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Evolution of association between renal and liver functions while awaiting heart transplant: An application using a bivariate multiphase nonlinear mixed effects model

Jeevanantham Rajeswaran, Eugene H Blackstone, and John Barnard

Department of Quantitative Health Sciences, and Heart and Vascular Institute, Cleveland Clinic, Cleveland, USA

Abstract

In many longitudinal follow-up studies, we observe more than one longitudinal outcome. Impaired renal and liver functions are indicators of poor clinical outcomes for patients who are on mechanical circulatory support and awaiting heart transplant. Hence, monitoring organ functions while waiting for heart transplant is an integral part of patient management. Longitudinal measurements of bilirubin can be used as a marker for liver function and glomerular filtration rate for renal function. We derive an approximation to evolution of association between these two organ functions using a bivariate nonlinear mixed effects model for continuous longitudinal measurements, where the two submodels are linked by a common distribution of time-dependent latent variables and a common distribution of measurement errors.

Keywords

Nonlinear model; mixed effects model; temporal decomposition; bivariate mixed effects model; evolution of correlation; additive regression

1 Introduction

In many longitudinal follow-up studies, we observe more than one longitudinal outcome; that is, we encounter multivariate longitudinal data. For example, we may observe serial measurements of postoperative normalized forced expiratory volume in 1 s and forced vital capacity after lung transplant.¹ However, we often tend to analyze these outcomes separately using readily available univariate longitudinal methods. When analyzing each separately, one ignores any association structure between these different outcomes. If we are interested in the effect of some predictors on all the longitudinal responses,² this may induce bias in the inferences. Further, we may also be interested in investigating associations among the longitudinal responses, particularly, as in this paper, evolution of the association among the

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Corresponding author: Jeevanantham Rajeswaran, Cleveland Clinic, JJNB-01, 9500 Euclid Avenue, Cleveland, OH 44195, USA. rajeswj@ccf.org.

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responses.^{3,4} In these situations, one has to analyze these multivariate longitudinal outcomes jointly. By using a multivariate model, one increases efficiency and power⁵ by borrowing strength across the multiple longitudinal response variables. Note that these different longitudinal outcomes may be of different types.^{6,7} For example, after mitral valve repair, we serially observe left ventricular ejection fraction, which is continuous, and graded severity of mitral regurgitation, which is ordinal. Hence, in this situation, we have mixed (continuous and ordinal) bivariate longitudinal data, and we may be interested in identifying factors related to both outcomes. Multivariate longitudinal models can be either marginal⁸ or conditional (mixed effects).⁹ When the multivariate longitudinal outcomes are all from a multivariate normal, one can use a multivariate linear regression model. In medical observational studies, as in ours, one often encounters highly unbalanced data in which the longitudinal measurements are measured at different time points for different patients and/or each patient can have a different number of measurements. In such situations, the latent variable (random effects) approach is more appropriate¹⁰ than a marginal approach. A detailed overview of the advantages and disadvantages of marginal and latent variable multivariate longitudinal models can be found in Verbeke et al.¹⁰

An important application of the latent variable is in the area of joint modeling. When we have more than one response of interest, for example, more than one longitudinal response,⁷ or one or more longitudinal responses and time-related event(s),¹¹ multiple responses can be linked together by introducing a common distribution for the latent variables (random effects). One of the advantages of this approach is that different types of longitudinal responses, for example, continuous and ordinal, can be modeled jointly; see, for example, Fieuws and Verbeke³ for further details. Shah et al.¹² extended linear mixed models to allow for multiple outcomes in longitudinal responses. Note that by modeling the multivariate longitudinal responses jointly, and hence utilizing the underlying covariance structure of the multivariate responses, we may obtain efficient estimation of the parameters. Because our focus is on the continuous bivariate longitudinal outcomes, for the rest of the paper we restrict our discussion to a continuous bivariate case. However, in most cases, extension to more than two longitudinal continuous or mixed type outcomes is straightforward.

In this paper, we introduce a bivariate mixed effects model to fit bivariate longitudinal outcomes. The bivariate model is an extended version of the univariate decomposition model proposed by Rajeswaran and Blackstone,¹³ in which the overall temporal trend is decomposed into phases with respect to time, and each phase is modulated by a random effect. That is, patient-specific random effects can be time varying.

