A flexible joint model for multiple longitudinal biomarkers and a time-to-event outcome: With applications to dynamic prediction using highly correlated biomarkers

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Abstract
In biomedical studies it is common to collect data on multiple biomarkers during study follow-up for dynamic prediction of a time-to-event clinical outcome. The biomarkers are typically intermittently measured, missing at some event times, and may be subject to high biological variations, which cannot be readily used as time-dependent covariates in a standard time-to-event model. Moreover, they can be highly correlated if they are from the same biological pathway. To address these issues, we propose a flexible joint model framework that models the multiple biomarkers with a shared latent reduced rank longitudinal principal component model and correlates the latent process to the event time by the Cox model for dynamic prediction of the event time. The proposed joint model for highly correlated biomarkers is more flexible than some existing methods since the latent trajectory shared by the multiple biomarkers does not require specification of a priori parametric time trend and is determined by data.

We derive an expectation-maximization (EM) algorithm for parameter estimation, study large sample properties of the estimators, and adapt the developed method to make dynamic prediction of the time-to-event outcome. Bootstrap is used for standard error estimation and inference. The proposed method is evaluated using simulations and illustrated on a lung transplant data to predict chronic lung allograft dysfunction (CLAD) using chemokines measured in bronchoalveolar lavage fluid of the patients.

KEYWORDS
censoring, dynamic prediction, joint model, longitudinal data, reduced rank functional principal component model

1 INTRODUCTION

In clinical studies, researchers are often interested in monitoring certain important clinical events and predicting the events using repeatedly measured response variables or biomarkers during follow-up. As an example we consider a lung transplant study in which multiple chemokines (biomarkers) in bronchoalveolar lavage fluid of the patients were measured repeatedly posttransplant. Of research interest is to evaluate biomarker predictiveness for some important clinical events such as chronic lung allograft dysfunction (CLAD). A conventional statistical approach is to fit a Cox regression model to the time-to-event data, which assumes that the effect of the biomarkers is constant over time. This assumption may not be valid in many clinical situations where biomarkers may change over time. To address this issue, we propose a flexible joint model framework that models the multiple biomarkers with a shared latent reduced rank longitudinal principal component model and correlates the latent process to the event time by the Cox model for dynamic prediction of the event time.
model in which those biomarkers are included as time-dependent covariates. However, such a model is deemed inapplicable if the biomarkers are only measured intermittently, missing at certain event times, or subject to measurement error (Prentice, 1982). Furthermore, some biomarkers are highly correlated because they belong to the same biological pathway. Including them directly into a regression model could suffer the collinearity problem and unstable model fit.

A popular approach to addressing the above issues in dynamic prediction is to model the biomarker(s) using a shared latent process and then incorporate the latent process into a survival model for the event of interest. A rich set of joint models have been developed using this approach for a single biomarker; see, among others, Wulfsohn and Tsiatis (1997); Elashoff et al. (2016); Song et al. (2002); Wang and Taylor (2001) and the references therein. Some joint models using this approach have also been developed for multiple biomarkers and time-to-event data, where the association among multiple endpoints is modeled through either latent class (Proust-Lima et al., 2009) or latent random variables (Huang et al., 2001; Chi & Ibrahim, 2006; Hatfield et al., 2011; Rizopoulos & Ghosh, 2011). These models assume that the multiple longitudinal outcomes exhibit correlated, but also to some extent, distinct patterns of trajectories so that their evolutionary paths are characterized separately. More recently, Luo (2014) and He and Luo (2016) introduced a multilevel model in which the longitudinal outcomes share a latent disease severity process that is expressed as a linear function of fixed and random effects, and an accelerated failure time model or Cox model is used for the event time. Their model allows for highly correlated biomarkers, but requires specification of a priori parametric time trend for the latent process, which is not always an easy task in practice.

The purpose of this paper is to study a flexible joint model framework where the multiple biomarkers for each subject are modeled using a shared latent reduced rank longitudinal principal component model and the latent process is correlated to the event time through a Cox model for dynamic prediction of the event. No priori parametric time trend assumption is required for the latent process in our model. As described later in Equation (2) of Section 2, each individual latent trajectory in our model is expressed as an additive function of the overall mean curve and several principal component curves, with the latter describing the modes of variation in individual trajectories. The principal component functions are estimated directly and weighted by mutually independent random effects. Compared to the traditional mixed effects method for functional principal component analysis, the reduced rank method estimates fewer parameters, so the fitted curve is generally more stable and accurate. In our joint model, the latent process estimation is data-driven and nonparametric in the sense that the overall mean and principal component functions are modeled by B-splines, which provides a flexible model to complement the models of Luo (2014) and He and Luo (2016). We point out that our model for the latent process is inspired by the reduced rank mixed effects framework for principal component analysis of functional data developed by James et al. (2000), which is well suited for situations with irregular and sparse observation time points across individuals as exhibited in the above mentioned lung transplant study. The reduced rank functional principal component approach has also been previously adopted by Yao (2007) to jointly model a single biomarker and an event time Yao (2007). Our work in this paper is a natural, but nontrivial extension of Yao (2007) from the single biomarker case to the multiple biomarkers case with some further developments. In particular, in addition to extending the estimation procedure to the multiple biomarker setting, we also develop large sample theory for the resulting estimator which has not been investigated previously even for the single biomarker case. We further develop a dynamic prediction tool based on the proposed joint model, which has high practical relevance for dynamic prediction of a clinical outcome from multiple highly correlated biomarkers. Lastly, we have implemented the proposed joint model in an R package JMM which is available for download at https://github.com/shanpengli/JMM.

