remained better than the landmark models. However, neglecting the slope in the dependence structure induced a large increase in the MSEP of the marginal estimator from the joint model which is provided in each graph in Figure 3 and Figure 2; for instance, for \((s, w) = (1, 3)\), the MSEP increases from 0.323 to 1.114 when neglecting the slope in the dependence structure. This underlines the great importance of correctly specifying the dependence function in these models. The examination of AUC differences (Figure 5 in Supplementary Material) led to the same conclusions, except that the AUC under case 1 was not systematically better then the one under case 2.

[Figure 3 about here.]

### 4.2.3 Case 3: Violation of the proportional hazards assumption

The robustness of the models to a violation of the proportional hazard assumption was checked by considering an interaction with \( \log(1 + t) \) for the parameters associated with the marker dynamics in the generation model:

\[
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= (\beta_0 + \beta_{0,X}X_i + b_{0i}) + (\beta_{1,1}X_i + b_{1i}) t + \epsilon_i(t), \\
\lambda_{k}(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_kX_i + \eta_{1,k} \log(1 + t)m_i(t) + \eta_{2,k} \log(1 + t) \frac{\delta m_i(t)}{\delta t} \right\}.
\end{align*}
\]

For all the prediction models, the estimation and prediction steps did not consider this interaction with \( \log(1 + t) \).

Boxplots of the differences of MSEP over the replicates are depicted in Figure 4. Even under this strong violation of the PH assumption, the performances of the two-stage landmark and joint models remained comparable. Furthermore one can note that the pseudo-value approach was not better than the models based on proportional hazards. Again, the same conclusions can be drawn from the differences in AUC (Figure 6 in Supplementary Material).
To illustrate the behavior of each model to this misspecification, Figure 5a depicts the time-varying coefficient $\eta_{1,k} \log(1 + t)$ used in the data generation and the time-invariant parameters estimated in the joint and two-stage landmark CS PH models for one random replicate. The landmark model permitted to obtain estimated parameters closer to the generated one (except for $s = 8$ because only 8 and 13 subjects experienced the event between 8 and $8 + w$ for $w = 1.5$ and $w = 3$, respectively) but these estimates had also large variances because of the considered information which might explain the non superiority of landmark approaches to this misspecification.

4.2.4 Case 4: Misspecification of the longitudinal trajectory of the marker

The last case explored the performances of the prediction models when the longitudinal trend of the marker was misspecified. Data were generated using a joint model with a biphasic shape of the marker:

$$
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= (\beta_0 + \beta_{01}X_i + b_{01}) + (\beta_1 + \beta_{11}X_i + b_{11})((1 + t)^{-1.2} - 1) + \\
&\quad (\beta_2 + \beta_{22}X_i + b_{22}) t + \epsilon_i(t), \\
\lambda_{k}^{i}(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_k X_i + \eta_{1,k} m_i(t) + \eta_{2,k} \frac{\delta m_i(t)}{\delta t} \right\}.
\end{align*}
$$

For the estimation of the predicted probabilities of event using joint and two-stage landmark models, we considered a linear trajectory over time for the marker. As shown in Figure 5b, the degree of misspecification of the longitudinal marker trend was severe but it was made on purpose to clearly show the impact of such misspecification.

Figure 6 displays the boxplots of differences in MSEP for the 8 pairs $(s, w)$. The landmark models performed much better than the joint models for landmark times $s = 1, 3, 5$; at landmark time $s = 8$, performances of joint and landmark models became roughly similar. Such result was expected. The joint model incorrectly assumed a linear trajectory for the marker on the whole follow-up while the landmark model, by considering only the longitudinal information collected until $s$, assumed a linear trajectory only until $s$ which was more realistic at earliest landmark times even if still far from being well specified. The same conclusions can be drawn from the examination of the AUC differences (Figure 4 in Supplementary Material), except that even at the latest landmark time (8 years), the landmark models remained much more discriminatory than the joint model.

Figure 5b illustrates the differences in the predicted current values of the marker used in the estimated models to predict the risk of recurrence for an hypothetical subject $\star$ with $b_\star = 0$ and $X_\star = 2.04$ in a randomly selected replication. The difference between the predicted levels of the marker are very different at the earliest landmark times between the joint and landmark models while they get closer at $s = 8$. Moreover the joint model actually uses the predicted current level of the marker rather than the predicted marker value in $s$ which does not necessarily follows the generated path.

To explore whether such differences were due to the severe misspecification of our example, we considered a second longitudinal marker trend in Section 2.1 of the Supplementary Material. This supplementary case considered a small degree of misspecification of the longitudinal marker by considering...
some slight fluctuations with splines in the generation model compared to the well-specified case 1. Although slightly misspecified, the superiority of joint model over landmark approaches previously found in case 1 almost completely disappeared. This confirmed the high sensitivity to any kind of misspecification of the marker trajectory in the joint model.

5 Discussion

With the development of personalized medicine, it is important to provide valid and powerful tools to clinicians for the computation of individual probabilities of specific events such as landmark conditional cumulative incidences. These predictions are expected to be used in clinical practice, notably to adapt individual strategies of treatment or to plan the patient-specific optimal screening time in clinical trials.

Several authors (Maziarz et al., 2017; Rizopoulos, 2011) already proposed estimators of the individual landmark conditional cumulative incidence \( \pi_k^*(s, w) \), but surprisingly none was formally validated using simulation studies. Our first objective was thus to formally define the quantity of interest \( \pi_k^*(s, w) \) and provide estimators (along with 95% confidence interval) both for the landmarking and the joint modelling approaches and properly validate them by comparing generated and estimated expressions of \( \pi_k^*(s, w) \). The computation of the generated quantity of interest was not obvious because it involved an integral over the latent structure shared by the longitudinal process and the survival process, the data being generated from a joint model. Note that in some papers, such quantity of interest is not correctly defined (Barrett and Su, 2017; Rizopoulos et al., 2017; Sweeting et al., 2016). The marginal estimator from the joint model obtained very good performance in general whereas it was showed that the conditional estimator from the joint model necessitates sufficient individual longitudinal information collected until the prediction time.

Quantification of the uncertainty around individual predictions is essential for the decision making in clinical practice. In the landmark approach no solution was ever proposed, and a vagueness prevailed in the joint modelling literature with some definitions conditional on the observations (Król et al., 2016; Maziarz et al., 2017; Proust-Lima and Taylor, 2009; Taylor et al., 2013), others taking into account the measurement error of observations either along with the population parameter uncertainty (Rizopoulos, 2011; Yu et al., 2008) or without (Desmée et al., 2017), and finally many skipping the uncertainty issue as in landmarking (Proust-Lima and Taylor, 2009; Rizopoulos et al., 2017; Sweeting et al., 2016). We thus introduced two definitions of uncertainty (conditioned or not on the observations) and proposed corresponding Monte Carlo methods to compute them in a unified manner for joint and landmark models. Compared to the joint model, the estimator based on the two-stage landmark cause-specific proportional hazards model confirmed its expected poor efficiency, with wide confidence intervals when only a few subjects experienced the event in the prediction window. Note that, although we chose to validate the estimators based on the confidence interval conditioned on the observations (using the corresponding adequate simulation setting), it would appear more natural to also account for the error of measurement of the biomarker history when providing confidence bands for individual follow-up.

Our second objective was to properly compare the landmark models and the joint model through several cases of well- and mis-specification. Indeed, a series of papers showed comparisons of prediction models in dynamic predictions (Goldstein et al., 2017; Huang et al., 2016; Sweeting et al., 2016) but none of them evaluated their robustness to misspecifications although most proposed methods were parametric. To our knowledge, only one contribution explored the problem of misspecification of prediction models (only longitudinal trajectory and functional dependency) very recently in a small simulation.
study and concluded to the superiority of joint models approach over landmark models (Rizopoulos et al., 2017).

In our extensive simulation study, we found that in the case of correctly specified model, the joint model performed better than the landmark models, as expected. In the case of misspecification of the dependence structure between the longitudinal process and the survival process, the difference of performances between approaches did not change as also concluded by Rizopoulos et al. (2017). But more importantly, the performance of misspecified models was much worse in terms of prediction error. Regarding the PH assumption, the two landmark models we proposed better dealt with this assumption than the joint model: dynamic pseudo-values did not require the PH assumption at all, and our cause-specific hazards landmark models limited the PH assumption to the prediction window with an administrative censoring at the end of it. Yet, the impact of PH assumption violation on the estimators derived from the joint model remained limited, suggesting that the violation of the PH assumption should be extreme to entail a tangible impact on the estimated cumulative incidences in the joint model. Finally, we showed that the correct specification of the marker trajectory was essential to provide good predictions with joint models (and with landmark models to a much lesser extent). We demonstrated the major loss of performance of the joint model in a severe case of misspecification to illustrate the limit but we also found in Supplementary Material that even a slight misspecification of the trajectory (usually considered as acceptable) impacted the prediction error of the models mainly, and eliminated for example the gain of using the joint model over the landmark model at shorter landmark times or when the horizon time increased. The previous simulation study also suggested this lack of robustness (Rizopoulos et al., 2017) although not emphasized.

As usual in prediction model development, comparisons were made in terms of both Mean Square Error of Prediction which measures a trade-off between calibration and discrimination, and Area Under the ROC Curve which only targets discriminatory power. With the perspective in mind of providing quantified individual predictions, we mostly relied on the prediction error to assess both calibration and discrimination even though most conclusions were also drawn from AUC examinations, yet sometimes to a lesser extent probably explained by the lesser sensitivity of AUC (Pencina et al., 2008) and the possibly preserved discriminatory power in the presence of worse calibration.