The paper is organized as follows. In Section 2, we briefly discuss the univariate multiphase mixed effects model and the motivation of this multiphase approach. In Section 3, a bivariate extension is introduced, and we propose an approximation to time-varying association between two longitudinal continuous responses. Then in Section 4, we illustrate the application of the evolution of association between two continuous longitudinal responses using glomerular filtration rate (GFR) and bilirubin longitudinal data in patients awaiting heart transplantation. A simulation study is carried out in Section 5, followed by brief concluding remarks in Section 6.

2 Univariate multiphase nonlinear mixed effects model

We now briefly discuss the motivation for this nonlinear modeling approach and present a univariate nonlinear multiphase mixed effects model. Detailed discussion of this model is given in Rajeswaran and Blackstone.¹³

The motivation for this multiphase approach is based on the Blackstone et al.¹⁴ multiphase parametric hazard modeling strategy of temporal decomposition to model time-to-event data. Briefly, the temporal trend of many longitudinal biological responses is nonlinear in nature.¹⁵ Hence, explicitly modeling the nonlinear trend is an important first step in longitudinal data analysis. Further, it is known that different risk factors can influence the longitudinal response at different time segments. For example, shortly after a medical intervention, the early values of GFR, a marker for renal function, may be influenced by preintervention GFR values and patient's age. However, patient comorbidities, such as diabetes and history of smoking, may influence late values of GFR, say, one year after the intervention. Gender and race, on the other hand, may be predictors for GFR regardless of time. In other words, there may be some factors that influence longitudinal responses early, some late, and some regardless of time. With these two objectives as our motivation, we describe the following additive modeling structure.

Let Y_{ij} be the j th ($j = 1, \dots, n_j$) continuous response for subject i ($i = 1, \dots, n$). We consider the following nonlinear mixed effects model

$$\mathbf{y}_i = \overline{\log} \left(\sum_{l=1}^L \mu_l(\mathbf{X}_{il}; \boldsymbol{\beta}_l, b_{il}) T_l(\mathbf{t}_i, \boldsymbol{\Theta}_l) \right) + \varepsilon_i \quad (1)$$

where, $\overline{\log}(\cdot)$ is a $n_j \times 1$ vector with $\log(\cdot)$ as its j th element; $\mathbf{t}_i$ is a $n_j \times 1$ vector of time point at which the longitudinal response vector $\mathbf{y}_i$ is observed, $\mathbf{X}_{il}$ s are matrices of baseline covariates of fixed effects that are not necessarily equivalent across the L phases, and $\boldsymbol{\beta}_l$ s are the corresponding fixed effect regression parameters related to the l th time phase. We assume that the subject-specific random effects in each phase are proportionally related to each other. That is, the vector $\mathbf{b}_i = (b_{i1}, \dots, b_{iL})^\top = (\gamma_1 b_i, \dots, \gamma_L b_i)^\top$, where γ_l are phase-specific random effect coefficients. We assume random effect $b_i \sim N(0, \tau^2)$. That is, the random effect is shared across the phases. By having subject-specific random effects in each time phase, we allow the possibility of having different random effects in different time phases. For the purpose of identifiability, we take, $\gamma_1 = 1$. It is further assumed that $\varepsilon_{ij} \sim N(0, \sigma^2)$ and is independent of the random effects b_i .

$T_l(t, \boldsymbol{\Theta}_l)$ is a function of time that depends only on time t and a shaping parameter vector $\boldsymbol{\Theta}_l$, and this function can be any of the forms or transformations of equation (2). $\mu_l(\mathbf{X}_{il}; \boldsymbol{\beta}_l, b_{il})$ is a function of covariates and random effect in the l th phase, with $\mu_l(\mathbf{X}_{il}; \boldsymbol{\beta}_l, b_{il}) = \exp\{\mathbf{X}_{il}\boldsymbol{\beta}_l + b_{il}\}$ ($l = 1, \dots, L$). That is, a phase-specific log-linear mixed effects model is modulated by the time functions $T_l(t, \boldsymbol{\Theta}_l)$. Hence, the effects of covariates $\mathbf{X}_{il}$ s are time varying. The additive flexible nonlinear components $T_l(t, \boldsymbol{\Theta}_l)$ in equation (1) can handle any nonlinear

and linear trends. Note that because $\mu(\cdot)$ and $T_l(\cdot)$ are positive, we have used the logarithmic transformation to have an unrestricted domain in the right side of equation (1).