This article is organized as follows. Details of the joint model formulation are given in Section 2.1. The maximum likelihood estimators and their asymptotic properties are given in Section 2.2. Section 2.3 outlines the derivation of a predictive accuracy measure. Application of this joint model to the lung transplant study is given in Section 3. Section 4 presents some simulation results to evaluate the proposed method. Section 5 gives some concluding remarks.

## 2 | MODEL AND ESTIMATION METHODS

### 2.1 | The joint model

Let \( Y_{ij}(t) \) be the \( j \)th biomarker measured on subject \( i \) at time \( t, i = 1, \ldots, n, j = 1, \ldots, J \), and \( t \in [0, \tau] \) for some known \( \tau > 0 \). We employ a latent process approach to model the inter-correlation among the \( J \) biomarkers and assume that they share a common subject-specific stochastic trend over time, namely \( \mu_i(t) \). This assumption is realistic if the biomarkers are in the same biological pathway and exhibit similar trajectories in preliminary data analysis. Specifically, the \( j \)th biomarker,
\( j = 1, \ldots, J \), is assumed to be

\[
Y_{ij}(t) = X_{ij}(t)^T \beta_{0j} + \mu_i(t) \beta_{1j} + \epsilon_{ij}(t),
\]

(1)

where \( X_{ij}(t) \) is a \( p_j \times 1 \) vector of possibly time-dependent covariates, \( \bar{\beta}_{0j} \) the associated regression coefficients, \( \mu_i(t) \) the latent process at time \( t \), \( \beta_{1j} \) the factor loading of \( \mu_i(t) \) for the \( j \)th outcome, and \( \epsilon_{ij}(t) \sim i.i.d. N(0, \sigma_j^2) \) the measurement error. Note that \( \beta_{11} \) is set to 1 for the purpose of identifiability. Write \( \beta_j = (\beta_{0j}, \beta_{1j}) \). We further assume the biomarkers are associated with the event risk through the latent process \( \mu_i(t) \) which characterizes the overall underlying trend shared by these biomarkers.

Following the reduced rank mixed effects model by James et al. (2000), the latent process \( \mu_i(t) \) in Equation (1) is characterized by an additive function of mean curve \( \mu(t) \) and principal component curves \( f_k(t), k = 1, \ldots, k \); the latter capture principal patterns of individual variation around the mean curve. Specifically,

\[
\mu_i(t) = \mu(t) + \sum_{k=1}^{k} f_k(t) \alpha_i = b(t)^T \vartheta + b(t)^T \Theta \alpha_i,
\]

(2)

where \( \mu(t) \) and \( f_k(t) \) are flexibly modeled by \( q \)-dimensional smooth basis spline functions \( b(t) \), \( \vartheta \) and \( \Theta \) are \( q \times 1 \) vector and \( q \times k \) matrix of spline coefficients, respectively, subject to \( \Theta^T \Theta = I \), and \( \int b(t)b(t)^T dt = I \), to impose orthogonality constraints on the principal component functions. The random effects \( \alpha_i = (\alpha_{i1}, \ldots, \alpha_{ik})^T \) represent individual variation in the relative weights of the principal component functions across study subjects, and are assumed to be \( N_k(0, D) \) with \( D \) being a \( k \times k \) diagonal matrix to avoid confounding with \( \Theta \). Models (1) and (2) indicate that the data correlations across time and between multiple biomarkers are characterized by the random effects \( \alpha_i \).

The hazard function of event times is assumed to take the form of a Cox regression:

\[
\lambda_i(t) = \lambda(t) \exp(Z_i(t)^T \eta + \gamma \mu_i(t)),
\]

(3)

where the baseline hazard function \( \lambda(t) \) is completely unspecified and \( Z_i(t) \) is a vector of possibly time-dependent covariates with unknown coefficients \( \eta \). The direction and magnitude of the association between the biomarker latent process \( \mu_i(t) \) and the event risk is characterized by the parameter \( \gamma \). Thus, testing \( \gamma = 0 \) is equivalent to testing the association between longitudinal and survival endpoints.