To conclude with recommendations, we emphasize the need to carefully define the quantity of interest, its estimator and the type of associated uncertainty. The several cases of misspecification warned us on the necessity to precisely specify the dependence structure between the longitudinal marker dynamics and the risk of event. Finally, the specification of the longitudinal marker trend should be studied with extreme care, especially when using joint modelling. Researchers should be warned that the use of sophisticated methods such as the joint models may allow obtaining accurate and efficient estimators only when they are correctly specified. Otherwise, estimators might be off the mark. Landmark models seem less sensitive to the misspecification of the longitudinal marker trajectory but are as sensitive as joint models regarding the dependence structure. In addition, they provide considerably less efficient estimators and may induce convergence problems, notably when the landmark time increases and thus the considered information is too poor.

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**Supplementary Materials**

A Web Appendix may be found in the source package of this article on arXiv. Detailed examples of the code can be found at https://github.com/LoicFerrer for practical use.

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(a) Evaluation of the estimators: distribution over the individuals $\star = 1, \ldots, N(s)$ of the relative bias (RB, in %). The dashed line represents the 0.

(b) Evaluation of the confidence intervals: distribution over the individuals $\star = 1, \ldots, 200$ of the coverage rates (CR) for the 95% confidence intervals of $\pi_{\mathcal{R}}^\mathcal{C}(s, w; \theta)$. The dashed line represents the 0.95.

(c) Evaluation of the estimator efficiency: distribution over the individuals $\star = 1, \ldots, 200$ of the mean relative changes ($\overline{\mathcal{R}C}$, in %) of the 95% confidence interval (CI) widths. The dashed line represents the 0.

Figure 1 – Evaluation of the estimators in terms of relative bias (a), coverage rates (b) and mean relative changes of the confidence intervals widths (c). Considered are the marginal estimator and the conditional estimator from the joint model (denoted JM-marg and JM-cond, respectively) and the estimator based on the two-stage cause-specific landmark model (denoted 2s-LM-PH).
Figure 2 – Boxplots of the differences ($\times 1000$) of Mean Square Error of Prediction (MSEP) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of correct specification of the joint model (case 1). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 499, 494, 486, 389$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. \( \text{ref} \) denotes the mean MSEP ($\times 1000$) using the marginal estimator from the joint model for each $(s, w)$. $N^\dagger(s)$ is the mean number of subjects at risk at $s$ and $D_{\text{Rec}}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

$\begin{align*}
N^\dagger(0) &= 1000 \\
D_{\text{Rec}}(0, \infty) &= 249 \\
N^\dagger(1) &= 947 \\
D_{\text{Rec}}(1, 1.5) &= 66 \\
D_{\text{Rec}}(1, 3) &= 123 \\
D_{\text{Rec}}(1, \infty) &= 206 \\
N^\dagger(3) &= 699 \\
D_{\text{Rec}}(3, 1.5) &= 52 \\
D_{\text{Rec}}(3, 3) &= 86 \\
D_{\text{Rec}}(3, \infty) &= 120 \\
N^\dagger(5) &= 482 \\
D_{\text{Rec}}(5, 1.5) &= 29 \\
D_{\text{Rec}}(5, 3) &= 43 \\
D_{\text{Rec}}(5, \infty) &= 54 \\
N^\dagger(8) &= 253 \\
D_{\text{Rec}}(8, 1.5) &= 6 \\
D_{\text{Rec}}(8, 3) &= 9 \\
D_{\text{Rec}}(8, \infty) &= 11
\end{align*}$
Figure 3 – Boxplots of the differences (×1000) of Mean Square Error of Prediction (MSEP) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of misspecification of the dependence function (case 2). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over \( R = 499, 498, 497, 428 \) replicates for 4 landmark times \( s = 1, 3, 5, 8 \) respectively, with 2 considered horizons \( w = 1.5 \) and \( w = 3 \). \( \bar{ref} \) denotes the mean MSEP (×1000) using the marginal estimator from the joint model for each \((s, w)\). \( \overline{N}'(s) \) is the mean number of subjects at risk at \( s \) and \( \overline{D}_{Rec}(s, w) \) is the mean number of recurrences occurred between \( s \) and \( s + w \).
Figure 4 – Boxplots of the differences (×1000) of Mean Square Error of Prediction (MSEP) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of substantial violation of the PH assumption (case 3). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over 485, 326, 294, 188 replicates for 4 landmark times s = 1, 3, 5, 8 respectively, with 2 considered horizons w = 1.5 and w = 3. ref denotes the mean MSEP (×1000) using the marginal estimator from the joint model for each (s, w). N(0) is the mean number of subjects at risk at s and DRec(s, w) is the mean number of recurrences occurred between s and s + w.
Figure 5 – Illustrative examples of the model behaviors on a randomly selected replicate for misspecified cases 3 and 4.
Figure 6 – Boxplots of the differences ($\times 1000$) of Mean Square Error of Prediction (MSEP) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of substantial misspecification of the longitudinal marker trajectory (case 4). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 500, 496, 476, 357$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. ref denotes the mean MSEP ($\times 1000$) using the marginal estimator from the joint model for each $(s, w)$. $N'(s)$ is the mean number of subjects at risk at $s$ and $D_{Rec}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

| $s$ | $w = 1.5$ | $w = 3$ |
|-----|-----------|-----------|
| 1   | ref = 2.329 | ref = 5.041 |
| 3   | ref = 11.870 | ref = 26.621 |
| 5   | ref = 10.644 | ref = 21.812 |
| 8   | ref = 3.030 | ref = 6.508 |

$N'(0) = 1000$
$D_{Rec}(0, \infty) = 249$

$N'(1) = 972$
$D_{Rec}(1, 1.5) = 46$
$D_{Rec}(1, 3) = 118$
$D_{Rec}(1, \infty) = 248$

$N'(3) = 730$
$D_{Rec}(3, 1.5) = 72$
$D_{Rec}(3, 3) = 125$
$D_{Rec}(3, \infty) = 178$

$N'(5) = 484$
$D_{Rec}(5, 1.5) = 45$
$D_{Rec}(5, 3) = 67$
$D_{Rec}(5, \infty) = 86$

$N'(8) = 238$
$D_{Rec}(8, 1.5) = 10$
$D_{Rec}(8, 3) = 14$
$D_{Rec}(8, \infty) = 18$
Web-based Supplementary Materials for ”Individual dynamic predictions using landmarking and joint modelling: validation of estimators and robustness assessment”

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1 Complete formulas of the estimators

This section details the formulations of the estimators defined in the main manuscript from the landmark cause-specific proportional hazards models and the joint model (Sections 2.3 and 2.2 of the main paper, respectively). Refer to the main manuscript for the notations. Please note that all these estimators involve the computation of integrals over time that can be avoided using product-integrals. Detailed information on this operation can be found in the supplementary material of Ferrer et al. (2016).

1.1 Joint model: marginal estimator

\[ \tilde{\pi}_k^*(s, w; \theta) = \frac{\int \Pr(s < T_* \leq s + w, \delta_* = k | X_*(s), b_*; \theta) \times \left( \sum_k \exp \left( - \sum_k \int_0^w \lambda_k^*(v|X_*(v), b_*; \theta) \, dv \right) \lambda_k^*(u|X_*(u), b_*; \theta) \, du \right) f(Y_*(s)|X_*(s), b_*; \theta) f(b_*|s < T_* \leq s + w, \delta_* = k, Y_*(s), X_*(s); \theta) \, db_* \right) }{\int \Pr(T_* > s | X_*(s), b_*; \theta) f(Y_*(s)|X_*(s), b_*; \theta) f(b_*|T_* > s, Y_*(s), X_*(s); \theta) \, db_*} \]

1.2 Joint model: conditional estimator

\[ \tilde{\pi}_k^*(s, w; \theta) = \frac{\Pr(s < T_* \leq s + w, \delta_* = k | X_*(s), \tilde{b}_k^*; \theta) f(Y_*(s)|X_*(s), \tilde{b}_k^*; \theta)}{\Pr(T_* > s | X_*(s), b_*; \theta) f(Y_*(s)|X_*(s), b_*; \theta)} \]

\[ = \left[ \int_s^{s+w} \exp \left( - \sum_k \int_0^w \lambda_k^*(v|X_*(v), \tilde{b}_k^*; \theta) \, dv \right) \lambda_k^*(u|X_*(u), \tilde{b}_k^*; \theta) \, du \right] f(Y_*(s)|X_*(s), \tilde{b}_k^*; \theta) \]

where \( \tilde{b}_k^* = \arg \max_b [\log f(T_* > s, Y_*(s), b|X_*(s); \theta)] \) and \( \tilde{b}_k^* = \arg \max_b [\log f(s < T_* \leq s + w, \delta_* = k, Y_*(s), b|X_*(s); \theta)] \).

1.3 Naive landmark cause-specific proportional hazards model: estimator

\[ \tilde{\pi}_k^*(s, w; \theta) = \Pr(s < T_* \leq s + w, \delta_* = k | T_* > s, \{ X_k^E; k = 1, \ldots, K \}, Y_*(t_{n_*(s)}); \theta) \]

\[ = \int_s^{s+w} \exp \left( - \sum_k \int_s^w \lambda_k^*(v|X_k^E, Y_*(t_{n_*(s)}); \theta) \, dv \right) \lambda_k^*(u|X_k^E, Y_*(t_{n_*(s)}); \theta) \, du \]
1.4 Two-stage landmark cause-specific proportional hazards model: estimator

\[ \hat{\pi}_k(s,w;\hat{\theta}) = \Pr(s < T_* \leq s + w, \delta_* = k|T_* > s, X_*(s), \hat{b}_*; \hat{\theta}) = \int_s^{s+w} \exp \left\{ -\sum_k \int_s^u \lambda_k^k(v|X_*(s), \hat{b}_*; \hat{\theta}) \, dv \right\} \lambda_k^k(u|X_*(u), \hat{b}_*; \hat{\theta}) \, du \]

where \( \hat{b}_* = \mathbb{E}(b_*|Y_*(s), X_*(s); \hat{\theta}) \).

