Bayesian joint models for longitudinal and survival data

Carmen Armero

Department of Statistics and Operations Research, Universitat de València
C/ Doctor Moliner 50, Burjassot. 46100 València, Spain

Abstract

This paper takes a quick look at Bayesian joint models (BJM) for longitudinal and survival data. A general formulation for BJM is examined in terms of the sampling distribution of the longitudinal and survival processes, the conditional distribution of the random effects and the prior distribution. Next a basic BJM defined in terms of a mixed linear model and a Cox survival regression models is discussed and some extensions and other Bayesian topics are briefly outlined.

KEYWORDS: Cox survival regression model; Dynamic prediction; Joint latent class models; Linear mixed models; Share-parameter and random-effects models.

1 Introduction

Longitudinal data are observations of one or more variables measured over time of each of the individuals in the study. They include observations between and within individuals that allow the assessment of general patterns of the target population as well as specific individual characteristics. These data are multivariate, clustered, and repeated measures. Longitudinal data of each individual could be understood as a time series. Panel data are longitudinal data in economic scenarios.

Survival times measure follow-up times from a defined starting point to the occurrence of a given event or endpoint of interest. Standard statistical techniques cannot be applied to survival data because they are subject to censoring and/or truncation schemes that usually do not provide complete experimental information.

Joint modeling of longitudinal and survival data is an increasing and productive area of statistical research that examines the association between longitudinal and survival processes. It enhances survival interests with the inclusion of internal time-dependent covariates assessed through longitudinal models as well as longitudinal objectives by allowing for the inclusion of non-ignorable dropout mechanisms through survival tools (Verbeke and Davidian, 2009; Ye and Yu, 2014). Joint models were introduced during the 1990s as a consequence of the research about the human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and cancer studies. Since then, they have been applied to a great variety of studies, mostly in epidemiological and biomedical areas.

The two key elements of the Bayesian reasoning (with regard to the frequentist one) are the conception of probability, that allows to measure uncertainty associated to parameters, models, hypotheses, missing data, etc. in probabilistic terms, and the use of Bayes’ theorem to sequentially update probabilities as more relevant information is obtained. As a result, Bayes inference offers a wide and attractive framework to joint models of longitudinal and survival analysis: posterior inferences for any outcome of interest depending on the parameters that makes unnecessary asymptotic approximations, a simple framework to easily incorporate historical data into the inferential process, or prediction of observable quantities directly assessed in probabilistic terms among others (Ibrahim et al, 2001).

The literature on joint models of longitudinal and survival data is enormous (Rizopoulos, 2012) is an excellent text within the frequentist methodology). Bayesian literature is not as extensive but too numerous to be cited here. References in this paper are only a very small part of all those that should appear in any more extensive work on the area. In any case, a reminder of the early works on the topic (Faucet and Thomas, 1996; Ibrahim et al., 2001; Wang and Taylor, 2001) is always more than convenient to have a historical perspective of the beginning research in the subject.
2 Bayesian joint models

2.1 General formulation

A BJM for longitudinal and survival data is a joint probability distribution for the observable longitudinal \((y)\) and survival variables \((s)\) as well as for the corresponding subject-specific random effects vector \((b)\) and the parameters and hyperparameters \((\theta)\) of the model. This density could be generally expressed as

\[
p(y, s, b, \theta) = p(y, s | b, \theta) p(b | \theta) p(\theta),
\]

where \(p(y, s | b, \theta)\) is the sampling distribution of \((y, s)\) given \((b, \theta)\), \(p(b | \theta)\) the conditional distribution of the random effects given \(\theta\), and \(p(\theta)\) the prior distribution for \(\theta\). Note that the subsequent formulation in the frequentist framework would not include the vector \(\theta\) and therefore its definition would be only written in terms of \(p(y, s, b), p(y, s | b)\) and \(p(b)\).

There are different proposals for the specification of \(p(y, s | b, \theta)\). All them provide a wide framework of the relationship between the longitudinal and the survival processes which facilitates the modeling into longitudinal and survival submodels with various types of connectors between them (Verbeke and Davidian 2009). The most popular structures for that relation are the so-called conditional models, share-parameter models, random-effects models, and the joint latent class models. Copula based models have also addressed that issue recently (Li et al., 2019).

