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Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group

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Abstract

Explicitly modeling underlying relationships between a survival endpoint and processes that generate longitudinal measured or reported outcomes potentially could improve the efficiency of clinical trials and provide greater insight into the various dimensions of the clinical effect of interventions included in the trials. Various strategies have been proposed for using longitudinal findings to elucidate intervention effects on clinical outcomes such as survival. The application of specifically Bayesian approaches for constructing models that address longitudinal and survival outcomes explicitly has been recently addressed in the literature. We review currently available methods for carrying out joint analyses, including issues of implementation and interpretation, identify software tools that can be used to carry out the necessary calculations, and review applications of the methodology.

Keywords

time-dependent; random effects; software; applications

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1. Introduction

The objective of this article is a summary of currently available methods for joint modeling of survival data and longitudinal nonsurvival data with emphasis on Bayesian approaches, including evaluations of strengths and weaknesses of the various methods. We explore the practical implications of applying Bayesian approaches to the joint modeling of longitudinal and survival-type outcomes, with the aim of providing recommendations for how such models could or should be constructed, illustrating how they might be used, and elucidating the potential advantages they present and their limitations. We also evaluate software currently available for carrying out calculations needed for designs and data analyses, and identify needs for further software development.

1.1. General background

The joint modeling of survival with longitudinal data continues to be an active area of statistical methodological research. Much of the work has addressed improving efficiency and reducing bias in the survival component [1]. Accordingly, most of the inferential objectives have concerned characterization of survival estimates. Nonetheless, researchers as early as McArdle *et al* [2] have focused on the quantitative changes in the longitudinal trajectory component of these joint models. More recently, researchers have focused on the magnitude of the association between the survival and longitudinal data-generating processes to show person-level correspondence between these outcomes [3–5].

Joint modeling can benefit the analyses of both longitudinal and survival outcomes. The use of longitudinal mixed models to incorporate the effects of time-varying covariables in the evaluation of survival endpoints more accurately represents the quantitative influence of these factors on the survival estimates, compared with direct inclusion of the factor × time terms into the survival regression. Including survival information into the evaluation of the longitudinal observations directly incorporates the effect of an informative missing-data mechanism into the assessment of trends in these observations. Accounting for a clinical outcome as an informative censoring event is especially important when inferences about a longitudinal process are the key objective. Other approaches such as list-wise deletion to remove the uncensored cases or some form of averaging to retain them do not portray the true data-generating mechanism accurately.

The precision of the estimates of the parameters of the survival model, the longitudinal model, or both and, therefore, the accuracy of inferences about the underlying data-generating mechanisms, may be increased by models that incorporate both kinds of outcome, especially if the outcomes are strongly associated. Increased sensitivity for detecting significant treatment effects can be particularly important when evaluating the longitudinal outcomes of RCTs. Practical and scientific considerations impose constraints that limit the trial size and result in designing studies to meet the criteria of primary study endpoints (e.g., overall or progression-free survival). Trial sizes are seldom large enough to provide adequate power for highly variable endpoints such as patient-reported outcomes (PROs), so that the increased sensitivity joint modeling can provide and offers the hope of detecting real treatment effects.

1.2. Patient-reported outcomes

Longitudinal values of objective measurements such as blood pressure and CD4 cell counts are familiar features of trials evaluating the effects of treatments or interventions on clinical outcomes such as disease progression or death. However, subjective measures also can be helpful for understanding the effects of the treatments or interventions. Indeed, corroborative support associating health outcomes as reflected in PROs can improve the interpretability of clinical measures. Moreover, information concerning how patients feel during and after treatment is a topic of growing interest, and addressing this information need will require more methodological development and more careful consideration when designing RCTs [1, 6, 7].

There has been an increase in the desire to evaluate the patients' perspectives by including specific questionnaires in clinical research programs [8–10]. Although the evaluation of subjective responses often is viewed as a soft science, the psychometrics used to develop, present, and analyze these data are at least as advanced as methods used for traditional clinical outcomes (e.g., overall survival). Nonetheless, results typically have been disappointing for various reasons, such as correct analyses not being based on appropriate study designs, inadequate data collection schedules, and nonmeaningful analyses driven by descriptive-only research hypotheses [1, 3, 4, 7].

The situation has been aggravated by the common practice of viewing quality of life (QOL) assessments or health outcomes information as supplementary information that is presented in separate trial protocols and analysis plans. This practice ignores the fact that these observations are like any other outcomes. Generally, symptom-based evaluations are more accepted by regulators (Food and Drug Administration PRO guidance) perhaps thereby elevating their status among other psychometrically-based constructs.

Experience from oncology trials suggests that there may be some practical constraints. The requirements for design and analysis of oncology clinical trials are well researched and documented [11, 12]. The prescribed endpoints are viewed as standard, particularly for developing oncology bio-pharmaceuticals, and essential for successful product registration and clinical use. However, as a practical matter, practitioners are trained and experienced in working with these standard outcomes, so that changing the methodology (e.g., from a Cox regression to a parametric non-PH model) generally would yield a different statistic but impart little or no additional useful clinical information upon which to base patient decisions. Hence, although joint modeling of survival and longitudinal data may improve oncology survival endpoint estimates, the pragmatism of regulators and practitioners might limit the widespread adoption of alternative approaches.