2 Complementary results for Simulation II: robustness assessment

2.1 Supplementary case: Weak misspecification of the longitudinal trajectory of the marker

This supplementary case aimed to check the performances of our proposed estimators when the longitudinal trend of the marker was misspecified. In contrast with the extreme case (case 4) in the main manuscript, we considered here a very slight misspecification of the longitudinal trajectory.

Data were generated using a joint model with a longitudinal marker evolution characterized by a combination of cubic B-splines functions:

\[
Y_i(t) = m_i(t) + \epsilon_i(t) = (\beta_0 + \beta_{0X}X_i + b_{0}) + \sum_{l=1}^{3} (\beta_l + \beta_{lX}X_i + b_{l}) B_l(t,3) + \epsilon_i(t),
\]

\[
\lambda_k^k(t) = \lambda_{k,0}(t) \exp \left\{ \gamma_kX_i + \eta_{k1}m_i(t) + \eta_{k2} \frac{\delta m_i(t)}{\delta t} \right\}.
\]

As shown in the example of individual trajectory depicted in Figure 1, this longitudinal trend slightly differed from the linear evolution assumed in the estimation and prediction steps. The distribution of the covariates and the coefficients used for the data generation are detailed in Section 3.4 of this Supplementary Material.

Figure 2 shows differences of MSEP for 8 pairs of landmark and horizon times (s = 1, 3, 5, 8 and w = 1.5, 3). The joint marginal and landmark two-stage estimators were comparable with no significant differences for all the pairs of landmark and horizon times, except slightly when w = 1.5 and s = 3 or s = 5. Indeed, considering a linear evolution in these times of prediction window does not seem to be incorrect, as illustrated in Figure 1. The results confirmed the poor accuracy of the conditional estimator from the joint model in the earlier landmark times, but this estimator became equivalent to the marginal estimator when the landmark time increased. Compared to the superiority of the joint model found in the well-specified case 1, these results confirm the high sensitivity of the estimators from the joint modelling approach to the correct specification of the longitudinal marker trend.

[Figure 1 about here.]

[Figure 2 about here.]

2.2 Assessment of model discrimination: computation of AUCs

When we are interested in the predictive accuracy of a model, a popular measure to check its performances in terms of discrimination is the area under the ROC curve, called AUC. We considered the AUC
definition adapted to the competing risks setting (Blanche et al., 2015):

\[
\text{AUC}_k^s(s, w) = \Pr (\hat{\pi}_k(r(s, w; \hat{\theta}) > \pi_{k,j}(s, w; \hat{\theta}) | \Delta_k^s(s, w) = 1, T_i > s, \Delta_k^j(s, w) = 0, T_j > s)
\]

where \(\Delta_k^i(s, w) = \mathbb{1}\{s < T_i \leq s + w, \delta_i = k\}\) with \(\delta_i = k\) the cause of event ; \(i\) and \(j\) two subjects for prediction. Thus, for any subject \(i\) at risk at \(s\), \(\Delta_k^i(s, w) = 1\) when subject \(i\) experiences the event of cause \(k\) within the time interval \((s, s + w]\), and \(\Delta_k^i(s, w) = 0\) when either he experiences the competing event between \(s\) and \(s + w\) or is event-free at \(s + w\).

Because this was a simulation study, the indicator of event \(\Delta_k^i(s, w)\) was known and the estimator could directly be expressed as

\[
\hat{\text{AUC}}_k^s(s, w) = \frac{\sum_{i=1}^{N_{\text{new}(0)}} \sum_{j=1}^{N_{\text{new}(0)}} \mathbb{1}\{T_i > s\}\mathbb{1}\{T_j > s\}\mathbb{1}\{\hat{\pi}_k^i(s, w; \hat{\theta}) > \pi_{k,j}(s, w; \hat{\theta})\} \Delta_k^i(s, w)(1 - \Delta_k^j(s, w))}{\sum_{i=1}^{N} \sum_{j=1}^{N} \mathbb{1}\{T_i > s\}\mathbb{1}\{T_j > s\}\Delta_k^i(s, w)(1 - \Delta_k^j(s, w))}
\]

Figures 3, 4, 5, 6, and 7 depict respectively the AUCs for the cases where the joint model is correctly specified (case 1), the dependence function is misspecified (case 2), the proportional hazards assumption is violated (case 3), the longitudinal trend of the marker is severely misspecified (case 4) or slightly misspecified (case 4.bis). Overall, these results were comparable to those obtained in terms of mean squared errors. The joint model discriminated slightly better than the two-stage landmark models when the joint model was well specified (Figure 3) or when the dependence function was misspecified (Figure 4), whereas in the case of strong violation of the PH assumption, these models were comparable (Figure 5). In the case of a misspecification of the longitudinal marker trajectory, the two-stage landmark models discriminated noticeably better than the joint model when this misspecification was strong (Figure 6), but the discrimination abilities of the models were comparable in case of weak misspecification (Figure 7).

[Figure 3 about here.]
[Figure 4 about here.]
[Figure 5 about here.]
[Figure 6 about here.]
[Figure 7 about here.]

### 3 Simulation data generation

#### 3.1 Model of data generation in the Cases 1 and 2

Data were generated according to the joint model:

\[
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t)\\
&= (\beta_0 + \beta_{0,X}X_i + b_{0i}) + (\beta_1 + \beta_{1,X}X_i + b_{1i})t + \epsilon_i(t),\\
\lambda_i^s(t) &= \lambda_{i,0}(t) \exp \left( \gamma_k X_i + \eta_{1,k} m_i(t) + \eta_{2,k} \frac{\partial m_i(t)}{\partial t} \right),
\end{align*}
\]
where $k$ is the cause of event (Recurrence; Death), $b_i = (b_{i0}, b_{i1})^\top \sim \mathcal{N}(0, D)$ with

$$D = \begin{pmatrix} 0.582 & 0.032 \\ 0.032 & 0.061 \end{pmatrix}$$

and $\epsilon_i(t) \sim \mathcal{N}(0, \sigma^2)$ with $\sigma = 0.268$. The other coefficients were $\beta_0 = -1.087, \beta_{0,X} = 0.465, \beta_1 = -0.066, \beta_{1,X} = 0.110, \gamma_{\text{Rec}} = 0.064, \gamma_{\text{Death}} = 0.208, \eta_{1,\text{Rec}} = 0.707, \eta_{1,\text{Death}} = 0.023, \eta_{2,\text{Rec}} = 2.140, \eta_{2,\text{Death}} = -0.462,$

and $\log(\lambda_{k,0}(t))$ was a combination of cubic B-splines with the same knot vector $(3 \times 10^{-5}, 6.579, 15.874)^T$ for all the events and the vector of spline coefficients $(-4.003, -4.107, -4.031, -8.806, -3.643)^T$ for the recurrence and $(-5.401, -3.484, -3.810, -1.171, -1.263)^T$ for the death.

The times of measurements were $t_{ij} = \sum_{l=0}^{j} a_{il}$ with $a_{i0} = 0, a_{il} = 0.4 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.15,0.15)$ for $l \in \{1, 2, 3\}, a_{il} = 0.6 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.2,0.2)$ for $l \in \{4, 5, 6, 7\}, a_{il} = 1 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.35, 0.35)$ for $l \in \{8, 9, 10\}, a_{il} = 2 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.6, 0.6)$ for $l \in \{11, 12\},$ and $a_{il} = 3.5 + u_{il}$ with $u_{il} \sim \mathcal{U}(-1, 1)$ for $l \in \{13, 14, 15, 16\}.$ The covariate $X_i$ corresponded to the PSA level before treatment initiation in the motivating data, and was thus generated following a normal distribution with mean 2.041 and variance 0.503. The censoring time was generated from a uniform distribution on $[1, 15]$.

### 3.2 Model of data generation in the Case 3

Data were generated according to the joint model:

$$
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= (\beta_0 + b_{0,X}X_i + b_{01}) + (\beta_1 + b_{1,X}X_i + b_{11})t + \epsilon_i(t), \\
\lambda_k^i(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_kX_i + \eta_{1,k}m_i(t) + \eta_{2,k}\frac{\delta m_i(t)}{\delta t} \right\},
\end{align*}
$$

with the same covariates, random effects and parameters than in the Cases 1 and 2.

### 3.3 Model of data generation in the Case 4

Data were generated according to the joint model:

$$
\begin{align*}
Y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= (\beta_0 + b_{0,X}X_i + b_{01}) + (\beta_1 + b_{1,X}X_i + b_{11})((1 + t)^{-1.2} - 1) + (\beta_2 + b_{2,X}X_i + b_{21})t + \epsilon_i(t), \\
\lambda_k^i(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_kX_i + \eta_{1,k}m_i(t) + \eta_{2,k}\frac{\delta m_i(t)}{\delta t} \right\},
\end{align*}
$$

where $k$ is the cause of event (Recurrence; Death), $b_i = (b_{i0}, b_{i1}, b_{i2})^\top \sim \mathcal{N}(0, D)$ with

$$D = \begin{pmatrix} 0.363 & 0.011 & 0.345 \\ 0.011 & 0.172 & 0.310 \\ 0.345 & 0.310 & 1.746 \end{pmatrix}$$

and $\epsilon_i(t) \sim \mathcal{N}(0, \sigma^2)$ with $\sigma = 0.273$. The other coefficients were $\beta_0 = -0.255, \beta_{0,X} = 0.799, \beta_1 = 0.949, \beta_{1,X} = 0.904, \beta_2 = -0.088, \beta_{2,X} = 0.207, \gamma_{\text{Rec}} = 0.064, \gamma_{\text{Death}} = 0.208, \eta_{1,\text{Rec}} = 0.707, \eta_{1,\text{Death}} = 0.023, \eta_{2,\text{Rec}} = 2.140, \eta_{2,\text{Death}} = -0.462,$

