Abstract

Joint models have received increasing attention during recent years with extensions into various directions; numerous hazard functions, different association structures, linear and non-linear longitudinal trajectories amongst others. Many of these resulted in new R packages and new formulations of the joint model. However, a joint model with a linear bivariate Gaussian association structure is still a latent Gaussian model (LGM) and thus can be implemented using most existing packages for LGM’s. In this paper, we will show that these joint models can be implemented from a LGM viewpoint using the R-INLA package. As a particular example, we will focus on the joint model with a non-linear longitudinal trajectory, recently developed and termed the partially linear joint model. Instead of the usual spline approach, we argue for using a Bayesian smoothing spline framework for the joint model that is stable with respect to knot selection and hence less cumbersome for practitioners.

1 Introduction

Latent Gaussian models (LGM’s) is a group of models that contains most statistical models used in practice. Indeed, most generalized linear mixed models (GLMM’s) and general additive models (GAM’s) that we are able to perform inference with, are examples of LGMs. In the context of joint models, this viewpoint has largely been under-presented and merely mentioned in [Martino et al. (2011)]. A joint model is unique in the sense that there are two different likelihoods and shared random effects in the model. Extensions of linear joint models like spatial random effects, non-linear trajectories and multiple end-points amongst others, are used in the context of joint models to address certain practical challenges. Each of these new joint models is still a latent Gaussian model and thus no special implementation package is needed for each one. The R-INLA package based on the INLA methodology [Rue et al. (2009)].
has been used extensively for latent Gaussian models and could thus be used for joint models as well. Most longitudinal likelihoods and hazard assumptions can be facilitated in this framework, leaving no need for developing a new joint model for each set of assumptions. As a particular example, we will focus on the recently proposed partially linear joint model by Kim et al. (2017).

Non-linear or partially linear joint models, in particular, is a natural extension to the linear joint model since this is often the case in real datasets. Kim et al. (2017) introduced a frequentist approach to fit a partially linear joint model using splines and presented a selection method for the knot set based on some model selection metrics. A Bayesian P-splines approach is adopted in a joint model framework by Köhler et al. (2017) where the number of knots are also based on the value of some model selection metrics. The approach proposed by Köhler et al. (2017) uses the R package bamiss and the authors commented that the implementation of this model is not computationally feasible.

In this paper, we present a Bayesian approach embedded within the R-INLA package (Rue et al., 2009) to fit a partially linear/non-linear joint model, without the burden of choosing a specific set of knots. We use a Bayesian smoothing spline model described by Lindgren and Rue (2008) and Yue et al. (2014), that is the solution of a stochastic differential equation (SDE) resulting in a second-order random walk (see Lindgren and Rue (2008) and Simpson et al. (2012) for further details) in contrast to the semi-parametric Bayesian method proposed by Rizopoulos and Ghosh (2011) that also depends on knot selection. Using this methodology, the model is stable with regards to the choice of the number and placement of the knots needed to form a spline basis as in Kim et al. (2017), since it is a continuous time model. Additionally, our approach introduces a hyperparameter pertaining to the spline component that is interpretable and can be used to assess the appropriateness of the non-linear component.

In Section 2, we present the partially linear joint model as defined by Kim et al. (2017). Also, we present various forms of the linear shared random effect that can be fitted using R-INLA, but not with most of the other available packages for joint models. The Bayesian smoothing spline is discussed in Section 3. Latent Gaussian models and a synopsis of the INLA methodology underpinning the R-INLA package is presented in Section 4. In this section, we also discuss how joint models fit into the LGM framework. In Section 5, we present an example of our approach and compare it to that presented in Kim et al. (2017) using the simulated PSA dataset presented in the jplm function in the JointModel package. The paper is concluded by concluding remarks in Section 6.
2 Partially linear joint model

A joint model consists of two marginal models, linked by shared, correlated random effects. The motivation for the construction of such a model is found in the biological or physical process generating the data, since multiple types of data generated by the same individual is inherently correlated. The joint modeling of time to event and longitudinal data is a fundamental tool in these type of studies since insights about the survival component can be gained from the longitudinal series (see Wulfsohn and Tsiatis (1997), Hu and Sale (2003), Tsiatis and Davidian (2004), Guo and Carlin (2004) amongst others for more details). This is especially beneficial in studies where the events are lengthy to observe or scarce. Usually, the model is constructed as the combination of a longitudinal model to analyze data measured at multiple time points based on the same investigative subject and a survival model for the time to event data. This setup is quite common in most studies where subjects are followed two-fold, biomarkers are collected at multiple time points to investigate the behaviour of some physical process (usually after some intervention/treatment) as well as the absence/presence of a certain linked event (usually a relapse or a fatal event).