The Food and Drug Administration has published guidance on general principles of including PROs into RCTs with the goal of achieving label claims based on these assessments [13]. There is, however, evidence that operationalization and methodological gaps remain when seeking to meet standards for inclusion of PRO measures in RCTs [14]. The CONSORT-PRO extension offers a checklist of considerations for inclusion of PROs in RCTs, which includes specific mention of interpreting PRO data in relation to clinical outcomes, including survival data [15]. Additionally, general references are available to

inform the design and analysis of clinical studies that include PROs as study endpoints [16]. Nonetheless, these references do not provide detailed recommendations and rationale that are needed to overcome the traditional methodological challenges such as showing compelling evidence of the association across time between PROs and clinical endpoints as well as the need for comprehensive inclusion of PROs in the study design and analysis plans (e.g., including properly timed and sufficient collection of PRO data to provide internal validity and statistical power). There are no well-developed standards for the use of PROs in registration designs or in routine clinical practice for oncology or other therapeutic areas [13]. Progress has been made, so opportunities exist for outlining appropriate design and analysis principles for incorporating PRO outcomes into these studies. That said, it still is advisable to consult informative references before undertaking the design and analysis of clinical studies that include PROs as study endpoints.

Patient-reported outcome assessments should be developed routinely with the goal of correspondence to other well-known endpoints using traditional methods such as cross-sectional correlation [17]. Demonstrating such correspondence at the patient level and longitudinally through the use of joint modeling would provide a more compelling rationale in support of the PRO validity. For example, when evaluating therapies for treating diabetes, PRO and longitudinal measurements should be linked to actual progression of diabetes, especially as manifested by recurrent events such as episodes of hypoglycemia.

Patient-level modeling of a recurring event, linked to a PRO trajectory, would inform the event antecedents thereby allowing characterization of factors associated with heterogeneity in treatment effect. Clinical trials often include many PROs in order to examine a wide range of patient outcomes. Under such a scenario, the correspondence between these different self-reported items and constructs would provide a much more data-informed picture upon which to evaluate the efficacy of an investigational compound.

1.3. Benefits of joint modeling [1, 18]

Joint models provide more efficient estimates of the treatment effects on the time to event and the longitudinal marker, and reduce bias in the estimates of the overall treatment effect [1, 5]. For example, if a particular drug reduces the hazard of a particular disease by 30%, then a joint model may lead to an estimated hazard ratio of 0.75, whereas a conventional model (e.g., a Cox model) that does not incorporate the longitudinal data into the analysis may yield a hazard ratio of 0.80. In this case, we say that the estimate based on the joint model is less biased than the Cox model estimate because 0.75 is closer to the true hazard ratio of 0.70. As a result, joint models are now increasingly used and often preferred over the Cox model alone because they yield more accurate and more precise estimates of the treatment effect. Greater efficiency implies higher power and smaller sample sizes in designing clinical trials. Thus incorporating the longitudinal data into the design of a study has the potential of yielding lower sample sizes with higher power compared with that of conventional designs based on time-to-event data alone.

1.4. Challenges of joint modeling

Some of the practical challenges are those encountered by any technology seeking penetration into established practices and beliefs: fear of the new, unknown risk consequences of new methods, and so on. Overcoming these challenges will take time and demonstration of the benefits of joint modeling, which is one of the aims of this article.

The methodology does rely on assumptions about the random effects. However, recent work has shown that the robustness of the assumptions about random effects increases with the number of observations per subject [19, 20].

1.5. Other considerations/applications/extensions

The joint modeling of survival with semicontinuous data, that is, data characterized by a large portion of responses equal to a single value (e.g., zero or one on a bounded 0–1 scale), may be used to estimate a treatment-to-progress effect on oncology symptom data in otherwise healthy clinical trial enrollees reporting a strong floor effect corresponding to a general lack of symptoms. Under this scenario, right-skewed data with a mode at zero can be represented as a longitudinal two-part model consisting of a mixture of a binary and a continuous process, respectively, indicating the absence/presence of a symptom and the intensity of a symptom. The post-progression nonignorable absence of longitudinal data, by design collected until disease progression, can be incorporated through the joint modeling of progression-free survival with the longitudinal mixture [3, 4].

2. Joint models

Joint models generally consist of two parts: a model for event occurrence and a model for trajectory of longitudinal measurements that share some parameters. These two parts can be linked in various ways, which fall into three major categories: (i) naively using *observed* values of longitudinal variables as covariates in a Cox or parametric survival model; (ii) a two-stage approach in which a model first is fit to the longitudinal data, and then the fitted values of the longitudinal trajectory for each individual are used as covariates in the time-to-event model; and (iii) using shared random effects in the models for the longitudinal and time-to-event likelihoods. Additional applications of joint models are described in what follows.

Joint models are not the same as survival models with time-varying covariates. The longitudinal data in these latter models just provide additional covariates to illuminate the survival process. The longitudinal observations in joint models are important in their own right, and the possibility of differential withdrawal (survival) raises the problem of differential bias and difficulty in understanding the true nature of the longitudinal process.