Conditional models were the first to be used in the initial studies on the subject. They express the joint sampling distribution of the longitudinal and survival process as follows:

\[
p(y, s | b, \theta) = p(y | s, b, \theta) p(s | b, \theta) \quad \text{(selection models)}
\]

\[
= p(s | y, b, \theta) p(y | b, \theta) \quad \text{(pattern-mixture models)}.
\]

Selection models are used when the interest of the study lies in the survival process while pattern-mixture models are appropriate for longitudinal purposes.

Shared-parameter models connect the longitudinal and the time-to-event processes by means of a common set of subject-specific random effects. This approach postulates conditional independence between the longitudinal and survival processes given the random effects and the parameters:

\[
p(y, s | b, \theta) = p(y | b, \theta) p(s | b, \theta).
\]

A clear disadvantage of these models is the stiffness of the correlation structure between the longitudinal and the survival processes. The random-effects approach (Henderson et al., 2000) has the same design that the shared-parameter models but allows for more flexibility (and thus more complexity) for the connection between the survival and the longitudinal processes, enabling that a part of the random effects associated to both processes are not common.

The joint latent class model (Proust-Lima et al., 2014) is based on finite mixtures: heterogeneity among the individuals is classified into a finite number of homogeneous latent clusters, which share the same longitudinal trajectory and risk function. Both processes are conditionally independent within the subsequent latent group as follows:

\[
p(y, s | G = g, b, \theta) = p(y | G = g, b, \theta) p(s | G = g, \theta),
\]

where \(G\) is the random variable that measures the uncertainty on the membership of each individual to each group, usually modelled by means of a multinomial logistic model.

The complete specification of a BJM includes the conditional distribution of the random effects, which can be both time-dependent and time-independent, and the choice of an a priori distribution for \(\theta\). After their specification and the obtention of data, Bayes’ theorem updates the current information in terms of the posterior distribution \(p(b, \theta | data)\) which allows posterior inferences for any outcome of interest depending on \(b\) and/or \(\theta\) and it is the main element for assessing posterior predictive distributions for new observable longitudinal and survival elements from
\[ p(y, s \mid data) = \int p(y, s \mid \mathbf{b}, \mathbf{\theta}) p(\mathbf{b}, \mathbf{\theta} \mid data) \, d(\mathbf{b}, \mathbf{\theta}), \] (2)

or separately via the marginal posterior predictive distributions \( p(y \mid data) \) and \( p(s \mid data) \).

### 2.2 A basic Bayesian joint model

The basic BJM is composed of the two most paradigmatic longitudinal and survival models such as the linear mixed model and the Cox survival regression model.

The natural territory of the linear mixed effects model is the normal distribution, whose conditional mean accounts for common population terms and individual-specific elements, the random effects, which are unique to each individual separately. Let \( y_{ij} \) denote the longitudinal response variable for the \( i \)-th, \( i = 1, \ldots, N \) individual registered at the time \( t_{ij}, j = 1, \ldots, n_i \). We assume the following linear mixed model for \( y_i = (y_{i1}, \ldots, y_{in_i})' \):

\[ (y_i \mid \beta, \mathbf{b}, \sigma^2) \sim \mathcal{N}(m_i = \mathbf{X}_i \beta + \mathbf{Z}_i \mathbf{b}_i, \sigma^2 \mathbf{I}), \] (3)

where \( \mathbf{X}_i \) is a \( n_i \times q \) matrix of covariates associated to the parametric vector \( \beta \), \( \mathbf{Z}_i \) is a matrix of covariates associated to random effects \( \mathbf{b}_i \), and \( \mathbf{I} \) is the \( n_i \times n_i \) identity matrix. Random effects \( \mathbf{b} = (b_1, \ldots, b_N)' \) are usually conditionally i.i.d. as \( (\mathbf{b}_i \mid \Sigma_{\mathbf{b}}) \sim \mathcal{N}(\mathbf{0}, \Sigma_{\mathbf{b}}) \) where \( \Sigma_{\mathbf{b}} \) is the variance-covariance matrix.