2.2 Estimation and inference

Let \( Y_i \) be the longitudinal measurements of all biomarkers and \( T_i \) the actual event time for subject \( i \) that may be censored by \( C_i, i = 1, \ldots, n \), so we observe \( \tilde{T}_i = \min(T_i, C_i) \) and \( \Delta_i = I(T_i \leq C_i) \). Noninformative censorship is assumed here; that is, \( T_i \perp C_i \). An underlying assumption in the joint model specified in (1), (2), and (3) is that \( Y_i \) and \( T_i \) are conditionally independent given the random effects \( \alpha_i \) and covariates \( X_i \) and \( Z_i \). The observed likelihood function is thus

\[
L(\psi; Y, T, \Delta) = \prod_{i=1}^{n} f(Y_i, \tilde{T}_i, \Delta_i | \psi)
\]
\[
= \prod_{i=1}^{n} \int f(Y_i | \alpha_i, \psi)f(\bar{T}_i, \Delta_i | \alpha_i, \psi)f(\alpha_i | \psi)d\alpha_i \\
= \prod_{i=1}^{n} \int f(Y_i | \alpha_i, \psi)[f(T_i | \alpha_i, \psi)^\Delta_i(1 - F(T_i | \alpha_i, \psi))^{1-\Delta_i}]f(\alpha_i | \psi)d\alpha_i,
\]

where \( \psi \) collects all the model parameters. The complete-data likelihood function \( L(\psi; Y, T, \Delta, \alpha) \) is defined based on (4) assuming the random effects \( \alpha_i \) are known.

Write \( \psi = (\phi, \Lambda) \), where \( \Lambda(t) = \int_{0}^{t} \lambda(u)du \) and \( \phi \) contains the remaining parameters. The maximum likelihood estimate \( \hat{\psi} \) maximizes the likelihood over a space in which \( \phi \) belongs to a bounded set and \( \Lambda \) is an increasing function in \( t \) with \( \Lambda(0) = 0 \). The likelihood function is difficult to maximize directly in the presence of integrals, so we consider to obtain \( \hat{\psi} \) through an Expectation-Maximization (EM) algorithm which iterates between an Expectation step (E-step) and a Maximization step (M-step) (Dempster et al., 1977; Elashoff et al., 2008). In the E-step we compute the expected value of complete-data log-likelihood with respect to \( \alpha_i \) conditional on \((Y_i, \bar{T}_i, \Delta_i, \psi^{(m)})\), where \( \psi^{(m)} \) is the current estimate of \( \psi \) and \( m = 0, 1, \ldots \) denotes iterations. Specifically, for any function \( h(\cdot) \) of \( \alpha_i \) that appears in the complete-data log-likelihood, its expectation can be evaluated by

\[
E\{h(\alpha_i)|Y_i, \bar{T}_i, \Delta_i, \psi^{(m)}\} = \int h(\alpha_i)f(\alpha_i|Y_i, \bar{T}_i, \Delta_i, \psi^{(m)})d\alpha_i \\
= \int h(\alpha_i)f(\alpha_i, Y_i, \bar{T}_i, \Delta_i | \psi^{(m)})f(\alpha_i | \psi^{(m)})d\alpha_i \\
= \int \frac{h(\alpha_i)f(Y_i, \bar{T}_i, \Delta_i | \alpha_i, \psi^{(m)})f(\alpha_i | \psi^{(m)})d\alpha_i}{\int f(Y_i, \bar{T}_i, \Delta_i | \alpha_i, \psi^{(m)})f(\alpha_i | \psi^{(m)})d\alpha_i}.
\]

The above integration can be computed via Gaussian quadrature which approximates integrals by a weighted sum of target functions evaluated at prespecified sample points (Vetterling et al., 1989).

In the M-step, \( \psi \) is updated using

\[
\psi^{(m+1)} = \arg\max_{\psi} Q(\psi; \psi^{(m)}),
\]

where \( Q(\psi; \psi^{(m)}) = E_{\psi|Y, T, \Delta, \psi^{(m)}}(\log L(\psi; Y, T, \Delta, \alpha)) \). More details are provided in Supporting Information.

The proposed joint model is semiparametric because the baseline hazard function \( \lambda(t) \) in Equation (3) is completely unspecified. This causes difficulty in estimating the standard errors of \( \hat{\phi} \) and further drawing statistical inference. As a result, we employ the nonparametric bootstrap strategy to compute the variance of parameter estimates. Suppose \( B \) bootstrap samples are formed by randomly sampling study subjects with replacement. The variance of \( \hat{\phi} \) can be estimated using \( 1/(B-1) \sum_{i=1}^{B} (\phi^{(i)} - \hat{\phi})^2 \), where \( \phi^{(i)} \) is the estimate from the \( i \)-th bootstrap sample and \( \hat{\phi} \) is the mean of \( \phi^{(i)} \) over all \( B \) samples.