The following discussion addresses some specific issues associated with the definition and choice of various modeling approaches.

2.1. Longitudinal models

Longitudinal observations typically are described by a linear (usually) mixed model, (e.g., [21])

$$Y_i(t_{ij}) = M_i(t_{ij}) + \varepsilon_{ij} = \mathbf{X}_i(t_{ij})\boldsymbol{\beta} + \boldsymbol{Z}_i(t_{ij})\mathbf{b}_i + \mathbf{u}_i\delta + \varepsilon_{ij} \quad \varepsilon_{ij} \sim \mathrm{IID}\left(0, \sigma_\varepsilon^2\right) \quad (1)$$

$\boldsymbol{\beta}$ is a vector of fixed effects with corresponding time-varying design/covariate matrix. $\mathbf{X}_i(t_{ij})$, $\mathbf{b}_i$ is a vector of (usually normally distributed) random effects with corresponding time-varying design/covariate matrix $\mathbf{Z}_i(t_{ij})$. $\mathbf{u}_i$ is a vector of time-invariant covariates (e.g., baseline measurements/assessments) contained in some larger set $\mathbf{U}_i(\mathbf{u}_i \in \mathbf{U}_i)$.

Expression (1) can be generalized in various ways. The time dependence of the observations could be expressed by a simple polynomial regression or a more complex functional representation such as a spline regression could be used. The residual errors might not be independently distributed. The longitudinal measurements could themselves be vectors, so that survival or time to event might depend on a collection of correlated biomarkers or other longitudinal measurements, and not on just a single observable.

2.2. Survival models

'Survival' does not necessarily mean death. It could refer to a number of 'terminating' events such as progression of cancer, progression to full AIDS, progression of kidney failure to requiring dialysis, etc. In principle, although this is not addressed here, the events could be recurrent (see also [22–24]).

Survival models usually are employed in later-stage clinical trials as part of the evaluation of efficacy with respect to terminating endpoints. However, time-to-event models can also be used for safety endpoint modeling during early stages of development. Time to occurrence of toxicity is of particular interest in phase I oncology trials, for example, where late-onset toxicities become a serious concern for the development of targeted therapies [25]. Bayesian dose-finding methods based on time-to-toxic events currently are modeled using a single survival model [26, 27], but its joint use with a continuous PRO-endpoint such as pK (pharmacokinetics = measures of exchanges of administered doses among body compartments) or pD (pharmacodynamics = biological response measures such as blood pressure, EEG, and tumor volume) would allow a more accurate determination of the proper dose. In general, pK/pD model analyses proceed sequentially or simultaneously. The sequential approach first fits a model to the pK data and then fits a pD model to pD data using the expected value of pK predictions as covariates. With the simultaneous, or joint, approach (e.g., [28, 29]), the entire pK/pD model is fitted simultaneously to all of the data using shared parameters. The details, which are crucial and sometimes controversial, are outside the scope of this article. A number of software packages can be used to analyze pK/pD models, for example, WinBugs with the WBDiff package [30, 31], GNU MCSim [32], or NonMEM 7 [33]; considerations governing the choice of software are discussed in [34, 35].

2.2.1. Proportional hazards time-to-event model—The idea behind a joint model is to link the component processes together through some shared parameters. Let $m_i(t)$ denote the complete true unknown patient-specific longitudinal trajectory, and let $M_i(t) = \{m_i(s); 0$

≤ s ≤ t denote the corresponding true unknown longitudinal profile up to time t. We define the proportional hazards time-to-event submodel

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha m_i(t)\right) \quad (2)$$

where $h_0(t)$ is the baseline hazard function, v_i & U_i denotes a set of baseline time-independent covariates, ϕ denotes the associated vector of log hazard ratios, and α denotes an interpretable association parameter. The quantity $\exp(\alpha)$ is the hazard ratio for a one-unit increase in $m_i(t)$, at time t. Including the true unobserved trajectory function, $m_i(t)$, into the linear predictor of the proportional hazards model provides a way to link the component submodels to form the joint modeling framework, that is, to combine the functional representation (1) of the longitudinal observations with the survival submodel. Formulation (2) assumes that the association is based on the current value of the longitudinal response at time t. The survival function follows naturally

$$S\left(t|M_i(t), v_i\right) = exp\left(-\int_0^t h_0(s) exp\left(\varphi^T v_i + \alpha m_i(s)\right) ds\right) \quad (3)$$

The time-dependent nature of the longitudinal process $m_i(t)$ means that the integral in (3) often will need to be calculated numerically, which complicates the estimation process.

In fact, the model does not have to depend only on the current value of a univariate longitudinal process [18, 36] and does not have to assume proportional hazards. Early work in the field of joint modeling chose the Cox model as the survival submodel of choice, which of course does not directly estimate the baseline hazard function [37–39]. This is both a strength and a weakness. Leaving the baseline hazard function unspecified avoids the need for assumptions about the underlying functional form. However, a parametric framework is more useful and convenient when the objective is to obtain absolute measures of risk, such as predictions of the outcomes for individual patients.