and $\log(\lambda_{k,0}(t))$ was a combination of cubic B-splines with the same knot vector $(3 \times 10^{-5}, 6.579, 15.874)^T$ for all the events and the vector of spline coefficients $(-4.003, -4.107, -4.031, -8.806, -3.643)^T$ for the recurrence and $(-5.401, -3.484, -3.810, -1.171, -1.263)^T$ for the death. The times of measurements were $t_{ij} = \sum_{l=0}^{j} a_{il}$ with $a_{i0} = 0, a_{il} = 0.4 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.15,0.15)$ for $l \in \{1, 2, 3\}, a_{il} = 0.6 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.2,0.2)$ for $l \in \{4, 5, 6, 7\}, a_{il} = 1 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.35, 0.35)$ for $l \in \{8, 9, 10\}, a_{il} = 2 + u_{il}$ with $u_{il} \sim \mathcal{U}(-0.6, 0.6)$ for $l \in \{11, 12\},$ and $a_{il} = 3.5 + u_{il}$ with $u_{il} \sim \mathcal{U}(-1, 1)$ for $l \in \{13, 14, 15, 16\}.$
$U(-0.2,0.2)$ for $l \in \{4,5,6,7\}$, $a_{il} = 1 + u_{il}$ with $u_{il} \sim U(-0.35,0.35)$ for $l \in \{8,9,10\}$, $a_{il} = 2 + u_{il}$ with $u_{il} \sim U(-0.6,0.6)$ for $l \in \{11,12\}$, and $a_{il} = 3.5 + u_{il}$ with $u_{il} \sim U(-1,1)$ for $l \in \{13,14,15,16\}$. The covariate $X_i$ was generated following a normal distribution with mean $2.041$ and variance $0.503$. The censoring time was generated from a uniform distribution on $[1,15]$.

### 3.4 Model of data generation in the Case 4.bis

Data were generated according to the joint model:

$$
\begin{align*}
Y_i(t) &= m_i(t) + e_i(t) \\
&= (\beta_0 + \beta_{0,X}X_i + b_{i0}) + \sum_{l=1}^{3} (\beta_l + \beta_{l,X}X_i + b_{il}) B_l(t,3) + e_i(t), \\
\lambda_i^k(t) &= \lambda_{k,0}(t) \exp \left\{ \gamma_kX_i + \eta_{1,k}m_i(t) + \eta_{2,k}\frac{\delta m_i(t)}{\delta t} \right\},
\end{align*}
$$

where $k$ is the cause of event (Recurrence; Death), $b_i = (b_{i0}, b_{i1}, b_{i2}, b_{i3})^\top \sim N(0,D)$ with $D = \begin{pmatrix} 0.536 & 0.084 & 0.012 & -0.275 \\ 0.084 & 4.487 & 4.186 & 2.005 \\ 0.012 & 4.186 & 6.442 & 3.966 \\ -0.275 & 2.005 & 3.966 & 3.968 \end{pmatrix}$ and $e_i(t) \sim N(0,\sigma^2)$ with $\sigma = 0.223$. $B_l(t,3)$ is the $l$th row of the cubic B-spline basis matrix defined with two internal knots placed at $t = 2$ and $t = 7$ and boundary knots at $t = 0$ and $t = 15$. The other coefficients were $\beta_0 = -1.003, \beta_{0,X} = 0.452, \beta_1 = -0.337, \beta_{1,X} = 0.790, \beta_2 = -0.687, \beta_{2,X} = 1.201, \beta_3 = -0.033, \beta_{3,X} = 0.692, \gamma_{\text{Rec}} = 0.500, \gamma_{\text{Death}} = 0.150, \eta_{1,\text{Rec}} = 0.918, \eta_{1,\text{Death}} = 0.068, \eta_{2,\text{Rec}} = 1.566, \eta_{2,\text{Death}} = -0.761$ and, $\log(\lambda_{k,0}(t))$ was a combination of cubic B-splines with the same knot vector $(3 \times 10^{-5}, 15.874)^\top$ for all the events and the vector of spline coefficients $(-3.931, -3.827, -7.564, -4.569)^\top$ for the recurrence and $(-4.549, -2.386, -2.585, -2.209)^\top$ for the death.

The times of measurements were $t_{ij} = \sum_{l=0}^{i} a_{il} + a_{i0} = 0$, $a_{il} = 0.4 + u_{il}$ with $u_{il} \sim U(-0.15,0.15)$ for $l \in \{1,2,3\}, a_{il} = 0.6+u_{il}$ with $u_{il} \sim U(-0.2,0.2)$ for $l \in \{4,5,6,7\}, a_{il} = 1+u_{il}$ with $u_{il} \sim U(-0.35,0.35)$ for $l \in \{8,9,10\}, a_{il} = 2 + u_{il}$ with $u_{il} \sim U(-0.6,0.6)$ for $l \in \{11,12\}$, and $a_{il} = 3.5 + u_{il}$ with $u_{il} \sim U(-1,1)$ for $l \in \{13,14,15,16\}$. The covariate $X_i$ was generated following a normal distribution with mean $2.041$ and variance $0.503$. The censoring time was generated from a uniform distribution on $[1,15]$.

### 4 Computational time of the procedures

The several prediction models presented in this manuscript notably differ by the considered observed information and the complexity of the computational procedures. Table 1 compares the computational times of these procedures to compute individual dynamic predictions for a randomly chosen subject, based on a randomly selected replication. This example was taken from the case 1 of the manuscript, which notably considered two competing events (Recurrence, Death), a linear evolution of the marker with two individual random effects, and 1000 subjects included in the learning sample at baseline. For the joint model, 9 quadrature points were used according to the pseudo-adaptive Gauss-Hermite (GH) technique in the learning step, whereas 9 quadrature points using the adaptive GH technique were used in the validation step. Based on the techniques defined in the manuscript, $L = 1000$ samples of parameters were used to compute the confidence intervals using each approaches. The computing times were obtained on a single CPU of a PC with an Intel i7 processor, 3.40 GHz and 32Go of RAM memory. The R code used for this example can be found at https://github.com/LoicFerrer/.
As expected, the estimation of the joint model was considerably longer than the estimation of the landmark models, notably because the joint likelihood involved an integral over the two individual random effects. Nevertheless the joint model required only one model estimation to predict the individual cumulative incidences at any pair of landmark and horizon times $(s, w)$, whereas the landmark model based on pseudo-values needed one estimation for each $s$, and one estimation for each $(s, w)$ was required for the landmark cause-specific proportional hazards model. For the same reasons, the number of subjects at risk and then the computation times of the estimation of the landmark models decreased when the landmark time $s$ increased. Note that the estimation of the naive landmark CS PH model was very fast because the model was only adjusted using the last observation carried forward (LOCF) method.

The computation of the individual cumulative incidences of events and their associated confidence intervals was much longer using the marginal estimator from the joint model than others due to the integral over the individual random effects which was involved in the estimator’s definition. Indeed, the conditional estimator from the joint model that approximates the integral by considering the modes of the posterior conditional distributions of the random effects was 2.5 times faster to compute than the marginal estimator. For the landmark approaches, the computation of the estimator from the landmark pseudo-value model was faster than the computation of the estimator from the cause-specific landmark model because the former directly modelled the quantity of interest and then its expression did not include integral over time. The confidence intervals were substantially faster to compute using the landmark pseudo-value model than others because in addition to the direct modelling, the technique of the former only involved bootstrapped parameters whereas in the landmark CS PH models a perturbation resampling technique was also applied.

## 5 Example of R code

The individual dynamic predictions can be computed in clinical practice using R codes. Please see the detailed examples available at [https://github.com/LoicFerrer/](https://github.com/LoicFerrer/). The functions which implement the estimators defined in the manuscript (the marginal and conditional estimators from the joint model, the naive and two-stage estimators from the cause-specific proportional hazards landmark model and the naive and two-stage estimators from the landmark model based on pseudo-values) and their associated confidence intervals are also included. Simulated data are provided.

Here is given the script used in Section 4.1 of the main manuscript to compute the individual cumulative incidences of event for two landmark times $s = 1, s = 5$ and a given horizon $w = 3$, in subjects at risk at $s$. Data were retrieved from a randomly selected replication. Two types of event were considered (Recurrence, Death), the longitudinal evolution of the marker was linear, the same covariate, called X in the code below, impacted the longitudinal and survival processes, and the dependency between these two processes was explained through the true current level and the true current slope of the marker.

```r
# Import two lists which contain the learning data and the validation data,
# at https://github.com/LoicFerrer/
load("data.RData")
ls()
# [1] "data_learn" "data_valid"
str(data_learn)
```

> # Import two lists which contain the learning data and the validation data,
> # at https://github.com/LoicFerrer/
> load("data.RData")
> ls()
> # [1] "data_learn" "data_valid"

```r
str(data_learn)
```
# List of 2
# $ surv: 'data.frame': 1000 obs. of 6 variables:
# $ long: 'data.frame': 8319 obs. of 4 variables:

str(data_valid)
# List of 3
# $ surv: 'data.frame': 500 obs. of 6 variables:
# $ long: 'data.frame': 4886 obs. of 4 variables:
# $ trueT: num [1:500] 11.04 7.67 12.82 ..

head(data_learn$surv, 3)
# id X time_of_Death Death time_of_Rec Rec
# 1 1 2.227805 2.106636 0 2.106636 0
# 2 2 1.452869 3.501039 0 3.501039 0
# 3 3 1.004715 2.991233 0 2.991233 1

head(data_learn$long, 3)
# id Y times X
# 1 1 0.6411969 0.0000000 2.227805
# 2 1 0.8455285 0.3296526 2.227805
# 3 1 1.2596015 0.6912898 2.227805

###############################
#### Using the joint model ####
###############################

# Load the 'JM' package to fit joint models with shared random effects
library(JM)

# Source the required functions to compute individual cumulative incidences of event.
# The file notably includes the functions 'JMCR.crLong' and 'survfitJMCR'
source("survfitJMCR.R")