Under conditions (C1)–(C5) (given in Supporting Information) and assuming B-spline knots are fixed, the following theorems establish the consistency and asymptotic normality for all the estimators in the joint model (1)–(3). The results are derived using modern empirical process theory, and detailed proofs are deferred to Supporting Information.

**Theorem 1.** Under assumptions (C1)–(C5), the maximum likelihood estimator \((\phi, \Lambda)\) is strongly consistent under the product metric of the Euclidean norm and the supremum norm on \([0, \tau]\); that is,

\[
\|\hat{\phi} - \phi_0\| + \sup_{t \in [0, \tau]} |\hat{\Lambda}(t) - \Lambda_0(t)| \to 0 \quad a.s.
\]

**Theorem 2.** Under assumptions (C1)–(C5), \( \sqrt{n}(\hat{\phi} - \phi_0, \hat{\Lambda}(t) - \Lambda_0(t)) \) weakly converges to a Gaussian random element in \( R^d \times L^\infty[0, \tau] \), where \( d \) is the dimension of \( \phi \) and \( L^\infty[0, \tau] \) is the metric space of all bounded functions in \([0, \tau]\).
2.3 Dynamic prediction

Since our joint model characterizes the association between biomarkers and event times, it can be used as a prognostic tool for dynamic prediction of event probabilities. Such prediction is conditional on biomarker measurements up to a given time point at which the event is yet to occur. Based on the predicted probability, physicians can better understand disease progression and make early decisions. We adopt the dynamic prediction accuracy measure developed by Proust-Lima and Taylor (2009) for latent-class joint models. This measure contrasts the predicted probability with observed data and thus can serve as an assessment tool to compare joint models for different sets of biomarkers in terms of their prediction accuracy.

For a new patient \(i\) who has not experienced the event at time \(s\), the objective is to predict the probability that \(T_i \leq s + t\) conditional on \(Y_i(s) = \{Y_{ij}(t|j), t_{ijk} \leq s, j = 1,...,J\}\) that contains all biomarker measurements up to time \(s\). This probability is defined as

\[
P_i(s + t, s; \psi) = P(T_i \leq s + t | T_i > s, Y_i(s); \psi).
\]  

(5)

Assuming \(T_i \perp Y_i\) given \(\alpha_i\), the probability (5) can be calculated as

\[
P(T_i \leq s + t | T_i > s, Y_i(s); \psi) = \int P(T_i \leq s + t | T_i > s, Y_i(s), \alpha_i; \psi)f(\alpha_i | T_i > s, Y_i(s); \psi)d\alpha_i
\]

\[
= \int P(T_i \leq s + t | T_i > s, \alpha_i; \psi)f(\alpha_i | T_i > s, Y_i(s); \psi)d\alpha_i
\]

\[
= \int S(s | \alpha_i; \psi) - S(s + t | \alpha_i; \psi)f(\alpha_i | T_i > s, Y_i(s); \psi)d\alpha_i,
\]

where \(S(\cdot | \alpha_i; \psi)\) is the survival function of \(T_i\) conditional on \(\alpha_i\). The posterior density \(f(\alpha_i | T_i > s, Y_i(s); \psi)\) is given by

\[
f(\alpha_i | T_i > s, Y_i(s); \psi) = \frac{f(T_i > s, Y_i(s); \psi)}{f(T_i > s, Y_i(s); \psi)}
\]

\[
= \frac{S(s | \alpha_i; \psi)f(Y_i(s) | \alpha_i; \psi)f(\alpha_i; \psi)}{\int S(s | \alpha_i; \psi)f(Y_i(s) | \alpha_i; \psi)f(\alpha_i; \psi)d\alpha_i}.
\]

Note that \(P_i(s + t, s; \psi)\) is calculated using \(\hat{\psi}\) estimated from the joint model. Denote the dynamic prediction rule \(\hat{S}(s + t | T_i > s, Y_i(s)) = S(s + t | T_i > s, Y_i(s); \hat{\psi}) = 1 - P_i(s + t, s; \hat{\psi})\). The measure of predictive accuracy evaluates the prediction error at time \(s + t\) conditional on the data history up to time \(s\):

\[
e_{\bar{Y},s}(s + t) = \frac{1}{N_s} \sum_{i=1}^{N_s} I(T_i > s + t)[1 - \hat{S}(s + t | T_i > s, Y_i(s))]
\]

\[
+ \Delta_i I(T_i \leq s + t)[0 - \hat{S}(s + t | T_i > s, Y_i(s))]
\]

\[
+(1 - \Delta_i)I(T_i \leq s + t)[1 - \hat{S}(s + t | T_i > s, Y_i(s))] \cdot \frac{\hat{S}(s + t | T_i > s, Y_i(s))}{\hat{S}(T_i | T_i > s, Y_i(s))}
\]

\[
+ [0 - \hat{S}(s + t | T_i > s, Y_i(s))][1 - \frac{\hat{S}(s + t | T_i > s, Y_i(s))}{\hat{S}(T_i | T_i > s, Y_i(s))}],
\]

where \(\Delta_i = I(T_i \leq s + t)\).
where \( N_s \) is the number of patients in the risk set at time \( s \).