Moreover, a fully nonparametric survival model raises the problem of bias, because an unspecified baseline hazard leads to underestimation of the standard errors of parameter estimates [40]. Consequently, bootstrapping is required to obtain appropriate standard errors when incorporating the Cox model as the survival model of choice. The computationally intense numerical integration required to fit these models is an undesirable aspect of this particular joint modeling framework.

Using parametric survival distributions such as the exponential, Weibull, or Gompertz distributions avoids this issue, but assuming a standard survival distribution can restrict the range of baseline hazard functions that can be captured accurately. This has motivated alternative approaches, for example, using B-splines [36] or piecewise constant baseline hazard functions (e.g., [36, 41], but certainly other authors as well).

2.2.2. Proportional cumulative hazards time-to-event model—The flexible parametric survival model of Royston and Parmar provides an alternative to the commonly used parametric distributions [42]. This has recently been incorporated into the joint

modeling framework [21] by modeling on the log cumulative hazard scale instead of on the log hazard scale,

$$\mathrm{H}\left(\mathrm{t}\middle|\mathrm{M_i(t)}, \mathrm{v_i}\right) = \mathrm{H_0(t)} exp\left(\varphi^{\mathrm{T}}\mathrm{v_i} + \alpha \mathrm{m_i(t)}\right)$$

Flexibility is incorporated by using restricted cubic splines to model the baseline log cumulative hazard function.

2.2.3. Accelerated failure time models—The accelerated failure time framework can be used as the survival submodel, with covariates incorporated as described by Cox & Oates [43]

$$\mathrm{S}\left(\mathrm{t}\middle|\mathrm{M_i(t)}, \mathrm{v_i}\right) = \mathrm{S_0}(exp\left(\varphi^{\mathrm{T}}\mathrm{v_i} + \alpha \mathrm{m_i(t)}\right) \mathrm{t})$$

where $S_0(.)$ is the baseline survivor function, such as the Weibull distribution, log-normal distribution, log-logistic distribution, and generalized gamma distribution.

2.3. Alternative association structures

The parametrization of models relating the risk of the event at time t to the true unobserved longitudinal profile at that time often is called the *current value* parameterization. This is not the only way to relate longitudinal and time-to-event observations. Exploring alternative, clinically meaningful, ways of linking the two processes expands the usefulness of the joint modeling framework.

2.3.1. Interaction effects—The joint model association structure just described assumes the same association between the true longitudinal value and the risk of event for all patients. Sometimes it may be more realistic to allow for different values of association for different patient subgroups. This can be achieved by forming interactions between the baseline covariates and the true unobserved longitudinal trajectory function, as follows:

$$\mathrm{h}\left(\mathrm{t}\middle|\mathrm{M_i(t)}, \mathrm{v_{i1}}, \mathrm{v_{i2}}\right) = \mathrm{h_0(t)} exp\left(\varphi^{\mathrm{T}}\mathrm{v_{i1}} + \alpha^{\mathrm{T}}\left[\mathrm{v_{i2}} \times \mathrm{m_i(t)}\right]\right)$$

The quantities v_{i1} and v_{i2}(v_{i1}, v_{i2} $\mathscr{E}U_i$) are time-invariant baseline covariates; v_{i1} is the same as in (2) and (3). The new covariates v_{i2} are interaction covariates that multiply the true longitudinal profiles (as above), so that the association parameters α can reflect different associations for different covariate patterns. The association structure reduces to the standard current value parameterization when $v_{i2} = 1$.

2.3.2. Time-dependent slope—The association structures described earlier incorporate the current value of the true longitudinal response. But they could as well incorporate the rate of change of the true longitudinal response, especially when the direction and strength of trend of a biomarker are as important as its level at any point in time. That is, (2) could be

generalized to include the slope $m_i'(t)$ of the longitudinal trajectory, so that the hazard function becomes

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\right) \quad (4)$$

where

$$m_i' = \frac{d\left(x_i^T(t)\beta + z_i^T(t) b_i\right)}{dt}$$

Ye *et al* incorporated this association structure into a two-stage regression calibration joint model [44]. Wolbers *et al* described the added benefit of including the rate of change of CD4 trajectories within a joint model framework to model the risk of progression to AIDS or death in HIV-positive patients [45].

2.3.3. Random effects parameterization—Yet another time-independent association structure includes only the random effects in the linear predictor of the survival submodel,

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha^T(\beta + b_i)\right) \quad (5)$$

This formulation includes both the population level mean of the random effect, plus the subject specific deviation. This model can be simplified by including only the subject-specific deviation,

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha^T b_i\right) \quad (6)$$

The association parameters in (5) and (6) have different interpretations. Suppose, for example, that the longitudinal trajectories are described by a random intercept and random slope model,

$$m_i(t) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})\, t$$

The hazard ratio at time t = 0 that reflects association between patient-specific values of the true longitudinal outcome at t = 0 can be evaluated using

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha_1 (\beta_0 + b_{0i})\right)$$

where $\exp(\alpha_1)$ is the hazard ratio for a one-unit increase in the baseline value of the longitudinal outcome, that is, the intercept. If only the subject-specific deviations are included (model (6)), then the hazard becomes

$$h\left(t|M_i(t), v_i\right) = h_0(t) exp\left(\varphi^T v_i + \alpha_2 b_{0i}\right)$$

which assumes that the association is based only on the subject-specific deviation from the population mean intercept. The function $h_0(t)$ does not include covariate effects that may be relevant at baseline, so the second factor adjusts the baseline hazard function to accommodate these effects.