The models are jointly fitted by sharing a set of random effects from the longitudinal submodel to the survival submodel. This provides insights into the biological process acting as the driving force behind various diseases such as prostate cancer (Serrat et al., 2015), ovarian cancer (Huang et al., 2018), AIDS (Guo and Carlin, 2004), Dermatomyositis (van Dijkhuizen et al., 2018) and Renal disease (Rizopoulos and Ghosh, 2011), to mention but a few. The exact form of the shared random effect can vary. The most popular form currently used is a linear random effect in time as the sum of a random intercept and random slope over time, as implemented in the R packages JM-bayes, JointModel and the function jplm of which the latter can incorporate a non-linear trajectory over time, in the longitudinal submodel. Both Bayesian and frequentist methods have been developed for joint models as summarized in the aforementioned packages, amongst others. The linear shared random effect assumption has recently been challenged by (Andrinopoulou and Rizopoulos, 2016). In this paper, however, we will focus on the case of linear shared random effects.

We denote $y$ and $s$ as the response vectors of the longitudinal and survival submodels, respectively. Additionally, $X$ and $Z$ is a set of available covariates for the longitudinal and survival submodels, respectively.

2.1 Longitudinal submodel

In various real-life situations, numerous datapoints are collected from the same individual at different timepoints. This forms a longitudinal series of data and cannot be modelled using standard techniques like generalized linear models since the assumption of independent and identically distributed observations
does not hold. Instead, conditional on the subject and/or group-specific random effects, the observations are independent and identically distributed in the context of a generalized linear mixed model.

For each individual \( i, i = 1, ..., N \) we have a vector of observations \( y_{ijk} = y_{ij}(t_{ijk}) \) at various timepoints \( t_{ijk} \), for groups \( j = 1, ..., N_t \) where \( k = 1, ..., N_{ij} \), such that \( \sum_i \sum_j N_{ij} = N_L \). The longitudinal submodel is a generalized mixed model for the longitudinal outcome in continuous time. We assume that the conditional longitudinal outcomes \( y_{ijk}|(\beta, X_{ijk}, u_{ijk}) \) are conditionally independent and follow a well-defined distribution, \( \mathcal{G} \) with some density function \( g \), linear predictor \( \eta_L \) and hyperparameters \( \theta_L \). In practice, a Gaussian likelihood is often assumed, although this is not necessary and any well-defined distribution can easily be facilitated in our computational procedure. The longitudinal submodel is as follows:

\[
y_{ijk}|(\beta, X_{ijk}, u_{ijk}) \sim \mathcal{G}(\eta_L = \alpha(t_{ijk}) + \beta^T X_{ijk} + u_{ijk}) 
\]

In essence, the submodel is composed by a set of fixed effects, \( \beta^T X_{ijk} \), and a set of random effects, \( \alpha(t_{ijk}) + u_{ijk} \). In this specification, \( \alpha \) denotes the longitudinal trajectory which can assume any form, also non-linear, with hyperparameters \( \theta_\alpha \). The random effects \( u \) are the shared components, linear in time, which forms the basis of the joint model. Specifically, we formulate,

\[
u_{ijk} = u_{ij}(t_{ijk}) = w_{ij} + v_{ij}t_{ijk} \]

where \( w_{ij} \) and \( v_{ij} \) follow a bivariate Gaussian distribution with zero mean, precision matrix \( Q_u \) (inverse covariance matrix) and correlation coefficient \( \rho \). This Gaussian assumption is mostly used in literature.

### 2.2 Survival submodel

Survival datasets are unique in the sense that the response for subject \( l \) consists of an event time, \( s_l \), as well as a censoring variable, \( c_l \), to indicate if the time was censored (\( c_l = 0 \)) or not (\( c_l = 1 \)). Right censoring is most commonly found in practice since this results from terminating a study before all subjects experienced the event. Let \( s_l^* \) be the event time, if the subject experienced the event (\( c_l = 0 \)) and suppose \( s^X \) is the last timepoint in the study period, then, in the case of right censoring, \( s_l = \min(s_l^*, s^X) \). The construction of the time variable \( s_l \) is slightly different under different censoring schemes, so we will focus on right censoring in this paper.

The specification of the form of the baseline hazard function \( h_0(t) \) can be achieved parameterically (exponential (constant hazard), Weibull (monotonic hazard), log-Gaussian or log-Logistic (non-monotonic) baseline hazard function) or semi-parametrically (Cox piecewise constant model). Each of the aforementioned models can be used in our computational procedure, so we will propose the survival submodel in a general form and later present the specific details.
for each case. The survival submodel is defined using the hazard rate as:

\[ h(t) = h_0(t) \exp(\gamma^T Z + \nu \circ (w_1, v_1 s) + m_i). \]  

(3)

and some hyperparameters \( \theta \). If \( \nu \circ (w_1, v_1 s) \) is independent of time, then we have a proportional hazards model. The plausibility of proportional hazards should be investigated using exploratory analysis of the empirical survival/hazard curves. The random effect \( m_i \) is used to model subject-specific variability in the survival time, often called a frailty component, resulting in a frailty variable \( \exp(m_i) \). The association between the longitudinal and survival sub-models is established by the term \( \nu \circ (w_1, v_1 s) \).