# Adaptation of the learning survival database to the competing risks framework
data_learn$surv$Event <- "Alive"
data_learn$surv$Event[data_learn$surv$Death == 1] <- "Death"
data_learn$surv$Event[data_learn$surv$Rec == 1] <- "Rec"
data_learn$surv$time_of_Event <- pmin(data_learn$surv$time_of_Rec,
                                      data_learn$surv$time_of_Death)
data_learn$CR <- JMCR.crLong(data = data_learn$surv,
                             statusVar = "Event",
                             censLevel = "Alive")

head(data_learn$CR, 6)
# id X time_of_Death Death time_of_Rec Rec Event time_of_Event strata status2
# 1 1 2.227805 2.106636 0 2.106636 0 Alive 2.106636 Rec 0
# 1.1 1 2.227805 2.106636 0 2.106636 0 Alive 2.106636 Death 0
# 2 2 1.452869 3.501039 0 3.501039 0 Alive 3.501039 Rec 0
# 2.1 2 1.452869 3.501039 0 3.501039 0 Alive 3.501039 Death 0
# 3 3 1.004715 2.991233 0 2.991233 1 Rec 2.991233 Rec 1
# 3.1 3 1.004715 2.991233 0 2.991233 1 Rec 2.991233 Death 0

# Adaptation of the validation survival database to the competing risks framework
data_valid$surv$Event[data_valid$surv$Death == 1] <- "Death"
data_valid$surv$Event[data_valid$surv$Rec == 1] <- "Rec"
data_valid$surv$time_of_Event <- pmin(data_valid$surv$time_of_Rec,
   data_valid$surv$time_of_Death)
# WARNING: use the JMCR.crLong function by specifying the 'levels' argument as follows.
# The 'strata' argument in the survival validation database has imperatively
# to be organized in the same order as its levels.
data_valid$CR <- JMCR.crLong(data = data_valid$surv,
   statusVar = "Event",
   censLevel = "Alive",
   levels = levels(data_learn$CR$strata)) ## Warning
head(data_valid$CR, 6)
# id  X time_of_Death Death time_of_Rec Rec Event time_of_Event strata status2
# 1 1  1.476506 5.714061 0 5.714061 0 Alive 5.714061 Death 0
# 1.1 1 1.476506 5.714061 0 5.714061 0 Alive 5.714061 Rec 0
# 2 2  1.797706 7.673092 0 7.673092 1 Rec 7.673092 Death 0
# 2.1 2 1.797706 7.673092 0 7.673092 1 Rec 7.673092 Rec 1
# 3 3  3.262949 9.419707 0 9.419707 0 Alive 9.419707 Death 0
# 3.1 3 3.262949 9.419707 0 9.419707 0 Alive 9.419707 Rec 0

## Learning step

# Estimation of the longitudinal sub-model (independent of the survival sub-model)
lmeFit <- lme(fixed = Y ˜ times * X, data = data_learn$long,
   random = ˜ times | id)
# Estimation of the survival sub-model (independent of the longitudinal sub-model)
coxFit <- coxph(formula = Surv(time_of_Event, status2) ˜ X:strata(strata) + strata(strata),
   data = data_learn$CR,
   model = TRUE, x = TRUE)
# Definition of the marker’s slope included in the joint model
dForm <- list(fixed = ˜ 1 + X,
   indFixed = c(2, 4),
   random = ˜ 1,
   indRandom = 2)
# Estimation of the joint model
jointFit <- jointModel(lmeFit, coxFit,
   timeVar = "times",
   parameterization = "both",
   method = "spline-PH-aGH",
   interFact = list(value = ˜ strata(strata) - 1,
      slope = ˜ strata(strata) - 1,
      data = data_learn$CR),
   derivForm = dForm, control = list(GHk = 9, lng.in.kn = 1),
   CompRisk = TRUE,
   verbose = TRUE)

## Computation of the predicted individual cumulative incidences of events
## with 95% confidence intervals based on 1000 Monte Carlo samples

# ID at risk at the landmark times s=1 and s=5
Ri1 <- data_valid$surv$Id[which(data_valid$trueT > 1)]
Ri5 <- data_valid$surv$Id[which(data_valid$trueT > 5)]
# Longitudinal database and survival database with subjects at risk at s=1
data_valid.s1 <- NULL
data_valid.s1$long <- data_valid$long[data_valid$long$times <= 1 &
  data_valid$long$id %in% Ri1,]
data_valid.s1$CR <- data_valid$CR[data_valid$CR$id %in% Ri1,]
# Longitudinal database and survival database with subjects at risk at s=5
data_valid.s5 <- NULL
data_valid.s5$long <- data_valid$long[data_valid$long$times <= 5 &
  data_valid$long$id %in% Ri5,]
data_valid.s5$CR <- data_valid$CR[data_valid$CR$id %in% Ri5,]

## Marginal estimator
# s=1, w=3
P1_3.JMmarg <- survfitJMCR(object = jointFit,
  newData.long = data_valid.s1$long,
  newData.surv = data_valid.s1$CR,
  idVar = "id",
  formT = ˜ X:strata(strata),
  tLM = rep(1, length(Ri1)),
  thor = 3,
  estimator = "marg",
  simulate = T,
  M = 1000,
  CI.levels = c(0.025, 0.975))
P1_3.JMmarg
# Estimator definition: marginal to the individual random effects
#
# Predicted individual cumulative incidences of events
#
# $Death
# | tLM | thor | Value |
#|-----|------|-------|
#| ID 1 | 1    | 3     | 0.07514737 |
#| ID 2 | 1    | 3     | 0.07108905 |
#| ID 3 | 1    | 3     | 0.07597429 |
#| (...) |
#
# $Rec
# | tLM | thor | Value |
#|-----|------|-------|
#| ID 1 | 1    | 3     | 0.1301004 |
#| ID 2 | 1    | 3     | 0.1050290 |
#| ID 3 | 1    | 3     | 0.1726383 |
#| (...) |
#
# Predicted individual cumulative incidences of events
# based on 1000 Monte Carlo samples
#
# $Death
# | tLM | thor | Mean   | Median | Lower (2.5%) | Upper (97.5%) |
#|-----|------|--------|-------|--------------|---------------|
#| ID 1 | 1    | 3      | 0.07655855 | 0.07595813 | 0.05954908 | 0.09866198 |
#| ID 2 | 1    | 3      | 0.07724854 | 0.07149081 | 0.05704207 | 0.09044535 |
#| ID 3 | 1    | 3      | 0.07769421 | 0.07656262 | 0.05441197 | 0.10801782 |
#| (...) |
# $Rec
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 1 3 0.1313873 0.1307075 0.10596253 0.1623071
# ID 2 1 3 0.1062217 0.1054323 0.08620265 0.1299271
# ID 3 1 3 0.1741073 0.1724545 0.12964078 0.2298147
# (...)

# s=5, w=3
P5_3.JMmarg <- survfitJMCR(object = jointFit,
    newData.long = data_valid.s5$long,
    newData.surv = data_valid.s5$CR,
    idVar = "id",
    formT = ˜ X:strata(strata),
    tLM = rep(5, length(Ri5)),
    thor = 3,
    estimator = "marg",
    simulate = T,
    M = 1000,
    CI.levels = c(0.025, 0.975))

P5_3.JMmarg
# Estimator definition: marginal to the individual random effects
# #
# # Predicted individual cumulative incidences of events
# # $Death
# tLM thor Value
# ID 1 5 3 0.1721675
# ID 2 5 3 0.1259304
# ID 3 5 3 0.1871697
# (...)
# # $Rec
# tLM thor Value
# ID 1 5 3 0.01770684
# ID 2 5 3 0.24186527
# ID 3 5 3 0.03426441
# (...)
# # Predicted individual cumulative incidences of events
# based on 1000 Monte Carlo samples
# # $Death
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.1729590 0.1724336 0.13513284 0.2145668
# ID 2 5 3 0.1266225 0.1250114 0.09317579 0.1667234
# ID 3 5 3 0.1885321 0.1861479 0.13515246 0.2491214
# (...)
# # $Rec
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.01817897 0.01785144 0.01166856 0.02671285
# ID 2 5 3 0.24515436 0.24351905 0.19302590 0.30336436
# ID 3 5 3 0.03545071 0.03463930 0.02166277 0.05431355
# (...)

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## Conditional estimator

s=1, w=3

P1_3.JMcond <- survfitJMCR(object = jointFit, 
newData.long = data_valid.s1$long, 
newData.surv = data_valid.s1$CR, 
idVar = "id", 
formT = X:strata(strata), 
tLM = rep(1, length(Ri1)), 
thor = 3, 
estimator = "cond", 
simulate = T, 
M = 1000, 
CI.levels = c(0.025, 0.975))

P1_3.JMcond

# Estimator definition: conditional to the MAP of the individual random effects
#
#
# Predicted individual cumulative incidences of events
#
# $Death
#
# tLM thor Value
# ID 1 1 3 0.07798428
# ID 2 1 3 0.07307276
# ID 3 1 3 0.07953390
# (...)

# $Rec
#
# tLM thor Value
# ID 1 1 3 0.1828431
# ID 2 1 3 0.1413761
# ID 3 1 3 0.2416013
# (...)

# Predicted individual cumulative incidences of events based on 1000 Monte Carlo samples
#
# $Death
#
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 1 3 0.07932089 0.07874783 0.06098413 0.10237902
# ID 2 1 3 0.07400522 0.07340157 0.05831713 0.09174712
# ID 3 1 3 0.08134418 0.07953099 0.05647367 0.11628135
# (...)