As stated previously, this measure of prediction accuracy can be used to compare across joint models with different or nested sets of covariates. Presumably, for pre-specified \( s \) and \( t \), including important biomarkers that are associated with the event of interest would reduce \( \hat{\epsilon}_{Y,s}(s+t) \). Its use is illustrated in Section 3.

### 3 | REAL DATA ILLUSTRATION ON THE LUNG TRANSPLANT STUDY

This study consists of 215 patients who received lung transplantation at the University of California, Los Angeles between January 1, 2000 and December 31, 2010 (Shino et al., 2013). Patients had a median follow-up of 3.5 years posttransplant. The primary endpoint of this study was Chronic Lung Allograft Dysfunction (CLAD), a major factor limiting long-term survival in lung transplant patients. CLAD was defined as a sustained drop of at least 20% in the FEV\(_1\) from the average of the two best posttransplant FEV\(_1\) measurements. The study also recorded concentrations of CXCR3 chemokine ligands MIG and IP10 in bronchoalveolar lavage fluid posttransplant, with a range of 1–8 and a median of 3 observations per patient. MIG and IP10 are highly correlated (\( r = 0.6 \)) since they are in the same biological pathway. Our preliminary analyses showed that elevated MIG and IP10 concentrations were associated with an increased risk of CLAD in univariate Cox regression, but lost statistical significance when included simultaneously due to the fact that the strong correlation between MIG and IP10 resulted in unstable effect estimates. Also as stated previously, MIG and IP10 were intermittently measured and subject to substantial biological variation, which could introduce bias in Cox regression if they were treated as time-dependent covariates. To solve these issues, we use the model proposed in Section 2 to assess predictive value of MIG and IP10 for the risk of CLAD. There were 108 (50.2%) CLAD events and 611 MIG/IP10 observations. The median time from transplantation to the biomarker sampling date was 4.1 months.

We used cubic B-splines with evenly-spaced knots to estimate the mean and principal component functions in model (2) when fitting the joint model for CLAD and log\(_2\)-transformed MIG and IP10. Longitudinal measurements of MIG and IP10 were fit on the log-transformed time scale given that the measurements became more sparse as time progressed. There was a high biological variation in MIG and IP10, and no baseline patient demographic or clinical factors were significantly associated with these biomarkers. For illustrative purposes, we included patient age (in years) at the time of receiving transplant as a covariate in model (1). Baseline covariates age, male gender (male, yes/no), single lung transplant (single, yes/no), and idiopathic pulmonary fibrosis (ipf, yes/no) were included in the survival sub-model (3). We first considered \( k = 2 \) principal component functions in the latent process, and repeatedly fit the joint model with varying number of knots. Log-likelihood and AIC values for knots 2, 4, up to 12 are given in Table 1. The lowest AIC is achieved when there were 8 knots. The log-likelihood increased to \(-3030.4\) when three principal component functions were considered, but the third principal component explained only 10% of the total variation. This percentage was calculated using the estimated \( D_{k,k+\kappa}, \kappa = 1, 2, 3 \), as discussed in Section 2.1. We are aware that it is a rough approximation of relative data variation given the fact that biomarker observation times varied from individual to individual, but a majority of the observations were obtained at about 1, 3, 6, and 12 months posttransplant. As a result, we choose the model with 8 knots and two principal component functions as our final model.

Maximum likelihood estimates of the final model are provided in Table 2 where the 95% confidence intervals were calculated based on standard errors derived from 100 bootstrap samples and the p-values were calculated using the Wald’s test. Since the estimated \( \sigma_1^2, \sigma_2^2, D_{11}, \) and \( D_{22} \) from the bootstrap samples were right-skewed, their 95% confidence intervals were calculated based on log-transformed estimates. Note that the two biomarkers MIG and IP10 were labeled as \( j = 1, 2 \), respectively. As expected, age is not associated with either MIG or IP10. The factor loading of \( \mu_i(t) \) for IP10 (\( \hat{\beta}_{12} \)) is 0.83
TABLE 2  Parameter estimates from the joint model with eight knots and two principal component functions