2.3 Possible linear association structures

The joint model is solely developed based on the shared effects from both submodels. A subset of the random effects in the longitudinal model enter the hazard rate model through the well-defined combination \( \nu \circ (w_1, v_1 s) \) as in (3). This combination can be time-dependent, resulting in an accelerated failure time model. The functional form of \( \nu \circ (w_1, v_1 s) \), where \( \circ \) is the component-wise product, can assume various structures, some commonly found are summarized below (Henderson et al., 2000):

\[
\begin{align*}
\nu \circ (w_1, v_1 s) &= \nu w_1 \quad (4) \\
\nu \circ (w_1, v_1 s) &= \nu(v_1 s) \quad (5) \\
\nu \circ (w_1, v_1 s) &= \nu(w_1 + v_1 s) \quad (6) \\
\nu \circ (w_1, v_1 s) &= \nu_1 w_1 + \nu_2 (v_1 s) \quad (7)
\end{align*}
\]

With the addition of (6) in the R-INLA package, all these functional forms, (4)-(7), can be assumed in R-INLA, while most currently available R-packages for joint models, as well as jplm, can only facilitate (6). Within our computational framework, the frailty variable should have a log-Gaussian distribution, a priori. The log-gamma frailty has been included in a test version and is discussed thoroughly in Martins and Rue (2014). In this paper, we will only focus on log-Gaussian frailties to not distract from the main aim.

3 Bayesian smoothing spline model

As noted previously, the main aim of this paper is to formulate a partially/non-linear joint model that can capture non-linear trajectories presented by the data as an LGM. Traditionally, these spline models have been based on selecting a number of knots or basis functions, \( B_k \), and then formulating a dependency structure through coefficients \( \lambda_k \), to give the random effect

\[ \alpha(t) = B(t) \lambda. \]

The choice of the placement and number of knots has been addressed in various different ways. Zhou and Shen (2001) proposed a knot relocation and search
method instead of the stepwise addition and deletion approach. A two-stage knot selection approach using wavelet decomposition and then statistical model selection techniques was proposed by [He et al. (2001)], while [Spiriti et al. (2013)] introduced a stochastic search algorithm as an improvement on multivariate adaptive regression splines (MARS) ([Friedman, 1991]) to produce a near-optimal knot set in the squared error sense. A Bayesian approach based on the joint posterior of the placement and number of knots using piecewise polynomials is presented in [Denison et al. (1998)], while [Leitenstorfer and Tutz (2007)] proposed using boosting techniques with radial basis functions. Irrespective of the method used to find a knot set, the main issue is that the number and locations of knots or basis functions can change the model in fundamental ways. The reason the model is unstable with respect to the choice of knots, is that the covariance structure is built on the spline coefficients $\lambda$, instead of on the spline $\alpha(t)$.

A different approach to spline models is implemented in the R-INLA package and described by [Lindgren and Rue (2008)] and [Yue et al. (2014)]. This approach is based on finite element methods, frequently used in numerics and mathematical modelling in general, where the focus is on approximating some continuous spline $\alpha(t)$ on a discrete set of knots. The covariance structure on $\lambda$ is derived by approximating the desired covariance structure of $\alpha(t)$, following the theory of numerical discrete approximations to continuous equations. Different choices of knots or basis functions will approximate the same continuous model, and, as the number of knots grow large, become stable (and converge to the continuous model), contrary to most used methods for spline regression.

For the second order random walk, the continuous SPDE model is

$$\alpha''(t) = W,$$

where $\alpha''$ denotes the second derivative and $W$ the Gaussian white noise process. For regular intervals, this can be approximated by

$$\alpha(t - 1) - 2\alpha(t) + \alpha(t + 1) \overset{d}{=} w_t,$$

where $w_t$ is Gaussian white noise with precision $\tau_\alpha$. The use of irregular locations is found in [Lindgren and Rue (2008)], and all good approximations (the definition of “good” is studied in numerical mathematics) will give very similar models. The next modelling challenge with the random walk order 2, is that the size of the spline (the range of values the spline can take) is difficult to interpret, and it depends on the total number of observations. This challenge was resolved by [Sørbye and Rue (2014)], and is implemented in R-INLA through the scale.model option. With this approach, we can interpret the “size” of the spline to be the overall deviation from a straight line (the straight line has second derivative equal to zero).
4 Latent Gaussian joint model

In this section we will briefly present the concept of latent Gaussian models and the INLA methodology. Preference is given to the details useful for this paper, further details can be found in Rue et al. (2009). Joint models as presented in this paper, are shown to be LGM’s and hence fit into the INLA framework.