# $Rec
#
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 1 3 0.1845178 0.1838128 0.1477782 0.2278376
# ID 2 1 3 0.1424508 0.1410770 0.1094119 0.1815720
# ID 3 1 3 0.2432991 0.2410676 0.1678992 0.3242795
# (...)

s=5, w=3

P5_3.JMcond <- survfitJMCR(object = jointFit, 
newData.long = data_valid.s5$long, 
newData.surv = data_valid.s5$CR,
idVar = "id",
formT = ~ X:strata(strata),
tLM = rep(5, length(Ri5)),
thur = 3,
estimator = "cond",
simulate = T,
M = 1000,
CI.levels = c(0.025, 0.975))
P5_3.JMcond
# Estimator definition: conditional to the MAP of the individual random effects
#
# Predicted individual cumulative incidences of events
#
# $Death
# tLM thor Value
# ID 1 5 3 0.1723353
# ID 2 5 3 0.1273586
# ID 3 5 3 0.1875795
# (...)
#
# $Rec
# tLM thor Value
# ID 1 5 3 0.01851501
# ID 2 5 3 0.24754646
# ID 3 5 3 0.03640618
# (...)
#
# Predicted individual cumulative incidences of events
# based on 1000 Monte Carlo samples
#
# $Death
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.1735219 0.1719451 0.13600771 0.2207591
# ID 2 5 3 0.1280152 0.1269849 0.09377241 0.1677724
# ID 3 5 3 0.1883834 0.1868395 0.13490875 0.2547082
# (...)
#
# $Rec
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.01902124 0.01876318 0.01242588 0.02763914
# ID 2 5 3 0.24939821 0.24869838 0.19645549 0.31078529
# ID 3 5 3 0.03744895 0.03642236 0.02331171 0.05648034
# (...)

###################################################
#### Using the two-stage landmark CS PH model ####
###################################################
# Load the 'nlme' and 'mstate' packages to fit the model
library(nlme)
library(mstate)  
# Source the required functions to compute individual cumulative incidences of event  
# The file notably includes the function 'CumInc'  
source("survfitLMCR.R")  

survfitLMCR <- function(tLM, thor, simulate = T, M = 1000, CI.levels = c(0.025, 0.975)) {  
# tLM: landmark time  
# thor: horizon window  
tpred <- tLM + thor  

## Learning step ##  
# ID at risk at the landmark time  
Ri <- data_learn$surv[which(data_learn$surv$time_of_Rec > tLM), "id"]  
nLM <- length(Ri)  
# One considers all data collected before the landmark time point for subjects still at risk  
LMlong <- data_learn$long[data_learn$long$times < tLM & data_learn$long$id %in% Ri, ]  
LMsurv <- data_learn$surv[data_learn$surv$id %in% Ri, ]  

# Estimation of the linear mixed model  
lmeFit <- lme(fixed = Y ˜ times*X,  
data = LMlong,  
random = ~ times| id)  

# BLUPs and parameters  
b <- ranef(lmeFit)  
sigma <- lmeFit$sigma  
D <- lapply(pdMatrix(lmeFit$modelStruct$reStruct), "*", sigma^2)[[1]]  
betas <- fixef(lmeFit)  

# Predicted level and slope of the marker at the landmark time  
Data.s <- data.frame(id = unique(LMlong$id),  
times = tLM,  
X = LMlong[!duplicated(LMlong$id), "X"])[-1, ]  
Xlong.s <- model.matrix(~ times"X", Data.s)  
Z.s <- model.matrix(~ times, Data.s)  
LMsurv$level <- as.vector(c(Xlong.s %*% betas) + rowSums(Z.s * b))  
Xlong_deriv.s <- model.matrix(~ X, Data.s)  
Zderiv.s <- model.matrix(~ 1, Data.s)  
LMsurv$slope <- as.vector(c(Xlong_deriv.s %*% betas[c(2, 4)]) + rowSums(Zderiv.s * b[, 2, drop = FALSE]))  

# Administrative censoring at the end of the prediction window  
LMsurv$tRecAC <- pmin(LMsurv$time_of_Rec, tpred)  
LMsurv$RecAC <- LMsurv$Rec  
LMsurv$RecAC[LMsurv$time_of_Rec < tpred] <- 0  
LMsurv$tDeathAC <- pmin(LMsurv$time_of_Death, tpred)  
LMsurv$DeathAC <- LMsurv$Death  
LMsurv$DeathAC[LMsurv$time_of_Death < tpred] <- 0  

# Estimation of the Cox model (Recurrence)  
coxFit1 <- coxph(Surv(tRecAC, RecAC) ˜ X + level + slope, data = LMsurv)  

# Estimation of the Cox model (Death)  
coxFit2 <- coxph(Surv(tDeathAC, DeathAC) ˜ X + level + slope, data = LMsurv)
## Computation of the predicted individual cumulative incidences of events

### Subjects at risk at tLM

```R
Ri_pred <- data_valid$surv$id[which(data_valid$trueT > tLM)]
nLM_pred <- length(Ri_pred)
```

### Computation of the predicted individual risk scores

```R
LMsurv_pred <- data_valid$surv[Ri_pred, ]
LMlong_pred <- data_valid$long[data_valid$long$times < tLM & data_valid$long$long$id %in% Ri_pred, ]
Xlong_pred <- split(data.frame(model.matrix(~ times*X, LMlong_pred)), LMlong_pred$id)
Z_pred <- split(data.frame(model.matrix(~ times, LMlong_pred)), LMlong_pred$id)
Y_pred <- split(LMlong_pred$Y, LMlong_pred$id)
V_pred <- lapply(Z_pred, function(x){
as.matrix(x) %*% D %*% t(as.matrix(x)) + diag(sigma^2, nrow(as.matrix(x))}
})
b_pred <- lapply(seq_len(length(Xlong_pred)), function(i, x, y, z, v) {
  D %*% t(as.matrix(z[[i]])) %*% solve(v[[i]]) %*% (y[[i]] - as.matrix(x[[i]]) %*% fixef(lmeFit)),
  x = Xlong_pred, y = Y_pred, z = Z_pred, v = V_pred
})
b_pred <- matrix(unlist(b_pred), ncol = 2, , byrow = T)
Data_pred.s <- data.frame(id = unique(LMlong_pred$id),
times = tLM,
  X = LMlong_pred[!duplicated(LMlong_pred$id), "X"])
Xlong_pred.s <- model.matrix(~ times*X, Data_pred.s)
Z_pred.s <- model.matrix(~ times, Data_pred.s)
LMsurv_pred$level <- as.vector(c(Xlong_pred.s %*% betas) + rowSums(Z_pred.s * b_pred))
Xlong_deriv_pred.s <- model.matrix(~ X, Data_pred.s)
Zderiv_pred.s <- model.matrix(~ 1, Data_pred.s)
LMsurv_pred$slope <- as.vector(c(Xlong_deriv_pred.s %*% betas[c(2, 4)]) +
  rowSums(Zderiv_pred.s * b_pred[, 2, drop = FALSE]))
```

### Baseline hazards estimates

```R
bh1 <- basehaz(coxFit1, centered = FALSE)
bh2 <- basehaz(coxFit2, centered = FALSE)
```

### Reasonably quick function that converts cause-specific hazards to cumulative incidence functions and extracts value at horizon

```R
toci <- function(bh1, bh2, HR1, HR2, tpred)
{
  h1 <- bh1
  names(h1)[1] <- "Haz"
  h1$Haz <- h1$Haz * HR1
  h1$cause <- 1
  h2 <- bh2
  names(h2)[1] <- "Haz"
  h2$Haz <- h2$Haz * HR2
  h2$cause <- 2
  Haz <- rbind(h1, h2)
  CI <- CumInc(Haz)
  idx <- sum(CI$time <= tpred)
  return(CI[idx, ])
}
```
# Individual cumulative incidences
ci <- matrix(NA, nLM_pred, 2)
for (i in 1:nLM_pred) {
  ci[i, ] <- as.numeric(toci(bh1, bh2, HR1[i], HR2[i], tpred))[2:3]
}

if (simulate){
  ## Computation of the predicted 95% confidence intervals based on M Monte Carlo samples
  ci.MC <- replicate(M, matrix( , nrow = nLM_pred, ncol = 2), simplify = FALSE)
  # Time-to-event data
t <- matrix(coxFit1$y, ncol = 2)[,1]
  Delta1 <- matrix(coxFit1$y, ncol = 2)[,2]
  Delta2 <- matrix(coxFit2$y, ncol = 2)[,2]
  # Parametric bootstrap
  aV <- lmeFit$apVar
  Pars <- attr(aV, "Pars")
  varFix <- lmeFit$varFix
  nbetas <- length(betas)
  nP <- length(Pars)
  mat <- matrix(0, nbetas + nP, nbetas + nP)
  mat[seq_len(nbetas), seq_len(nbetas)] <- varFix
  mat[nbetas + seq_len(nP), nbetas + seq_len(nP)] <- aV
  coef_coxFit1.MC <- mvrnorm(M,
    mu = coxFit1$coef,
    Sigma = coxFit1$var)
  coef_coxFit2.MC <- mvrnorm(M,
    mu = coxFit2$coef,
    Sigma = coxFit2$var)
  coef_long.MC <- mvrnorm(M, c(betas, Pars), Sigma = mat)

  for(l in seq_len(M)){
    betas.MC <- coef_long.MC[l, seq_len(nbetas)]
    sigma.MC <- exp(coef_long.MC[l, nbetas + nP])
    lmeSt <- lmeFit$modelStruct
    lmeSt$reStruct[[1]] <- pdNatural(lmeSt$reStruct[[1]])
    coef(lmeSt) <- coef_long.MC[l, -c(seq_len(nbetas), nbetas + nP)]
    Pars.D.MC <- coef(lmeSt, unconstrained = FALSE)
    D.MC <- matrix(c(Pars.D.MC[1], rep(Pars.D.MC[3], 2), Pars.D.MC[2]), 2, 2)
    diag(D.MC) <- diag(D.MC)^2
    D.MC[upper.tri(D.MC, diag = FALSE)] <-
      D.MC[lower.tri(D.MC, diag = FALSE)] <-
      Reduce("*", D.MC)"'