The Cox proportional hazards model expresses the hazard function \( h(t) \) of the survival time \( T_i \) of individual \( i \) as the product of a common baseline hazard function, \( h_0(t) \), which determines the shape of \( h(t) \), and an exponential term with the relevant covariates as follows:

\[ h_i(t \mid M_i(t), \gamma, \alpha, h_0(t)) = h_0(t) \exp\{d_i^\prime \gamma + \alpha m_i(t)\}, \] (4)

where \( M_i(t) = \{m_i(l), 0 \leq l \leq t\} \) represents the true longitudinal trajectory of individual \( i \) up to time \( t \), \( \mathbf{d}_i \) is a vector of baseline covariates associated to coefficients \( \gamma \), and \( \alpha \) is the coefficient of association between the longitudinal and the survival process. Obviously, if \( \alpha \) were zero the survival and the longitudinal process would be independent.

The last element of the BJM is the prior distribution for \( \mathbf{\theta} \) which includes all the parameters and hyper-parameters of the longitudinal model, \( \beta, \Sigma_{\mathbf{b}} \) and \( \sigma^2 \), as well as the subsequent of the survival process, \( \gamma, \alpha \) and the ones in \( h_0(t) \). Prior independence is the simplest assumption for the joint prior distribution for \( \mathbf{\theta} \). Priors for \( \beta, \gamma \) and \( \alpha \) are commonly elicited as normal distributed centered at zero with wide variances, inverse Wishart for \( \Sigma_{\mathbf{b}} \) and inverse gamma for \( \sigma^2 \) (Guo and Carlin, 2004), although options such as uniform or half-Cauchy distributions for variances seem more appropriate (Gelman, 2006).

Simple extensions of the basic BJM introduce complexity into the longitudinal and the survival modeling such as the distribution of the random effects, the baseline hazard function, and the connectors between the longitudinal and the survival processes. More flexible longitudinal trajectories in terms of splines are in Tang and Tang (2015). Khöler et al. (2016) also extend this flexibility to the survival part of the BJM. Additional terms in the conditional mean \( m_i(t) \) that account for serial correlation not explained by the random effects \( \mathbf{b} \) are considered via Ornstein-Uhlenbeck stochastic processes and Brownian motions in Wang and Taylor (2001) and Armero et al. (2018), respectively. Multivariate \( t \) or Laplace distributions have also been considered as appropriate models for the random effects (Tian et al., 2016).

The basic model for \( h_0(t) \) is defined in terms of the Weibull distribution. Semi-parametric choices (Ibrahim et al., 2014) result in more flexible baseline shapes that could be subject to regularisation through prior distributions in case of overfitting and instability. The shared-parameter model (SPM) in (3) is known as the trajectory model (Zhang et al., 2017) because the true longitudinal mean operates as a temporal covariate in the survival model. Other types of SPM connectors include directly the random effects as covariates in the survival model, different classes of links with regard to individual subgroups, or even time-dependent slope components (Gould et al., 2015).
3 Some extensions and other topics

Bayesian inference offers a natural environment to address complex models with sophisticated longitudinal and/or survival structures. In the case of the survival submodels, administrative right censoring is the most usual pattern but also interval-censoring and left truncation (Armero et al., 2018) can be considered. More complex structures include cure rate models (Yu et al., 2004) or even spatial terms in the hazard function (Martins et al., 2016). Survival submodels with more that one event of interest include, among others, recurrent and competing risks models (Hu et al., 2009). BJM’s with non-normal longitudinal response focused on ordinal longitudinal processes defined in terms of proportional-odds cumulative logit models and longitudinal zero-inflated counts are in Armero et al. (2016) and Zhu et al. (2018), respectively. Luo (2014) accounts for BJM with multivariate longitudinal binary, ordinal cumulative probabilities, and continuous outcomes.