4.1 Latent Gaussian models and INLA

Hierarchical Bayesian additive models are widely used in various applications. A specific subset of Bayesian additive models is the class of latent Gaussian models (LGM). An LGM can be efficiently modelled using the INLA methodology implemented in the R-INLA package. This class comprises of well-known models such as mixed models, temporal and spatial models. An LGM is defined as a model having a specific hierarchical structure, as follows: The likelihood is conditionally independent based on the likelihood parameters (hyperparameters), $\theta$, and the linear predictors, $\eta_i$, such that the complete likelihood can be expressed as

$$
\pi(y|\eta, \theta) = \prod_{i=1}^{N} \pi(y_i|\eta_i(X), \theta).
$$

(9)

The linear predictor is formulated as follows:

$$
\eta_i = \beta_0 + \beta^T X_i + u_i(z_i) + \epsilon_i
$$

(10)

where $\beta$ represent the linear fixed effects of the covariates $X$, $\epsilon$ is the unstructured random effects and $\gamma$ represents the known weights of the unknown non-linear functions $u$ of the covariates $z$. The unknown non-linear functions, also known as structured random effects, $u$ include spatial effects, temporal effects, non-separable spatio-temporal effects, frailties, subject or group-specific intercepts and slopes etc. This class of models include most models used in practice since time series models, spline models and spatial models, amongst others, are all included within this class. The main assumption is that the data, $Y$ is conditionally independent given the partially observed latent field, $X$ and some hyperparameters $\theta$. The latent field $X$ is formed from the structured predictor as $(\beta, u, \eta)$ which forms a Gaussian Markov random field with sparse precision matrix $Q(\theta_2)$, i.e. $X \sim N(0, Q^{-1}(\theta_2))$. A prior, $\pi(\theta)$ can then be formulated for the set of hyperparameters $\theta = (\theta_1, \theta_2)$. The joint posterior distribution is then given by:

$$
\pi(X, \theta) \propto \pi(\theta) \pi(X|\theta) \prod_i \pi(Y_i|X, \theta)
$$

(11)

The goal is to approximate the joint posterior density (11) and subsequently compute the marginal posterior densities, $\pi(X_i|Y), i = 1...n$ and $\pi(\theta|Y)$. Due to the possibility of a non-Gaussian likelihood, the Laplace approximation to approximate this analytically intractable joint posterior density. The sparseness assumption on the precision of the latent Gaussian field ensures efficient computation (Rue and Held (2005)).
4.2 Joint models as latent Gaussian models

In this section, we will briefly show that the joint model is indeed an LGM as defined in Section 4.1. The likelihood for the survival submodel from Section 2.2 is

\[ \pi_S(s|Z, \gamma) = \prod_{l=1}^{N} \pi_l(s|Z, \gamma) = \prod_{l=1}^{N} f_l(s)[1 - F_l(s)]^{1-c} \]

where \( f_l(s) = h_l(s) \exp \left( - \int_{0}^{s} h_l(u) du \right) \) from (3). The likelihood for the longitudinal biomarker from Section 2.1 is

\[ \pi_L(y|X, \beta) = \prod_{i=1}^{N_L} g(y_i). \]

The associated linear predictors are

\[
\eta^S = \gamma^T Z + \nu \circ (w_l, v_l s) + m_l \\
\eta^L = \alpha(t) + \beta^T X + u.
\] (12)

Note that each longitudinal observation is connected to the latent field through the linear predictor \( \eta^L \) in (1) and each survival time through the linear predictor \( \eta^S \) in (3). Now consider the hyperparameters \( \theta = \{\theta_l, \theta_S, \theta_m, \tau_a, \nu, Q_u, \rho\} \), the latent field \( X = (\eta^L, \eta^S, \beta, \gamma, v, w, m, \alpha) \) conditioned on \( \theta \) has a Gaussian distribution with precision matrix \( Q(\theta) \). From this construction of the latent field, the observations \( \{y_{ijk}\}, \{s_l, c_l\} \) have a complete likelihood that depends on \( X \) only through one of the linear predictors, \( \{\eta^L\}, \{\eta^S\} \). Finally the hyperparameters \( \theta \) are assigned a prior distribution \( \pi(\theta) \). Hence, the partially linear joint model as presented here, is an LGM and we can thus use the INLA methodology for efficient Bayesian inference. A simple example using a simulated dataset with a non-linear longitudinal trend is available in Appendix 7.1 for illustration purposes.

5 Example: PSA study

In prostate cancer studies, Prostate-specific Antigen (PSA) has been identified as a biomarker for the status of prostate cancer. High levels of PSA are indicative of increased risk of prostate cancer or recurrence. Radiation therapy is a common course of treatment often prescribed for patients with prostate cancer. If successful, the PSA levels are expected to drop and remain at a low level. On the contrary, PSA levels will drop initially and then rise again (Zagars et al., 1995). Hence, it is desirable to develop a flexible model to capture this nonlinear temporal trend of PSA levels per patient. A challenge is that the follow-up of PSA is stopped when salvage hormone therapy is initiated, which is known to change the PSA level or when prostate cancer recurred, resulting in possibly informative drop-out. If this informative drop-out is unaccounted for, it can lead to considerable bias in the PSA trajectory estimation. The objective of
this analysis is thus, to identify the trajectory of post-radiation PSA change, while correctly accounting for the informative drop-out. More details about the clinical impact of such a study can be found in Proust-Lima and Taylor (2009).