    # Computation of the actualized marker's dynamics in the learning sample
    Xlong <- split(data.frame(model.matrix( ~ times*X, LMlong)), LMlong$id)
    Z <- split(data.frame(model.matrix( ~ times, LMlong)), LMlong$id)
    Y <- split(LMlong$Y, LMlong$id)
    V.MC <- llapply(Z, function(x){
      as.matrix(x) %*% D.MC %*% t(as.matrix(x)) + diag(sigma.MC^2, nrow(as.matrix(x))))}
    b.MC <- llapply(seq_len(length(Xlong)),
      function(i, x, y, z, v) {
        D.MC %*% t(as.matrix(z[[i]])) %*% solve(v[[i]]) %*% (y[[i]] - as.matrix(x[[i]])) %*% betas.MC),
        x = Xlong, y = Y, z = Z, v = V.MC)
b.MC <- matrix(unlist(b.MC), ncol = 2, , byrow = T)
LMsurv.MC <- LMsurv
LMsurv.MC$level.MC <- as.vector(c(Xlong.s %*% betas.MC) + rowSums(Z.s * b.MC))
LMsurv.MC$slope.MC <- as.vector(c(Xlong_deriv.s %*% betas.MC[c(2, 4)]) + rowSums(Zderiv.s * b.MC[ , 2, drop = FALSE]))
Xsurv.MC <- model.matrix(~ 0 + X + level + slope, LMsurv.MC)

# Computation of the actualized individual risk scores in the validation sample
V_pred.MC <- lapply(Z_pred, function(x){
as.matrix(x) %*% D.MC %*% t(as.matrix(x)) + diag(sigma.MC^2, nrow(as.matrix(x)))
})
b_pred.MC <- lapply(seq_len(length(Xlong_pred)),
  function(i, x, y, z, v) {
    D.MC %*% t(as.matrix(z[[i]])) %*
    solve(v[[i]]) %*% (y[[i]] - as.matrix(x[[i]]) %*% betas.MC),
    x = Xlong_pred, y = Y_pred, z = Z_pred, v = V_pred.MC
})
b_pred.MC <- matrix(unlist(b_pred.MC), ncol = 2, , byrow = T)
LMsurv_pred.MC <- LMsurv_pred
LMsurv_pred.MC$level_pred.MC <-
  as.vector(c(Xlong_pred.s %*% betas.MC) + rowSums(Z_pred.s * b_pred.MC))
LMsurv_pred.MC$slope_pred.MC <-
  as.vector(c(Xlong_deriv_pred.s %*% betas.MC[c(2, 4)]) + rowSums(Zderiv_pred.s * b_pred.MC[ , 2, drop = FALSE]))
Xsurv_pred.MC <- model.matrix(~ 0 + X + level + slope, LMsurv_pred.MC)
HR1.MC <- as.numeric(exp(Xsurv_pred.MC %*% coef_coxFit1.MC[l,]))
HR2.MC <- as.numeric(exp(Xsurv_pred.MC %*% coef_coxFit2.MC[l,]))

# Perturbation-resampling
set.seed(l)
nu_event <- 4 * rbeta(nLM, 1/2, 3/2)
haz1.MCPR <- haz2.MCPR <- N1.PR <- N2.PR <- NULL
for(i in 1:nLM){
  haz1.MCPR[i] <- mean(nu_event * as.numeric(t >= t[i]) *
    exp(c(Xsurv.MC %*% coef_coxFit1.MC[l,])))
  haz2.MCPR[i] <- mean(nu_event * as.numeric(t >= t[i]) *
    exp(c(Xsurv.MC %*% coef_coxFit2.MC[l,])))
  N1.PR[i] <- mean(nu_event * as.numeric(t <= t[i]) * Delta1)
  N2.PR[i] <- mean(nu_event * as.numeric(t <= t[i]) * Delta2)
}
Haz1.MCPR <- data.frame(hazard = cumsum(diff(c(0,N1.PR[order(t)])) /
  haz1.MCPR[order(t)]),
  time = t[order(t)])
Haz2.MCPR <- data.frame(hazard = cumsum(diff(c(0,N2.PR[order(t)])) /
  haz2.MCPR[order(t)]),
  time = t[order(t)])

# Cumulative incidences after parametric bootstrap and perturbation-resampling
for(i in 1:nLM_pred){
  ci.MC[[i]] <- as.numeric(toci(Haz1.MCPR, Haz2.MCPR, HR1.MC[i], HR2.MC[i], tpred)[2:3])
}
cat(paste("Monte Carlo sample: ", l, "/", M, sep = ""), "\n")
res.MC <- replicate(2, matrix( , nrow = nLM_pred, ncol = 6), simplify = F)
for(k in 1:2) {
  for (i in seq_len(nLM_pred)) {
    res.MC[[k]][i,] <- c(tLM,
thor,
mean(sapply(ci.MC, function(x) x[,k])[,i]),
median(sapply(ci.MC, function(x) x[,k])[,i]),
quantile(sapply(ci.MC, function(x) x[,k])[,i], probs = CI.levels[1]),
quantile(sapply(ci.MC, function(x) x[,k])[,i], probs = CI.levels[2]))

})
colnames(res.MC[[k]]) <- c("tLM", "thor", "Mean", "Median",
paste("Lower", " (", CI.levels[1] * 100, ",%"), sep = ""),
paste("Upper", " (", CI.levels[2] * 100, "%"), sep = ""))
rownames(res.MC[[k]]) <- sapply(Ri_pred, function(x) paste("ID", x))

res <- replicate(2, matrix(, nrow = nLM_pred, ncol = 3), simplify = F)
for(k in 1:2) {
  for (i in seq_len(nLM_pred)) {
    res[[k]][i,] <- c(tLM, thor, ci[i,k])
  }
colnames(res[[k]]) <- c("tLM", "thor", "Value")
rownames(res[[k]]) <- sapply(Ri_pred, function(x) paste("ID", x))
}
names(res) <- names(res.MC) <- c("Rec", "Death")

result <- {
  if (simulate)
    list(res = res, res.MC = res.MC, simulate = simulate, M = M)
  else list(res = res, simulate = simulate, M = M)
}
rm(list = ".Random.seed", envir = globalenv())
class(result) <- "survfitLMCR"
return(result)

# s=1, w=3
P1_3.2sLMPH <- survfitLMCR(tLM = 1,
  thor = 3,
simulate = T,
  M = 1000,
  CI.levels = c(0.025, 0.975))
P1_3.2sLMPH

# Predicted individual cumulative incidences of events
#
# $Rec
#
#  tLM  thor  Value
#  ID 1  1  3 0.11472941
#  ID 2  1  3 0.09965338
#  ID 3  1  3 0.16704735
# (...)
#
# $Death
#
#  tLM  thor  Value
#  ID 1  1  3 0.07755851
#  ID 2  1  3 0.08732394
#  ID 3  1  3 0.08023811
# (...)
#
# Predicted individual cumulative incidences of events
# based on 1000 Monte Carlo samples
#
# $Rec
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 1 3 0.11332436 0.1118789 0.08164853 0.1488563
# ID 2 1 3 0.09858466 0.0980073 0.07424215 0.1257947
# ID 3 1 3 0.16982380 0.1674375 0.10726483 0.2540990
# (...)
#
# $Death
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 1 3 0.07734816 0.07608985 0.04895068 0.1098262
# ID 2 1 3 0.08598385 0.08609996 0.06279178 0.1119255
# ID 3 1 3 0.08069485 0.07685824 0.04198228 0.1380541
# (...)

# s=5, w=3
P5_3.2sLMPH <- survfitLMCR(tLM = 5,
                         thor = 3,
                         simulate = T,
                         M = 1000,
                         CI.levels = c(0.025, 0.975))

P5_3.2sLMPH
# Predicted individual cumulative incidences of events
#
# $Rec
# tLM thor Value
# ID 1 5 3 0.01891257
# ID 2 5 3 0.27924131
# ID 3 5 3 0.03760378
# (...)
#
# $Death
# tLM thor Value
# ID 1 5 3 0.2004973
# ID 2 5 3 0.1405373
# ID 3 5 3 0.1595905
# (...)

# Predicted individual cumulative incidences of events
# based on 1000 Monte Carlo samples
#
# $Rec
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.02050010 0.01884418 0.007745837 0.04296857
# ID 2 5 3 0.27184453 0.26945235 0.17597514 0.36897579
# ID 3 5 3 0.03948784 0.03655589 0.015824254 0.08138946
# (...)
#
# $Death
# tLM thor Mean Median Lower (2.5%) Upper (97.5%)
# ID 1 5 3 0.1997381 0.1993476 0.13393412 0.2732692
# ID 2 5 3 0.1409608 0.1405373 0.08532541 0.2102408
# ID 3 5 3 0.1595905 0.15824254 0.08413382 0.2657962
# (...)

...
References

Blanche, P., Proust-Lima, C., Loubère, L., Berr, C., Dartigues, J.-F., and Jacqmin-Gadda, H. (2015). Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. *Biometrics* **71**, 102–113.