The associations assuming time independence must be interpreted cautiously. For example, linking the random coefficients of the spline terms when the random effects of a longitudinal trajectory function are described by complex functions such as fractional polynomials or splines leads to uninterpretable association parameters. From a computational perspective, however, the time-independent association structures are particularly useful because they lead to directly computable closed functional forms for the cumulative hazard function.

2.4. Bayesian methods for joint modeling of longitudinal and survival data

The methods reviewed thus far for joint modeling have been based on a frequentist approach. The parameters were obtained by maximizing the likelihood or partial likelihood [46]. However, it often may be advantageous to apply a Bayesian approach. In the Bayesian paradigm, asymptotic approximations are not necessary, model assessment is more straightforward, computational implementation is typically much easier, and historical data can be incorporated easily into the inference procedure. This section describes three Bayesian approaches [47–49], all of which use the Wulfsohn and Tsiatis [39] general model building approach.

All three Bayesian approaches use a proportional hazards model for the survival component of the model. Where they differ is in the modeling of the longitudinal component. Ibrahim, Chen, and Sinha [48] used a random effects model with a multivariate outcome. Faucett and Thomas [47] used a univariate random effects model. Wang and Taylor [49] also used a random effects model but included an integrated Ornstein-Uhlenbeck process that added more flexibility to the trajectory curve, but greatly increased the number of parameters in the model and the computational complexity. Note: an integrated Ornstein-Uhlenbeck process is the only nontrivial random process that is stationary, Gaussian, and Markovian, and allows linear transformations of the space and time variables. It is used commonly to model the error distribution in semiparametric regression models, e.g., [50]. All of these approaches used Gibbs sampling to obtain realizations from the joint posterior distribution of the parameters.

Faucett and Thomas [47] took a Bayesian approach to solving the same random effects and proportional hazards models as Wulfsohn and Tsiatis [39]. They used non-informative priors on all the parameters in order to achieve similar results to maximum likelihood approaches. Wang and Taylor [49]) introduced another Bayesian method for jointly modeling longitudinal and survival data.

Joint models can become very complex very quickly, especially when multiple events are considered and the longitudinal observations are multivariate. This is especially true when the models include subject-specific random effects that must be removed or accounted for. Frequentist methods attempt to do this by integrating with respect to the distributions of these random effects, an approach that can become computationally unstable, if not

altogether infeasible, when there are many such effects or when the models are very complex. Bayesian approaches provide a practicable way to address complex models that incorporate multivariate survival, multivariate longitudinal observations (e.g., multiple symptoms—pain, breathing difficulties, cardiovascular symptoms—see [36] for an example). Moreover, the application of Bayesian methods do not require assuming normality for the distributions of the random quantities.

2.5. Additional considerations

Even though survival depends on 'true' longitudinal model $M_i(t_{ij})$, only the observed longitudinal values $Y_i(t_{ij})$ are known, so that the censoring implied by the survival component may be informative. If the hazard function depends on the entire longitudinal trajectory, there may be bias because only snapshots in time and not the whole trajectory are observed [18]. This potential problem could be addressed by an appropriate longitudinal model relating outcome to time, for example, via spline regression.

The joint modeling framework can be used to assess the effect of a longitudinal trajectory of observable values on the probability of occurrence of some event. Some care is needed in the interpretation because the analysis of the survival component incorporates time-dependent covariates that necessarily are measured with error even though models such as those described earlier are functions of the unknown true longitudinal trajectories.

The framework also can be used to assess the potential effect of the occurrence of an event on the distribution of observed outcomes, which raises some issues. The event occurrence may cause a subject to withdraw from observation so that the opportunity for subsequent longitudinal measurements is lost. This poses a potential informative censoring issue because the probability of the event may depend on the actual or true values of the observations not made. Standard time-to-event methods such as proportional hazard models cannot be used when this happens.

Sweeting and Thompson compared three approaches with joint modeling via simulation and via application to the prediction of abdominal aortic aneuryism growth and rupture [51]. The three approaches were (1) naively using *observed* values of longitudinal variables as covariates in a Cox or parametric survival model, (2) using shared random effects in the models for the longitudinal and time-to-event likelihoods, and (3) using a two-stage approach in which a model was first fit to the longitudinal data and then the fitted values of the longitudinal trajectory for each individual were used as covariates in the time-to-event model. Software for the analyses of these models is readily available, including the jm and joineR packages available in R. The supplementary material for their paper provides code for carrying out Bayesian analyses using WinBUGS or OpenBUGS. Sweeting and Thompson found that naively using the observed data as covariates (approach 1) led to severe underestimation, that using fitted values as covariates (approach 3) led to bias and poor coverage properties, but that the shared effect method (approach 2), although not perfect, performed acceptably well.