5.1 Partially linear joint model

In Kim et al. (2017) a partially linear joint model is proposed utilizing a spline component to capture the non-linear trajectory. They developed a procedure using BIC for the knot selection needed to fit this spline. In this paper, however, we use the Bayesian smoothing spline model as presented in Section 3 to capture the non/semi-linear trajectory of PSA levels using INLA. This approach facilitates a computationally efficient and user-friendly implementation of these types of models, and is stable with regards to the knot set. This approach produces reproducible and reliable results. The joint model under consideration in this application from 12, is:

\[
\log(\text{PSA}) (t) = \eta^L + \epsilon(t) \\
\eta^S (s) = h_0(s) \exp(\eta^S)
\]

where \( \epsilon \sim N(0, \sigma^2_\epsilon) \). We assume a Weibull baseline hazard function, hence \( h_0(s) = \kappa s^{\kappa-1} \) which is non-constant over time. The exponential baseline hazard function with constant hazard can be achieved as a special case when \( \kappa = 1 \). In Kim et al. (2017) the functional form \( \nu \circ (w, vs) = \nu (w + vs) \) as in (13) is used, which is the most commonly used form of shared effects in joint models. This form has now been included in the R-INLA package using the model "intslope". To facilitate a more general structure, we also consider \( \nu \circ (w, vs) = \nu_1 w + \nu_2 (vs) \) as in (14), hence the linear predictors are formulated as:

\[
\eta^L = \alpha(t) + \beta \log(\text{PSA}_{\text{base}}) + w + vt \\
\eta^S_1(s) = \gamma \log(\text{PSA}_{\text{base}}) + \nu(w + vs)
\] (13)

and

\[
\eta^L = \alpha(t) + \beta \log(\text{PSA}_{\text{base}}) + w + vt \\
\eta^S_2(s) = \gamma \log(\text{PSA}_{\text{base}}) + \nu_1 w + \nu_2 (vs)
\] (14)

where

\[
\begin{bmatrix} w \\ v \end{bmatrix} \sim N \left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_w & \rho \sigma_w \sigma_v \\ \rho \sigma_w \sigma_v & \sigma^2_v \end{bmatrix} \right)
\]

and \( \alpha(t) \) is a second order random walk model as described in Section 3. Within the INLA framework, the number of groups for the local spline should be specified. This number should have minimal influence on the estimated result due to the construction presented in Section 3. On the contrary, it is well-known that the number of knots greatly influence the estimated spline using more traditional methods as in Kim et al. (2017). This conjecture is further discussed in the presentation of the results for the dataset under discussion.
5.2 Bayesian inference

The linear predictors under consideration contains various components of the latent field and also some hyperparameters. The prior for the latent field is assumed to be multivariate Gaussian. The regression coefficients for the fixed affects are assigned vague independent Gaussian priors. Following Simpson et al. (2017), we assign penalized complexity priors for the hyperparameters in the model as far as possible.

The random walk order two model \( \alpha(t) \) in (8) has one hyperparameter, \( \tau \) which is assigned a penalized complexity prior with prior density

\[
\pi(\tau) = \lambda_\alpha \tau^{-\frac{3}{2}} \exp(-\lambda_\alpha \tau^{-\frac{1}{2}})
\]

such that \( P(\sqrt{\tau} > 1) = 0.01 \), i.e. \( \lambda_\alpha = \ln(0.01) \), which is the Gumbel type 2 distribution. The bivariate random effect \( [w, v] \) assumes a bivariate Gaussian prior with covariance matrix \( \tau_{w,v}^{-1}R^{-1}, R \geq 0 \) with a penalized complexity prior for \( \tau_{w,v} \) as the Gumbel type 2 distribution with parameter \( \log(0.01) \), as well.

The motivation for employing penalized complexity priors for the precision hyperparameters are founded in the fact that the usual priors for the variance components, i.e. independent inverse-gamma priors as in Huang et al. (2018), overfits and cannot contract to the simpler model in which the respective model component has trivial variance. This is especially important in the case of joint models since the effect of overfitting is exacerbated by the influence of the shared random effect on all the linear predictors.