Ferrer, L., Rondeau, V., Dignam, J., Pickles, T., Jacqmin-Gadda, H., and Proust-Lima, C. (2016). Joint modelling of longitudinal and multi-state processes: application to clinical progressions in prostate cancer. *Statistics in Medicine* **35**, 3933–3948.
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Figure 2 – Boxplots of the differences ($\times 1000$) of Mean Square Error of Prediction (MSEP) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of weak misspecification of the longitudinal marker trajectory (case 4.bis). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 499, 497, 479, 439$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. ref denotes the mean MSEP ($\times 1000$) using the marginal estimator from the joint model for each $(s, w)$. $\overline{N}(s)$ is the mean number of subjects at risk at $s$ and $\overline{D}_{Rec}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

| $s$ | $w=1.5$ | $w=3$ |
|-----|----------|--------|
| 1   | ref = 0.866 | ref = 1.071 |
| 3   | ref = 0.785 | ref = 2.500 |
| 5   | ref = 2.649 | ref = 5.472 |
| 8   | ref = 3.281 | ref = 6.651 |

$\overline{N}(0) = 1000$
$\overline{D}_{Rec}(0, \infty) = 249$
$\overline{N}(1) = 870$
$\overline{D}_{Rec}(1, 1.5) = 125$
$\overline{D}_{Rec}(1, 3) = 201$
$\overline{D}_{Rec}(1, \infty) = 287$
$\overline{N}(3) = 568$
$\overline{D}_{Rec}(3, 1.5) = 64$
$\overline{D}_{Rec}(3, 3) = 99$
$\overline{D}_{Rec}(3, \infty) = 132$
$\overline{N}(5) = 365$
$\overline{D}_{Rec}(5, 1.5) = 29$
$\overline{D}_{Rec}(5, 3) = 42$
$\overline{D}_{Rec}(5, \infty) = 54$
$\overline{N}(8) = 172$
$\overline{D}_{Rec}(8, 1.5) = 6$
$\overline{D}_{Rec}(8, 3) = 10$
$\overline{D}_{Rec}(8, \infty) = 12$
Figure 3 – Boxplots of the differences of Area Under ROC Curve (AUC) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of correct specification of the joint model (case 1). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 499, 494, 486, 389$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. $\bar{\text{ref}}$ denotes the mean AUC using the marginal estimator from the joint model for each $(s, w)$. $\bar{N}^\dagger(s)$ is the mean number of subjects at risk at $s$ and $\bar{D}_{\text{Rec}}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

$\bar{N}^\dagger(0) = 1000$
$\bar{D}_{\text{Rec}}(0, \infty) = 249$
$\bar{N}^\dagger(1) = 947$
$\bar{D}_{\text{Rec}}(1, 1.5) = 66$
$\bar{D}_{\text{Rec}}(1, 3) = 123$
$\bar{D}_{\text{Rec}}(1, \infty) = 206$
$\bar{N}^\dagger(3) = 699$
$\bar{D}_{\text{Rec}}(3, 1.5) = 52$
$\bar{D}_{\text{Rec}}(3, 3) = 86$
$\bar{D}_{\text{Rec}}(3, \infty) = 120$
$\bar{N}^\dagger(5) = 482$
$\bar{D}_{\text{Rec}}(5, 1.5) = 29$
$\bar{D}_{\text{Rec}}(5, 3) = 43$
$\bar{D}_{\text{Rec}}(5, \infty) = 54$
$\bar{N}^\dagger(8) = 253$
$\bar{D}_{\text{Rec}}(8, 1.5) = 6$
$\bar{D}_{\text{Rec}}(8, 3) = 9$
$\bar{D}_{\text{Rec}}(8, \infty) = 11$
Figure 4 – Boxplots of the differences of Area Under ROC Curve (AUC) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of misspecification of the dependence function (case 2). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 499, 498, 497, 428$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. $ar{\text{ref}}$ denotes the mean AUC using the marginal estimator from the joint model for each $(s, w)$. $\bar{N}^+(s)$ is the mean number of subjects at risk at $s$ and $\bar{D}_{\text{Rec}}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

- $\bar{N}^+(0) = 1000$
- $\bar{D}_{\text{Rec}}(0, \infty) = 249$
- $\bar{N}^+(1) = 947$
- $\bar{D}_{\text{Rec}}(1, 1.5) = 66$
- $\bar{D}_{\text{Rec}}(1, 3) = 123$
- $\bar{D}_{\text{Rec}}(1, \infty) = 206$
- $\bar{N}^+(3) = 699$
- $\bar{D}_{\text{Rec}}(3, 1.5) = 52$
- $\bar{D}_{\text{Rec}}(3, 3) = 86$
- $\bar{D}_{\text{Rec}}(3, \infty) = 120$
- $\bar{N}^+(5) = 482$
- $\bar{D}_{\text{Rec}}(5, 1.5) = 29$
- $\bar{D}_{\text{Rec}}(5, 3) = 43$
- $\bar{D}_{\text{Rec}}(5, \infty) = 54$
- $\bar{N}^+(8) = 253$
- $\bar{D}_{\text{Rec}}(8, 1.5) = 6$
- $\bar{D}_{\text{Rec}}(8, 3) = 9$
- $\bar{D}_{\text{Rec}}(8, \infty) = 11$
Figure 5 – Boxplots of the differences of Area Under ROC Curve (AUC) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of substantial violation of the PH assumption (case 3). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 485, 326, 294, 188$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. $\overline{\text{ref}}$ denotes the mean AUC using the marginal estimator from the joint model for each $(s, w)$. $\overline{N}(s)$ is the mean number of subjects at risk at $s$ and $\overline{D}_{\text{Rec}}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

$\overline{N}(0) = 1000$

$\overline{D}_{\text{Rec}}(0, \infty) = 352$

$\overline{N}(1) = 965$

$\overline{D}_{\text{Rec}}(1, 1.5) = 76$

$\overline{D}_{\text{Rec}}(1, 3) = 183$

$\overline{D}_{\text{Rec}}(1, \infty) = 327$

$\overline{N}(3) = 689$

$\overline{D}_{\text{Rec}}(3, 1.5) = 101$

$\overline{D}_{\text{Rec}}(3, 3) = 162$

$\overline{D}_{\text{Rec}}(3, \infty) = 215$

$\overline{N}(5) = 422$

$\overline{D}_{\text{Rec}}(5, 1.5) = 48$

$\overline{D}_{\text{Rec}}(5, 3) = 71$

$\overline{D}_{\text{Rec}}(5, \infty) = 86$

$\overline{N}(8) = 199$

$\overline{D}_{\text{Rec}}(8, 1.5) = 9$

$\overline{D}_{\text{Rec}}(8, 3) = 14$

$\overline{D}_{\text{Rec}}(8, \infty) = 17$
Figure 6 – Boxplots of the differences of Area Under ROC Curve (AUC) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of substantial misspecification of the longitudinal marker trajectory (case 4). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over $R = 500, 496, 476, 357$ replicates for 4 landmark times $s = 1, 3, 5, 8$ respectively, with 2 considered horizons $w = 1.5$ and $w = 3$. ref denotes the mean AUC using the marginal estimator from the joint model for each $(s, w)$. $\bar{N}^f(s)$ is the mean number of subjects at risk at $s$ and $\bar{D}_{\text{Rec}}(s, w)$ is the mean number of recurrences occurred between $s$ and $s + w$. 

- $\bar{N}^f(0) = 1000$
- $\bar{D}_{\text{Rec}}(0, \infty) = 249$
- $\bar{N}^f(1) = 972$
- $\bar{D}_{\text{Rec}}(1, 1.5) = 46$
- $\bar{D}_{\text{Rec}}(1, 3) = 118$
- $\bar{D}_{\text{Rec}}(1, \infty) = 248$
- $\bar{N}^f(3) = 730$
- $\bar{D}_{\text{Rec}}(3, 1.5) = 72$
- $\bar{D}_{\text{Rec}}(3, 3) = 125$
- $\bar{D}_{\text{Rec}}(3, \infty) = 178$
- $\bar{N}^f(5) = 484$
- $\bar{D}_{\text{Rec}}(5, 1.5) = 45$
- $\bar{D}_{\text{Rec}}(5, 3) = 67$
- $\bar{D}_{\text{Rec}}(5, \infty) = 86$
- $\bar{N}^f(8) = 238$
- $\bar{D}_{\text{Rec}}(8, 1.5) = 10$
- $\bar{D}_{\text{Rec}}(8, 3) = 14$
- $\bar{D}_{\text{Rec}}(8, \infty) = 18$
Figure 7 – Boxplots of the differences of Area Under ROC Curve (AUC) between the marginal estimator from the joint model (denoted JM-marg) and alternatives in the case of weak misspecification of the longitudinal marker trajectory (case 4.bis). Considered are the conditional estimator from the joint model (JM-cond), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo value model (2s-LM-PV). The distributions are depicted over \( R = 499, 497, 479, 439 \) replicates for 4 landmark times \( s = 1, 3, 5, 8 \) respectively, with 2 considered horizons \( w = 1.5 \) and \( w = 3 \). \( \bar{\text{ref}} \) denotes the mean AUC using the marginal estimator from the joint model for each \((s, w)\). \( N^\dagger(s) \) is the mean number of subjects at risk at \( s \) and \( D_{\text{Rec}}(s, w) \) is the mean number of recurrences occurred between \( s \) and \( s + w \).
Table 1 – Computation time (in seconds) for each step of the procedures to compute individual cumulative incidences of two competing events in the case of correct specification of the joint model (case 1). Considered are the marginal and conditional estimators from the joint model (denoted JM-marg and JM-cond, respectively), the estimators from cause-specific landmark models using a two-stage or naive approach (2s-LM-PH and Naive-LM-PH, respectively) and the two-stage pseudo-value model (2s-LM-PV). Based on a randomly selected replication, the predictions were computed for a randomly chosen subject ▲ for 2 landmark times s = 1 and s = 5 and one considered horizon w = 3.

| (s, w)   | Estimation of the model | Computation of $\hat{\pi}(s, w; \hat{\theta})$ | Computation of the confidence intervals |
|----------|-------------------------|-----------------------------------------------|----------------------------------------|
| JM-marg  | 461.329                 | 1.308                                        | 1253.320                                |
| JM-cond  | 461.329                 | 0.541                                        | 497.445                                 |
| Naive-LM-PH | 0.009                  | 0.018                                        | 172.033                                 |
| 2s-LM-PH | 0.873                   | 0.022                                        | 538.849                                 |
| 2s-LM-PV | 1.275                   | 0.004                                        | 1.397                                   |