3. Software

3.1. JM joint modeling R package [52]

The JM package is designed to fit a variety of joint models for normal longitudinal responses and time-to-event data using maximum likelihood. The package is extensively documented, with worked examples. The main arguments of the key function in the package (jointModel()) are a linear mixed effects object as returned by the lme() function from the nlme package and a survival object returned by the coxph() or survreg() functions in the survival package. A number of relative risk and accelerated failure time survival model options are available, including Weibull, piecewise proportional hazards, Cox proportional hazards, and proportional hazards with a spline-approximated baseline risk function. A wiki page, http://rwiki.sciviews.org/doku.php?id=packages:cran:jm provides information on continuing developments plus detailed analyses of real data sets. No special expertise appears to be required to use the package other than a knowledge of what is being calculated.

3.2. joineR R package [53]

The joineR package implements methods for analyzing data from longitudinal studies based on an extended Wulfsohn and Tsiatis model [39] in which the response from each subject consists of a time sequence of repeated measurements and a possibly censored time-to-event outcome. The modeling framework for the repeated measurements is a linear model with random effects and/or correlated error structure. The model for the time-to-event outcome is a Cox proportional hazards model with log-Gaussian frailty. Stochastic dependence is captured by allowing the Gaussian random effects of the linear model to be correlated with the frailty term of the Cox proportional hazards model. If $\lambda_{i(t)}$ denotes the hazard for subject i and Y_{ij}, the jth repeated measurement on subject i, the model specifies latent vectors U_i and V_i that follow zero-mean multivariate normal distributions, realized independently for different subjects. Given U_i and V_i, the repeated measurements submodel is

$$y_{ij}=x_{ij}\beta_{ij}+a_{ij}{}^{\top}U_i+Z_{ij}$$

and the hazard submodel is

$$\lambda_{i(t)}=\lambda_0(t)exp\left(w_{ij}+b_{ij}{}^{\top}V_i\right)$$

where x_{ij}, a_{ij}, w_{ij}, and b_{ij} are vectors of possibly time-varying explanatory variables and the Z_{ij} are mutually independent, $Z_{ij} \sim N(0, \tau^2)$. Although this model formulation is flexible in principle, the computational cost of evaluating the likelihood restricts routine implementation of the model to low-dimensional U_i and V_i.

The package is well documented, and an accompanying report clearly describes its use with a number of examples. No special level of expertise appears to be necessary to use the package other than a knowledge of what is being calculated.

3.3. Bayesian joint models in WinBUGS (or OpenBUGS) and SAS®

Guo and Carlin describe the application of the Markov chain Monte Carlo (MCMC) approach as implemented in WinBUGS [54] to a joint analysis of longitudinal data and survival times [55]. The code for carrying out the analysis is available from the website http://www.biostat.umn.edu/~brad/software.html. In addition to the WinBUGS code, the website also provides code for carrying out similar calculations using the NLMIXED procedure in SAS® written by Oliver Schabenberger. The joint model approach uses shared latent random effects that appear in both the longitudinal and survival submodels. The longitudinal submodels are of the form

$$y_{ij}=\mu_i(t_{ij})+W_{1i}(t_{ij})+\varepsilon_{ij}$$

where y_{ij} denotes the measurement on subject i at the jth measurement occasion for that subject, t_{ij} denotes the corresponding time point, $\mu_{i(t_{ij})}$ denotes the possibly time-dependent fixed effects, and $W_{1i}(t_{ij}) = U_{1i} + U_{2i}t_{ij}$ is the sum of random intercept and slope effects corresponding to subject i. The survival submodels express the logarithm of the hazard at time t as

$$log\left(\lambda_{i(t)}\right)=log(h_0(t))+\xi_{i(t)}+W_{2i}(t)$$

where h(t) is a baseline hazard that depends on the model used (exponential/Weibull or Cox proportional hazards), $\xi_{i(t)}$ denotes possibly time-dependent fixed effects, and $W_{2i}(t)$ denotes the random effect contribution, generally expressed as

$$W_{2i}(t)=\gamma_1 U_{1i}+\gamma_2 U_{2i}+\gamma_3(U_{1i}+U_{2i}t)+U_{3i}$$

where the shared U_{1i} and U_{2i} are as for the longitudinal model and U_{3i} is an optional random frailty term that is independent of U_{1i} and U_{2i}. The models were applied jointly and separately to data from a trial comparing two antiretroviral drugs. The parameter estimates from the separate and joint models were similar, but the joint model provided a more accurate and clinically realistic estimate of the median survival time as a function of baseline characteristics. Simulations of the performance of the method in three scenarios indicated satisfactory performance in all cases.

3.4. JMBayes R package [56]

This package fits shared parameter models for the joint modeling of normal longitudinal responses and event times under a Bayesian approach using JAGS, WinBUGS, or OpenBUGS. The package has a single model-fitting function that accepts as main arguments a linear mixed effects object fit returned by function lme() of package nlme and a Cox model object fit returned by function coxph() of package survival. The method allows for joint models with relative risk survival submodels with Weibull or B-spline approximated baseline hazard functions. The association structure between the longitudinal and survival process can be specified in various ways. One can optionally use the classic joint model

formulation of Wulfsohn and Tsiatis (1997), or define possibly time-dependent, term so as to include terms, such as the time-dependent slope (i.e., the derivative of the subject-specific linear predictor of the linear mixed model), and the time-dependent cumulative effect (i.e., the integral of the subject-specific linear predictor of the linear mixed model), or combine these two possibilities, or include only the random effects of the linear mixed model in the linear predictor of the survival submodel. The package also provides functionality for computing dynamic predictions for the longitudinal and time-to-event outcomes.