5.3 Results

The two aforementioned models were both fitted using R-INLA (for more details see the Appendix) and was also fitted using jplm for comparison purposes (the code is available in Web Appendix A). Firstly, the estimated post-treatment PSA trajectories are presented in Figure 1. It is apparent that the number of knots changes the shape of the estimated trajectory to a large extent. For a low number of knots, the estimated trajectory is strictly convex but as the number of knots increase, the trajectory contains concave and convex parts. This challenge is not present in the trajectories estimated using R-INLA. Even for differing number of groups and knot placement, the shape of the estimated trajectory is preserved. It is clear from Figure 1 that the trajectories estimated from R-INLA are supported by the data to a larger extent than some of the trajectories estimated from jplm. This behaviour of a spline is inherent in the formulation and construction of the spline model as a combination of basis functions with associated random weights, as opposed to the formulation as presented in Section 3 and implemented in R-INLA. Secondly, the resulting estimated joint model is presented. The results are summarized in Table 1. It is evident that the two estimation procedures provide similar results.
Figure 1: Estimated non-linear post PSA trajectory using R-INLA and \texttt{jplm}

although the uncertainty from using \textit{R-INLA} is higher. This is an expected result from a Bayesian viewpoint. It is quite clear from Table\ref{table:results} that the hazard of informative dropout is correlated with the longitudinal PSA biomarker since $\nu = 0.919$ with 95\% credible interval (0.645; 1.193). This result confirms that the joint model approach is supported by the data and should be preferred to the separate models. The structure of the association term as in (13) is quite restrictive but has been used extensively. We also investigate the possibility of changing the association structure to (14) and present the results in Table\ref{table:results2}.

In comparison, the results between models 1 and 2 are very similar for the fixed effects and variance hyperparameters. The interesting difference between the two models as presented in Tables\ref{table:results} and \ref{table:results2} is that the values of $\nu_1$ and $\nu_2$ are quite different from each other, and from $\nu$ in Table\ref{table:results}. This implies that the structure of the shared effect presented in (13) is not supported by the data in this example and the more flexible model as in (14) should rather be used. The model in (14) is not available in most of the packages mentioned throughout the paper, but is feasibly implemented in the \textit{R-INLA} package.

In Figure\ref{fig:trajectories} we present some of the longitudinal trajectories and survival curves (or in the context of this application, the non-dropout probabilities) for individual patients based on (14). The vertical line indicates the time at which the dropout (solid) or censoring (dashed) occurred. The stepwise curve is the
Table 1: Results for the PSA dataset using R-INLA and jplm for the specification in (13)

| Parameter | Posterior Mode | Posterior SD | Point estimate | Standard error |
|-----------|----------------|--------------|----------------|----------------|
| Joint model 1 - INLA | | | Joint model 1 - jplm | |
| $\beta$ | 0.450 | 0.061 | 0.443 | 0.004 |
| $\gamma$ | 0.743 | 0.198 | 0.742 | 0.041 |
| $\sigma^2$ | 0.091 | 0.005 | 0.089 | 0.003 |
| $\sigma^2_w$ | 0.226 | 0.143 | NA | NA |
| $\sigma^2_v$ | 0.342 | 0.053 | 0.328 | 0.003 |
| $\rho$ | -0.131 | 0.149 | -0.172 | 0.025 |
| $\nu$ | 0.921 | 0.137 | 1.122 | 0.121 |
| $\kappa$ | 0.806 | 0.092 | NA | NA |

Table 2: Results for the PSA dataset using R-INLA for the specification in (14)

| Parameter | Posterior Mode | Posterior SD |
|-----------|----------------|--------------|
| Joint model 2 - INLA | | |
| $\beta$ | 0.389 | 0.098 |
| $\gamma$ | 0.698 | 0.193 |
| $\sigma^2$ | 0.125 | 0.007 |
| $\sigma^2_w$ | 0.166 | 0.105 |
| $\sigma^2_v$ | 0.201 | 0.032 |
| $\sigma^2_\epsilon$ | 0.365 | 0.203 |
| $\rho$ | -0.431 | 0.257 |
| $\nu_1$ | 1.025 | 0.270 |
| $\nu_2$ | 0.562 | 0.308 |
| $\kappa$ | 0.817 | 0.093 |

Kaplan-Meier estimate of the survival curve for all patients, the solid curve indicates the estimated mean survival curve from our model and the dashed curve is the patient-specific survival curve.

The association between the PSA biomarker and the risk of dropout is evident from Figure 2. Patients with the distinctive decrease-increase behaviour are at higher risk of dropout (lower survival function) and most eventually dropped out as indicated by the solid vertical line. We have included two patients (8 and 15) whose dropout times are censored but based on their PSA biomarker levels, their survival functions are higher than the mean survival and they would thus be considered for non-dropout. On the contrary, patients 37 and 38 display the typical decrease-increase behaviour and their survival functions indicate the higher probability of dropout. The patient specific results can be used for dynamic predictions to identify those patients who are most at risk of dropout, amongst other things. The appropriateness of our proposed model is clear from the detailed discussion of this specific example. The method can be applied to
various other datasets usually used in joint model analysis using the \textit{R-INLA} package.