Joint models are complex models. Their practical implementation is challenging and consequently, an important issue in Bayesian computation. In addition to the general software for Bayesian models, we would like to mention the R packagesJMbayes(Rizopoulos, 2016) and bamlss(Umlauf et al., 2018; Umlauf et al., 2019). Furgal et al. (2019) is a recent review on the subject which can currently be completed with Niekerk et al. (2019), which explores BJM via R-INLA based on the Integrated Nested Laplace Approximations (INLA) methodology. Model diagnosis and model selection in BJM are very relevant issues that have been given little attention. Some papers to be quoted are Zhu et al. (2012), which accounts for influence measures for carrying out sensitivity analysis to BJM, and Zhang et al. (2014) that derives a novel decomposition of the AIC and BIC criteria into additive components that allow to assess the goodness of fit for each component of the joint model. Huang and Dagne (2011) consider BJM with skew-normal distribution and measurement errors in covariates, Armero et al. (2016) deals with dynamic estimation and prediction, and finally Alvare s et al. (2020) introduces sequential Monte Carlo methods to update the posterior distribution as more information becomes available.

References

1. D. Alvares, C. Armero, A. Forte, and N. Chopin. Sequential Monte Carlo methods in Bayesian joint models for longitudinal and time-to-event data. Statistical Modelling, doi.org/10.1177/1471082X20916088, 2020.
2. C. Armero, C. Forné, M. Rué, A. Forte, H. Perpinán, G. Gómez, and M. Baré. Bayesian joint ordinal and survival modeling for breast cancer risk assessment. Statistics in Medicine, 35:5267-5282, 2016.
3. C. Armero, A. Forte, H. Perpinán, M. J. Sanahuja, and S. Agustí. Bayesian joint modeling for assessing the progression of Chronic Kidney Disease in children. Statistical Methods in Medical Research, 27(1):298-311, 2018.
4. C. L. Faucett and D. C. Thomas. Simultaneously modelling censored survival data and repeatedly measured covariates: A Gibbs sampling approach. Statistics in Medicine, 15:1663-1685, 1996.
5. A. K. Furgal, A. Sen, and M. Taylor, J. Review and comparison of computational approaches for joint longitudinal and time-to-event models. International Statistical Review, 87(2):393-418, 2019.
6. A. Gelman. Prior distributions for variance parameters in hierarchical models. Bayesian Analysis, 1(3):515-533, 2006.
7. A. L. Gould, M. E. Boye, M. J. Crowther, J. G. Ibrahim, G. Quartey, S. Micallef f, and F. Y. Boisg. Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group. Statistics in Medicine, 34:121-133, 2017.
8. X. Guo and B. P. Carlin. Separate and Joint Modeling of Longitudinal and Event Time Data Using Standard Computer Packages. The American Statistician, 58(1):16-24, 2004.
9. R. Henderson, P. Diggle, and A. Dobson. Joint modelling of longitudinal measurements and event time data. Biostatistics, 1(4):465-480, 2000.
10. W. Hu, G. Li, and N. Li. A Bayesian approach to joint analysis of longitudinal measurements and competing risks failure time data. Statistics in Medicine, 28:1601-1619, 2009.
11. Y. Huang and G. Dagne. A Bayesian Approach to Joint Mixed-Effects Models with a Skew-Normal Distribution and Measurement Errors in Covariates. *Biometrics*, 67:260-269, 2011.

12. J. G. Ibrahim, M.-H. Chen, and D. Sinha. *Bayesian Survival Analysis*. New York: Springer, 2001.

13. J. G. Ibrahim, M.-H. Chen, D. Zhang, and D. Sinha. Bayesian Analysis of the Cox model. In J. P. Klein, H. C. van Houwelingen, J. G. Ibrahim, and T. H. Scheike, editors, *Handbook of Survival Analysis*, chapter 2, pages 27-49. Chapman & Hall/CRC, Boca Raton, 2014.

14. M. Köhler, N. Umlauf, A. Beyerlein, C. Winkler, A.-G. Ziegler, and S. Greven. Flexible bayesian additive joint models with an application to type 1 diabetes research. *Biometrical Journal*, 59:1144-1165, 2016.

15. Z. Li, V. M. Chinchilli, and M. Wang. A Bayesian joint model of recurrent events and a terminal event. *Biometrical Journal*, 61:187-202, 2019.