| Model parameter | Estimate   | 95% CI          | p-Value |
|-----------------|------------|-----------------|---------|
| $\beta_{01}$ (MIG: age) | -0.02      | (-0.04, 0.01)   | 0.16    |
| $\beta_{02}$ (IP10: age) | -0.01      | (-0.03, 0.01)   | 0.15    |
| $\beta_{12}$    | 0.83       | (0.76, 0.91)    | <0.0001 |
| $\sigma_1^2$    | 4.47       | (3.44, 5.18)    |         |
| $\sigma_2^2$    | 2.87       | (2.15, 3.36)    |         |
| $D_{11}$        | 28.5       | (6.5, 262.2)    |         |
| $D_{22}$        | 15.4       | (6.2, 29.6)     |         |
| $\eta_1$ (age) | 0.003      | (-0.02, 0.03)   | 0.80    |
| $\eta_2$ (male) | 0.09       | (-0.34, 0.51)   | 0.69    |
| $\eta_3$ (single) | 0.23       | (-0.29, 0.75)   | 0.39    |
| $\eta_4$ (ipf) | -0.41      | (-0.91, 0.10)   | 0.11    |
| $\gamma$       | 0.22       | (0.03, 0.42)    | 0.0251  |

FIGURE 1  Estimated cumulative baseline hazard function from the lung transplant study

with a $p$-value of < 0.0001, indicating a strong association between the two biomarkers. Conditional on the latent process $\mu(t)$, MIG has a little higher variability than IP10 as suggested by the estimates of $\sigma_1^2$ and $\sigma_2^2$. The first principal component function explains approximately 65% of total variation in the latent process. The model detects a statistically significant association between the latent biomarker process and CLAD ($\gamma = 0.22$, 95% CI: 0.03–0.42, $p = 0.0251$); a higher level of MIG/IP10 is associated with an increased risk of CLAD, with a hazard ratio of 1.25 (95% CI: 1.03–1.52). None of the demographic or clinical factors are associated with CLAD after controlling for the latent biomarker process. The estimated cumulative baseline hazard function (Figure 1) indicates that there is an approximately constant hazard of CLAD following lung transplantation. To fit this joint model, it took 23 min to obtain the point estimates of the parameters and 71 h to complete 100 bootstrap.

The model estimated mean curve of MIG and IP10 is quite consistent with the empirical mean by LOESS method as shown in Figure 2A, though the fit tends to be poor at the lower and upper ends of data range. It is apparent that the IP10 concentration on average is lower than MIG, which explains why the factor loading $\beta_{12}$ of the latent process for IP10 is less than 1. Figure 2B shows the estimated principal component functions $f_{\alpha_k}(t)$, $x = 1, 2$. The first principal component function changes very little over time, acting similar to a random-intercept in linear mixed effect models. The second principal component varies around zero with no clear overall trend going up or down as time progresses, which is consistent with the fluctuations shown by the LOESS curves in Figure 2A. This principal component captures local biological variations in MIG and IP10 that are not accounted for by the first principal component. We also examined the distribution of estimated $\alpha_i$ from the joint model (Figure S1, Supporting Information). There is no obvious deviation from the normality assumption.
FIGURE 2  (A) Joint model estimated mean curve (thick line) as compared to the LOESS curve (thin line). Observed data points for MIG and IP are labeled as circle and triangle, respectively. (B) Joint model estimated principal component functions (PCFs)

TABLE 3  Simulated estimation bias (and empirical standard deviation (SD)) for the joint model (1)–(3) under three different scenarios. Each entry is based on 100 replications and the sample size is 215

| Parameter | \( \beta_01 \) | \( \beta_02 \) | \( \beta_{12} \) | \( \sigma^2_1 \) | \( \sigma^2_2 \) | \( D_{11} \) | \( D_{22} \) | \( \gamma \) |
|-----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Model 1   | True value      | -0.4            | -0.3            | 0.8             | 1.0             | 1.0             | 2.0             | 1.0             | 0.5             |
| (Low-medium variability, Gaussian random effects) | Bias             | 0.003           | 0.003           | <0.001          | -0.021          | -0.005          | 0.189           | -0.033          | -0.013          |
| Model 2   | True value      | -0.02           | -0.01           | 0.8             | 4.5             | 3.0             | 28.0            | 15.0            | 0.3             |
| (High variability, Gaussian random effects) | Bias             | <0.001          | 0.002           | <0.014          | 0.35            | 0.21            | 7.59            | -4.49           | -0.030          |
| Model 3   | True value      | -0.02           | -0.01           | 0.8             | 4.5             | 3.0             | 12.0            | 8.0             | 0.3             |
| (Medium-high variability, Gamma random effects) | Bias             | -0.001          | <0.001          | -0.007          | 0.04            | 0.03            | 2.42            | -1.62           | -0.025          |