6 Conclusion

Joint models is one of the most common approaches used to analyze clinical time to event data. Consequently, various extensions and generalizations have been developed, each with its own implementation structure. There are various R packages available as mentioned, from both frequentist and Bayesian viewpoints. In this paper, however, we showed that any joint model with linear association structure, is indeed a simple latent Gaussian model and all tools for LGM’s can thus be applied in the context of joint models. One of the most established and popular tools for LGM’s, is the INLA framework embedded in the \textit{R-INLA} package. This affords the use of complicated joint models with relative ease, even as the models evolve in complexity. Model based evaluation of the assumptions, like the assumed association structure or non-linearity, is done with little effort within the \textit{R-INLA} framework since a multitude of joint model structures can be facilitated in this framework.

As an example, we focused on a partially linear joint model with a spline component to accommodate for non-linear longitudinal trajectories. Instead of the usual splines approach with a set of basis functions and corresponding regression coefficients. From a Bayesian perspective, priors are usually assumed for the regression coefficients. We proposed an alternative approach, that assumes priors for the spline itself. This results in a spline component where the user is relieved of the burden of knot selection. Subsequently, we assumed penalized complexity priors to achieve shrinkage in the joint model. The applicability of this proposal was illustrated using data from a Prostate cancer study using PSA levels and time to dropout.

Ultimately, the developments presented in this paper grants the application of complexities in joint models, such as non-linear or spatial components, not readily available for practical use in most other R packages. The proposed approach is useful and wieldy for practitioners and statisticians alike, using the \textit{R-INLA} package for efficient implementation.

Supplementary Materials

Web Appendix A, referenced in Section 5.3 is available with this paper at the Biometrics website on Wiley Online Library.

References

Andrinopoulou, E.-R. and Rizopoulos, D. (2016). Bayesian shrinkage approach for a joint model of longitudinal and survival outcomes assuming different
association structures. *Statistics in Medicine*, 35(26):4813–4823.

Denison, D., Mallick, B., and Smith, A. (1998). Automatic Bayesian curve fitting. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 60(2):333–350.

Friedman, J. H. (1991). Multivariate adaptive regression splines. *The Annals of Statistics*, pages 1–67.

Guo, X. and Carlin, B. P. (2004). Separate and joint modeling of longitudinal and event time data using standard computer packages. *The American Statistician*, 58(1):16–24.

He, X., Shen, L., and Shen, Z. (2001). A data-adaptive knot selection scheme for fitting splines. *IEEE Signal Processing Letters*, 8(5):137–139.

Henderson, R., Diggle, P., and Dobson, A. (2000). Joint modelling of longitudinal measurements and event time data. *Biostatistics*, 1(4):465–480.

Hu, C. and Sale, M. E. (2003). A joint model for nonlinear longitudinal data with informative dropout. *Journal of Pharmacokinetics and Pharmacodynamics*, 30(1):83–103.

Huang, Y., Lu, X., Chen, J., Liang, J., and Zangmeister, M. (2018). Joint model-based clustering of nonlinear longitudinal trajectories and associated time-to-event data analysis, linked by latent class membership: with application to AIDS clinical studies. *Lifetime data analysis*, 24(4):699–718.

Kim, S., Zeng, D., and Taylor, J. M. (2017). Joint partially linear model for longitudinal data with informative drop-outs. *Biometrics*, 73(1):72–82.

Köhler, M., Umlauf, N., Beyerlein, A., Winkler, C., Ziegler, A.-G., and Greven, S. (2017). Flexible Bayesian additive joint models with an application to type 1 diabetes research. *Biometrical Journal*, 59(6):1144–1165.

Leitenstorfer, F. and Tutz, G. (2007). Knot selection by boosting techniques. *Computational Statistics & Data Analysis*, 51(9):4605–4621.

Lindgren, F. and Rue, H. (2008). On the second-order random walk model for irregular locations. *Scandinavian Journal of Statistics*, 35(4):691–700.

Martino, S., Akerkar, R., and Rue, H. (2011). Approximate Bayesian inference for survival models. *Scandinavian Journal of Statistics*, 38(3):514–528.

Martins, T. G. and Rue, H. (2014). Extending integrated nested Laplace approximation to a class of near-Gaussian latent models. *Scandinavian Journal of Statistics*, 41(4):893–912.

Proust-Lima, C. and Taylor, J. M. (2009). Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: a joint modeling approach. *Biostatistics*, 10(3):535–549.
Rizopoulos, D. and Ghosh, P. (2011). A Bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event. *Statistics in Medicine*, 30(12):1366–1380.

Rue, H. and Held, L. (2005). *Gaussian Markov random fields: theory and applications*. CRC press.

Rue, H., Martino, S., and Chopin, N. (2009). Approximate Bayesian inference for latent Gaussian models by using integrated nested laplace approximations. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 71(2):319–392.

Serrat, C., Rué, M., Armero, C., Piulachs, X., Perpiñán, H., Forte, A., Páez, Á., and Gómez, G. (2015). Frequentist and Bayesian approaches for a joint model for prostate cancer risk and longitudinal prostate-specific antigen data. *Journal of Applied Statistics*, 42(6):1223–1239.