16. S. Luo. A Bayesian approach to joint analysis of multivariate longitudinal data and parametric accelerated failure time. *Statistical Methods in Medical Research*, 33:580-594, 2014.

17. R. Martins, G. L. Silva, and V. Androuzib. A Bayesian approach to joint analysis of multivariate longitudinal data and parametric accelerated failure time. *Statistics in Medicine*, 35(19):3368-3384, 2016.

18. J. V. Niekerk, H. Bakka, and H. Rue. Joint models as latent gaussian models - not reinventing the wheel. arXiv:1901.09365v1, 2019.

19. C. Proust-Lima, M. Sène, J. M. G. Taylor, and H. Jacqmin-Gadda. Joint latent class models for longitudinal and time-to-event data: A review. *Statistical Methods in Medical Research*, 23:74-90, 2014.

20. D. Rizopoulos. *Joint models for longitudinal and time-to-event data*. New York: Chapman and Hall/CRC, 2012.

21. D. Rizopoulos. The R package JMbayes for fitting joint models for longitudinal and time-to-event data using mcmc. *Journal of Statistical Software*, 72(7):1-45, 2016.

22. A.-M. Tang and N.-S. Tang. Semiparametric bayesian inference on skew-normal joint modeling of multivariate longitudinal and survival data. *Statistics in Medicine*, 34(5):824-843, 2015.

23. Y. Tian, E. Li, and M. Tian. Bayesian joint quantile regression for mixed effects models with censoring and errors in covariates. *Computational Statistics*, 31:1031-1057, 2016.

24. N. Umlauf, N. Klein, and A. Zeileis. BAMLSS: Bayesian additive models for location, scale and shape (and beyond). *Journal of Computational and Graphical Statistics*, 27(3):612-627, 2018.

25. N. Umlauf, N. Klein, T. Simon, and A. Zeileis. bamlss: A Lego toolbox for flexible Bayesian regression (and beyond), arxiv 1909.12345, 2019.

26. G. Verbeke and M. Davidian. Joint models for longitudinal data: Introduction and overview. In G. Fitzmaurice, M. Davidian, V. G., and M. G., editors, *Longitudinal Data Analysis*, chapter 13, pages 319-326. Chapman & Hall/CRC, Boca Raton, 2009.

27. Y. Wang and J. M. G. Taylor. Jointly Modeling Longitudinal and Event Time Data With Application to Acquired Immunodeficiency Syndrome. *Journal of the American Statistical Association*, 96(455):895-905, 2001.

28. W. Ye and M. Yu. Joint models of longitudinal and survival data. In J. P. Klein, H. C. van Houwelingen, J. G. Ibrahim, and T. H. Scheike, editors, *Handbook of Survival Analysis*, chapter 26, pages 523-548. Chapman & Hall/CRC, Boca Raton, 2014.

29. M. Yu, N. Law, J. Taylor, and H. Sandler. Joint longitudinal survival-cure models and their application to prostate cancer. *Statistica Sinica*, 14(4):835-862, 2004.
30. D. Zhang, M. H. Chen, J. G. Ibrahim, M. E. Boye, P. Wang, and W. Shen. Assessing model fit in joint models of longitudinal and survival data with applications to cancer clinical trials. *Statistics in Medicine*, 33:4715-4733, 2014.

31. D. Zhang, M. H. Chen, J. G. Ibrahim, M. E. Boye, and W. Shen. Bayesian Model Assessment in Joint Modeling of Longitudinal and Survival Data with Applications to Cancer Clinical Trials. *Journal of Computational and Graphical Statistics*, 26(1):121-133, 2017.

32. H. Zhu, J. Ibrahim, Y. Y. Chi, and N. Tang. Bayesian influence measures for joint models for longitudinal and survival data. *Biometrics*, 68(3):954-964, 2012.

33. H. Zhu, S. M. DeSantis, and S. Luo. Joint modeling of longitudinal zero-inflated count and time-to-event data: A Bayesian perspective. *Statistical Methods in Medical Research*, 27(4):1258-1270, 2018.