3.5. Bayesian/frequentist fit package (JMFit) [57]

The JMfit package is a joint modeling frequentist SAS software package that fits several types of shared parameter joint models. The longitudinal model is allowed to be a linear mixed model, and the survival model is allowed to be a piecewise constant hazards model with random effects. Six types of trajectories can be used for the longitudinal model. The software produces maximum likelihood estimators of the parameters, standard errors and the AIC and BIC goodness of fit statistics. This is the first joint modeling software package that allows for simultaneously fitting and evaluating joint models. It includes decompositions of the AIC and BIC statistics that allow the user to assess the contribution of the longitudinal data to the survival component of the model.

3.6. stjm Stata package [58]

The stjm package implements joint modeling of a normal longitudinal response and a time-to-event using maximum likelihood, with an emphasis on parametric time-to-event models. The package is documented with examples in the help file and an associated Stata journal paper. The data setup is consistent with standard survival analysis with time-varying covariates, requiring only a single call to the main function, stjm, to fit a joint model. The longitudinal outcome can be modeled flexibly using fixed/random polynomials or splines. The survival probabilities can be modeled using exponential, Weibull, Gompertz proportional hazards models, the Royston–Parmar flexible parametric model, Weibull-Weibull and Weibull-exponential mixture models, and spline-approximated baseline (log) hazard function.

Associations between the survival and longitudinal components can be expressed by the current longitudinal measurement value at a time point, the slope of the longitudinal trajectory at that time point, and random effects with or without a fixed mean; all of these can be considered separately or in combination. Estimation of the parameters can be accomplished using nonadaptive or fully adaptive Gauss–Hermite quadrature. No special level of expertise is required other than a knowledge of what is being calculated.

4. Examples of applications

4.1. HIV/AIDS

Immunologic and virologic markers are measured repeatedly over time on each patient in clinical trials of therapies for diseases associated with human immunodeficiency virus (HIV). The intervals between data collection times vary in length, and missing data are quite common. The markers are prone to measurement error and high within patient variability

because of biological fluctuations [59–61]. Modeling these covariates over time is preferable to using the raw data [46, 62–65]. In addition, models provide estimates for time points where data are not available. Many HIV clinical trials focus on the opportunistic infections (OI) associated with HIV disease where the survival endpoint is the time to development of the OI [66–73]. In these trials, immunologic and virologic markers might be utilized as time-varying predictor variables.

The most common measure used to assess immunological health is the CD4+ lymphocyte count or CD4 count for short. Higher CD4 counts indicate a stronger immune system that is more prepared to resist infection. Lower CD4 counts indicate a higher risk of an OI. Viral load is a measure of the amount of virus in the blood plasma. A lower viral load is preferable and may indicate successful treatment of the disease. A patient's success on treatment is often evaluated by these two markers. When a patient begins a successful treatment regimen, the viral load may drop drastically and fall below a detectable level. The CD4 count may take longer to respond or may not respond at all. As viral load decreases, we may expect the CD4 count to increase as the immune system has time to recover. However, CD4 count is slower to respond than viral load. Because of this complex relationship between the immunologic and virologic markers, we may want a multivariate model for longitudinal covariates. These trajectories are generally difficult to model parametrically; therefore, we may want to allow for more flexibility in the curve by considering semiparametric or nonparametric models [50, 74].

4.2. Cancer vaccine trials

In cancer vaccine (immunotherapy) trials, vaccinations are given to patients to raise the patients' antibody levels against the tumor cells. In these studies, the time-to-event end point is often the time to disease progression or time to death. A successful vaccine activates the patient's immune system against future tumor growth so that a patient's antibody production increases to help eradicate tumors. Therefore, measurements of these antibodies may be associated with the time-to-event and may help the clinician to evaluate the vaccination before the event occurs. Ibrahim, Chen, and Sinha [48] presented a Bayesian joint model in a cancer vaccine study for patients with malignant melanoma. They performed a survival analysis adjusting for longitudinal immunological measures. The primary measures of antibody response were the IgG and IgM antibody titers. The levels of these markers were conjectured to be associated with the clinical outcome and were therefore monitored during follow-up. These markers are prone to measurement error so that the raw data should not be used in a survival analysis. A method that jointly models the longitudinal marker as well as the survival outcome is necessary.