Simpson, D., Lindgren, F., and Rue, H. (2012). Think continuous: Markovian Gaussian models in spatial statistics. *Spatial Statistics*, 1:16–29.

Simpson, D., Rue, H., Riebler, A., Martins, T. G., Sørbye, S. H., et al. (2017). Penalising model component complexity: A principled, practical approach to constructing priors. *Statistical Science*, 32(1):1–28.

Sørbye, S. H. and Rue, H. (2014). Scaling intrinsic gaussian markov random field priors in spatial modelling. *Spatial Statistics*, 8:39–51.

Spiriti, S., Eubank, R., Smith, P. W., and Young, D. (2013). Knot selection for least-squares and penalized splines. *Journal of Statistical Computation and Simulation*, 83(6):1020–1036.

Tsiatis, A. A. and Davidian, M. (2004). Joint modeling of longitudinal and time-to-event data: an overview. *Statistica Sinica*, pages 809–834.

van Dijkhuizen, E. P., De Iorio, M., Wedderburn, L. R., and Deakin, C. T. (2018). Clinical signs and symptoms in a joint model of four disease activity parameters in juvenile dermatomyositis: a prospective, longitudinal, multi-center cohort study. *Arthritis research & therapy*, 20(1):180.

Wulfsohn, M. S. and Tsiatis, A. A. (1997). A joint model for survival and longitudinal data measured with error. *Biometrics*, pages 330–339.

Yue, Y. R., Simpson, D., Lindgren, F., Rue, H., et al. (2014). Bayesian adaptive smoothing splines using stochastic differential equations. *Bayesian Analysis*, 9(2):397–424.

Zagars, G. K., Pollack, A., Kavadi, V. S., and von Eschenbach, A. C. (1995). Prostate-specific antigen and radiation therapy for clinically localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics*, 32(2):293–306.
7 Appendix

7.1 Computational considerations for joint models in using INLA

The likelihood of a joint model basically consists of two types of likelihoods and this can be facilitated in the INLA framework. It is essential to construct the response matrix and the covariate matrices correctly for the estimation procedure. For the purpose of this paper, we will present only the case where the joint model consists of longitudinal and survival submodels. This can be extended to include more marginal submodels in the case of multiple endpoint modeling.

Within the context of this paper, consider the following structured predictors of the longitudinal and survival submodels, respectively:

\[
\eta^L_{ijk} = \alpha(t_{ijk}) + \beta^T X_{ijk} + w_{ij} + v_{ijk} \\
\eta^S(s) = \gamma^T Z_i + \nu \phi(w_i, v_i) \tag{15}
\]

Consider the case where the data consists of \(N, i = 1, ..., N\) observations for each of the \(N\) individuals, so that in total there are \(N_L\) longitudinal observations and correspondingly \(N_S = N\) event times and censoring indicators \((s_i, c_i), i = 1, ..., N\). The data is then composed as a list in which each variable consists of \(N_L + N_S\) elements. To achieve this, we include zeros for fixed effects if the covariate is not included in that specific submodel and NA’s for the random effects. In the case of (15), the new response is defined as a list of the \(y_{ijk}\) and \((s_i, c_i)\). The fixed effect covariates are constructed as \((X, 0_1, ..., N_S)\) and \((0_1, ..., N_L, Z)\) while the random effects are constructed as \((\alpha, NA_1, ..., N_S)\).

The main contribution in this area is the estimation of \(\alpha\). Most of the commonly used approaches to estimate the non-linear trend involve the use of knots. This method was also used in Kim et al. (2017). In this paper we propose the use of a time-continuous spline model manifested as a second-order random walk presented in Section 3.

7.2 Example: Simulated joint model

In this example we simulated data from the following scenario:

\[
\eta^L(t) = t^2 + v_i \\
\eta^S = \beta s v_i
\]
where $v_i \sim N(0, \sigma^2_v)$ are the subject-specific random effects that are shared in this joint model. The aim of this example is to illustrate the practical method to fit a joint model in R-INLA. The R code is available at [http://www.r-inla.org/examples/case-studies/van-niekerk-bakka-and-rue-2019](http://www.r-inla.org/examples/case-studies/van-niekerk-bakka-and-rue-2019).

### 7.3 Example: PSA study - computational framework information

The R code used to obtain the results as presented in Section 5 is available at [http://www.r-inla.org/examples/case-studies/van-niekerk-bakka-and-rue-2019](http://www.r-inla.org/examples/case-studies/van-niekerk-bakka-and-rue-2019)

The computational time needed was 83.2 and 15.7 seconds, respectively, for models 2 and 1 fitted using the INLA package. The computer used is an Apple Macbook Pro i5 3.1GHz with 16GB 2133 MHz LPDDR3.
Figure 2: Post PSA trajectories and Survival functions for specific patients