To assess the predictive accuracy of this joint model, \( ePr \) was calculated as given in Section 2.3, using MIG and IP10 data up to 6 months posttransplant to predict CLAD occurrence in the next 1.5 years (i.e., in 2 years post-transplant), and was further compared with its counterparts in two other joint models using either MIG or IP10 alone to predict CLAD. These specific time points are clinically meaningful since the lung transplant patients are more closely monitored with the first half year following transplantation. The predictive accuracy measure \( ePr \) is 0.26 when MIG and IP10 were jointly modeled, and is 0.33 for both MIG and IP10 when they were modeled separately. This suggests that MIG and IP10 combined provide more accurate prediction for CLAD, and an improvement of 21% is observed in this study.

4  | SIMULATION STUDIES

We conducted a series of simulations to evaluate the performance of the proposed model and its estimation procedure under different settings, for which the results are summarized in Table 3. Specifically, we examined the impact of the level of variability or noise in the latent process (i.e., the variance of the random effects \( \alpha_i \)) on parameter estimation and also investigated whether the estimators were sensitive to mis-specification of the distributional assumption for the random effects. The following three scenarios were considered:

- Model 1 (low-medium variability, Gaussian random effects): The two dimensional random effects \( \alpha_i \) associated with the latent process were simulated from Gaussian distributions with a variance of 2.0 and 1.0 for the first and second principal component functions, respectively. Subjects were followed on \( t \in [0, 9] \), and two longitudinal outcomes were measured at every 0.5 time interval from baseline until the occurrence of the event or the end of the study. The baseline hazard was constant and set to value of 0.08 for all \( t \), and the overall event rate was 78%. Since the longitudinal outcomes
were censored by the survival endpoint, the median number of visits per subject was 4. The knots of the B-splines for the latent process \( \mu_i(t) \) were evenly spaced on [0, 9] and the number of knots was set to 8, same as what was chosen for the lung transplant study discussed in Section 3. The covariate \( X_i \sim N(0,2) \) and was time-fixed.

- Model 2 (high variability, Gaussian random effects): Similar to Model 1 with the following modifications. The random effects \( \alpha_i \) were simulated from Gaussian distributions with a variance of 28.0 and 15.0, respectively. These values were chosen based on the estimates for \( D_{11} \) and \( D_{22} \) in the lung transplant study. In addition, the true values for the remaining parameters were also set close to the estimates in the lung transplant study to mimic the real data. The median number of visits per patient was 4.

- Model 3 (medium-high variability, Gamma random effects): Similar to Model 1 with the following modifications. The random effects \( \alpha_i \) were simulated from Gamma distributions with a variance of 12.0 and 8.0, respectively. This simulation aims to investigate whether the proposed estimation procedure is robust when the normality assumption for \( \alpha_i \) is violated. Specifically, \( \alpha_{i1} \) and \( \alpha_{i2} \) were generated from Gamma distributions with the shape and scale parameters set to (3,2) and (2,2), respectively. Both distributions are asymmetric with a longer right tail. Note that the variance of these random effects is at a level in between its counterpart in Models 1 and 2. We centered the random effects at the mean of their Gamma distributions to make sure the expectation was zero.

For these models we looked at a sample size of 215, same as that of the lung transplant study. A joint model with 8 knots was fit to each simulated dataset. We report the bias and standard deviation (SD) which was estimated using the empirical standard deviation of the estimates from 100 simulations. To illustrate how the estimators behave as the sample size increases, we performed simulations under the scenario of Model 1 with \( n = 500 \), and the results are reported in Table S1 (Supporting Information).

For the data generated from Model 1, the proposed estimation approach produces quite small bias for all the parameters except \( D_{11} \), the variance of the random effect associated with the first principal component function, but this bias shrinks when the sample size increases to 500 (Table S1, Supporting Information). Figure 3 indicates that the estimated cumulative baseline hazard functions from 20 randomly selected simulated datasets on average agree well with the true cumulative hazard.

Regarding the data that mimic the lung transplant study with a high level of variability in the latent process (Model 2), we observe relatively small estimation bias and variability for the fixed effects \( \hat{\beta}_{01}, \hat{\beta}_{02}, \) and \( \hat{\beta}_{12} \) in the longitudinal sub-model and the coefficient \( \gamma \) for the latent process in the survival sub-model, but the estimates for \( D_{11} \) and \( D_{22} \) show a larger bias.