4.3. Health related quality of life studies

The collection of QOL data in clinical trials has become increasingly common, particular when the survival benefit of a treatment is anticipated to be small or moderate. In fact, one might argue that QOL is at times an even more important factor in treatment decisions for a patient than any modest survival benefit. Besides the trade-offs between survival benefits and therapeutic adverse effects on QOL, QOL may be predictive of survival. A survival model that incorporated both treatment and QOL information is necessary. Often a QOL

survey instrument is administered to patients at a number of prespecified time points during follow-up. Complete QOL data for patients at all of the specified collection times are frequently unavailable, and measurement errors may occur for any single QOL assessment because of the imperfect reliability of the instrument. A joint modeling of longitudinal and survival data is not only able to evaluate the therapeutic impacts on both QOL and survival outcome but also able to investigate the prognostic impact of patients' QOL. The measurement errors as well as the missingness of QOL assessments can also be managed by the longitudinal submodel of a joint model. Because different facets of QOL, such as appetite, mood, and physical well-being, are often assessed with a survey instrument, a multivariate model for the longitudinal QOL is necessary to model different dependence structures among observations.

4.4. Renal graft failure

Rizopoulos and Ghosh [36] developed a semiparametric model for time to event data with multivariate longitudinal observations for each subject. Spline models were used to express the true trajectories of the longitudinal observations, in order to capture with some fidelity the highly nonlinear pattern of variation demonstrated by the longitudinal observations. That is, given the values of the random effects corresponding to individuals, a known link function of the expected value of a sequence of measurements could be expressed in terms of a true, unknown, function that the authors approximated using splines. The approximation had two parts: a time-independent part and a time-dependent part, both with fixed and random effects. The relative hazard for the event time model was assumed to depend on the true longitudinal trajectories and on various random effects corresponding to latent effects shared with the longitudinal observations. A key point that the authors made is the need for careful consideration of how the models should be parametrized, and they discussed in some detail alternative ways to express the models. They also described some tools for evaluating the effect of different choices of parameterizations. The plethora of random and latent effects in the models makes a Bayesian approach attractive and practical.

The approach was applied to data on 407 patients with chronic kidney disease undergoing primary renal transplantation; the longitudinal data consisted of three markers related to graft function and survival. Joint modeling of the multiple outcomes was needed to evaluate association of each with graft failure risk after adjusting for others. Application of alternative models showed that correction for the effects of the other markers affected the strength of the association between a marker and the risk of graft failure. The spline function representation economically captured the main features of the subject-specific longitudinal trajectories, which were markedly nonlinear. The authors also observed that '…observed data may not contain enough information to distinguish between the different paramterizations without prior knowledge.'

4.5. Scleroderma lung study

Huang *et al* [75] described the application of joint modeling with competing risks to the analysis of data from a comparison of the effects of oral cyclophosphamide on the progression of scleroderma-related interstitial lung disease as expressed by changes from baseline in percent forced vital capacity (FVC) or the occurrence of (i) disease-related

withdrawal or (ii) treatment failure or death. The joint model used included a linear mixed effects submodel for the longitudinal outcomes (values of FVC over time), a proportional hazards competing risks survival submodel with cause-specific hazards including frailty, and a regression model for the covariance matrix of the multivariate latent random effects. This latter model incorporates separate regression models for the diagonal and off-diagonal elements, and allows the covariance matrices to vary among subjects, which is a new feature. Bayesian methods (MCMC) were used to avoid high-dimensional integration to remove latent effects.

Patients were assigned at random to a year of treatment with cyclophosphamide or placebo, and followed for a subsequent year. In addition to treatment and time, the covariates included baseline FVC and baseline lung fibrosis, plus their interactions with treatment. A linear spline fixed effects model was used with a change point at month 18. Two models for the covariance structure of the random effects were used, one that assumed homogeneity across subjects and one that modeled heterogeneity of the covariance matrices. It turned out that there was insufficient evidence from these data to reject the assumption of covariance matrix homogeneity. Simulation studies demonstrated that the heterogeneity model leads to almost unbiased parameter estimates, while the homogeneity model can lead to large biases in some parameter estimates.

5. Discussion and recommendations

The objective of this report was to illustrate how joint modeling methods actually can provide value for drug development. It was not our aim to provide another review of joint modeling methods, because there are many very good reviews, but rather to provide motivation to sponsors to use the methods and a jumping-off point for statisticians wanting to apply them. The key message is that joint modeling methods can be used, perhaps even routinely, to link survival-type outcomes with longitudinal measurements to get better insights into both.

One of the considerations that make joint modeling challenging is the complexity of the calculations that result from the need to integrate with respect to the distributions of the random effects even with fairly simple situations that involve a single longitudinal outcome and a single survival event. This in particular is why the more recent developments in the field have employed Bayesian methods to remove the need for explicit multivariate integration. Bayesian methods also provide a way to incorporate multiple longitudinal outcomes and multiple competing survival events. They also provide a path for addressing even more complex models that could include recurrent as well as absorbing effects.

We sought to accomplish our goal by describing specific areas of application that could benefit from joint modeling, by outlining in some detail how the calculations proceed, by identifying software that can be used to carry out the calculations (perhaps the most crucial part), and by identifying published applications that actually used joint modeling methods. The technical and practicability obstacles to using joint modeling for many applications in medical product development have pretty well been overcome. It is not clear, however, that sufficient attention has been given to the interpretability and clinical interpretation of the

results of analyses based on joint models, primarily because most discussions of joint model methods have been in the technical statistical literature. The challenge now is to encourage statisticians and managers in the pharmaceutical and medical product industries to embrace rather than resist the new, to their benefit and to the benefit of the public at large.

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