![Figure 3](image-url)
and variation. In other words, although the high variability or noise in the latent process affects the estimation accuracy on $D_{11}$ and $D_{22}$, it does not seem to have a noticeable effect on the estimation of the fixed effects parameters $\beta_{01}, \beta_{02}, \beta_{12}$ and $\gamma$. We also note that when the normality assumption for the random effects is violated (Model 3), the bias for $\beta, \gamma$, and the variance of the measurement error terms $\sigma_1^2$ and $\sigma_2^2$ remains small, suggesting that these parameter estimates seem to be robust to violation of the random effects normality assumption. Furthermore, the bias for $D_{11}$ and $D_{22}$ in Model 3 tends to be smaller than that in Model 2, suggesting again that the estimation accuracy for $D_{11}$ and $D_{22}$ would improve as the amount of noise in the latent process decreases.

We further investigated the sensitivity of parameter estimation with regards to the chosen knot number for the latent process. A series of joint models were fit to the data generated from Model 2 (an 8-knot model), but with the knot number set to 4, 6, 8, 10, and 12. As shown in Table S2, Supporting Information, the parameters $\beta_{01}, \beta_{02}, \beta_{12},$ and $\gamma$ consistently have small bias and variability regardless of the knot number specified. A larger bias is observed for $\sigma_1^2$ and $\sigma_2^2$ when the knot number is far below the true value, but this bias reduces as the knot number increases. The knot number has a marked impact on $D_{11}$ and $D_{22}$; both have a considerable bias and estimation variation when the knot number is either too small or large compared to the true value 8.

5 | DISCUSSION

We have developed a new flexible joint model for dynamic prediction of a clinically meaningful event from highly correlated biomarkers. We model the multiple biomarkers for each individual using a shared latent reduced rank longitudinal principal component model and then correlates the latent process to the event time of interest. B-splines are used to estimate the overall mean and principal component functions of the latent process. Our approach uses data to determine the functional form of the individual latent trajectories and thus is more flexible than the parametric latent trajectories used in previous work. We further establish asymptotic properties for semi-parametric maximum likelihood estimators and develop a dynamic prediction tool under this model. As illustrated in the real data example, combining information from multiple highly correlated biomarkers can lead to improved prediction accuracy for the event of interest than using a single biomarker alone. Our simulation results indicate the random effects variance parameters are often more difficult to estimate especially when there is substantial variation in the latent process, but they do not seem to have a noticeable effect on the estimation accuracy of the fixed effects $\beta$ and the association parameter $\gamma$ between the longitudinal and survival endpoints. In addition, estimation of the fixed effects in the longitudinal sub-model and the association between the latent process effect and the event risk is not very sensitive to mis-specification of the number of knots for the B-splines, whereas reasonable estimates of the principal component random effects may only be obtained when the assumed knot number is not far off from the value that can adequately capture data variation across time.

We note from simulations that the parameter estimation seems to be quite robust to misspecification of random effects distributions, which is consistent with similar findings in the literature. Song et al. (2002) relaxed the normality assumption for the random effects in joint models and only required that the random effects have a smooth density. Their findings indicate that estimation of certain model parameters, including the fixed effects at the longitudinal endpoint, are remarkably robust to misspecification of the random effects distributions. Actually this robustness property may stem from linear mixed effects models as shown in a recent study by Schielzeth et al. (2020) and related references therein. However, the theoretical basis of this phenomenon is still unclear, which warrants further research.

We point out that our approach and results have some limitations. First, the estimator’s asymptotic properties are derived by assuming the number of knots is fixed for the B-splines, whereas a full data-driven approach would ideally allow the flexibility of estimating the number of knots together with the remaining model parameters. However, proving the asymptotic properties under the latter scenario is challenging, which definitely warrants future research. Second, the maximum likelihood estimates of the model parameters are computed using an EM algorithm, in which the E-step involves intractable integrals that are approximated by Gaussian quadratures. The time cost of fitting such a model increases exponentially with the dimension of random effects, which is a well known computational challenge for most joint models. It would be of interest to develop more efficient computational methods, such as Laplace approximation (Williamson et al., 2018) or adaptive quadratures (Tseng et al., 2016), to reduce the computational cost. Lastly, estimation of the parameters in the survival sub-model involves risk set assessment at all the observed event times, which leads to a computation complexity of $O(n^2)$ and is thus not scalable to super large $n$ data. Our group is currently engaged in developing more efficient algorithms for joint models of longitudinal and event time data and the findings will be reported in a sequel paper.
A further question is how to extend the current model to a more general setting where the biomarkers can be grouped into multiple biological pathways so that different pathways have distinct trajectories, but biomarkers from the same pathway share similar trends over time. Another related question is how to identify pathways and/or biomarkers that are most predictive of the clinical event. Further methodological developments are needed to answer these research questions.

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CONFLICT OF INTEREST
The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

OPEN RESEARCH BADGES
This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in the Supporting Information section.

This article has earned an open data badge “Reproducible Research” for making publicly available the code necessary to reproduce the reported results. The results reported in this article were partially reproducible due to their computational complexity.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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