The generic equation $G(t, \Theta)$ for the multiphase model was originally described as a model of cumulative mortality by Hazelrig et al.¹⁶ and then used in a multiphase hazard model to fit time-to-event data by Blackstone et al.¹⁴ We transform these equations into the conditional expectation domain. The family of equations is given as

$$G(t, \Theta) = \frac{|\nu| - \nu}{2|\nu|} + \frac{\nu}{|\nu|} \left[1 + \phi(m) \left(\frac{|m| - m}{2|m|} + \frac{|\nu|t}{\rho(t_{1/2})} \right)^{-1/\nu} \right]^{-1/m} \quad (2)$$

where $m > 0$ and/or $\nu > 0$, $\phi(m) = m$ if $m > 0$, and $\phi(m) = -1$ if $m = 0$. $\Theta \equiv (m, \nu, t_{1/2})$ is the shaping parameter, $\rho(t_{1/2})$ is a function of $t_{1/2}$, m , and ν . Using the fact that $G(t_{1/2}) = 1/2$, one can deduce the function $\rho(t_{1/2})$ in terms of m , ν , $t_{1/2}$. In survival terminology, Blackstone et al.¹⁴ called $t_{1/2}$ the *half life time*. Natural constraints on G are that $G(0, \Theta) = 0$ and $G(t, \Theta) \rightarrow 1$ as $t \rightarrow \infty$. When $m < 0$ and $\nu < 0$, $G(0, \Theta) = 0$, and this violates the constraints. Thus, this generic formulation (2) does not exist for $m < 0$ and $\nu < 0$. Hence, the generic formulation (2) simplifies into three cases: (i) $m > 0$ and $\nu > 0$, (ii) $m > 0$ and $\nu < 0$, and (iii) $m < 0$ and $\nu > 0$. Detailed discussion of the shapes of the function and some of the transformation used in the modeling and limiting cases ($m \rightarrow 0^+$ or $\nu \rightarrow 0^+$) can be found in Rajeswaran and Blackstone.¹³ Any forms or transformations of equation (2) can be used as the time function, $T_l(t, \Theta_l)$. In our data analysis experience, $T_l(t, \Theta_l) = \frac{\partial G(t, \Theta)}{\partial t}$ is the most commonly used function for the early phase and $T_l(t, \Theta_l) = \frac{g(t)}{1 - G(t, \Theta)}$ is the most commonly used function for the late phase.

Remark

Because the focus of this paper is to assess evolution of association between two longitudinal responses over time, and not on identifying baseline factors associated with the longitudinal responses, we drop the fixed covariate part from the model (1) and write as follows

$$y_i = \log \left(\sum_{l=1}^L \exp(\beta_{0l} + \gamma_l b_i) T_l(\mathbf{t}_i, \Theta_l) \right) + \varepsilon_i \quad (3)$$

where β_{0l} is the l th phase-specific fixed intercept.

3 Bivariate multiphase nonlinear mixed effects model

We suppose, for subject i , that there are two correlated longitudinal continuous responses $\mathbf{Y}_i^1, \mathbf{Y}_i^2$. Note that, for subject i , the longitudinal response k ($k = 1, 2$) is observed at n_i^k distinct time points. That is, $\mathbf{Y}_i^k = (Y_{i1}^k, Y_{i2}^k, \dots, Y_{in_i^k}^k)$, ($k = 1, 2$).

We now extend the univariate nonlinear multiphase model in equation (3) to a bivariate setup, where we have two correlated longitudinal responses as follows

$$\mathbf{y}_i^1 = \widetilde{\log} \left(\sum_{l=1}^{L_1} \exp(\beta_{0l}^1 + \gamma_l^1 b_i^1) T_l(\mathbf{t}_i, \boldsymbol{\Theta}_l^1) \right) + \varepsilon_i^1 \quad (4)$$

$$\mathbf{y}_i^2 = \widetilde{\log} \left(\sum_{l=1}^{L_2} \exp(\beta_{0l}^2 + \gamma_l^2 b_i^2) T_l(\mathbf{t}_i, \boldsymbol{\Theta}_l^2) \right) + \varepsilon_i^2$$

The main features of this bivariate extension are as follows:

1. The longitudinal responses can be of different nature. For example, $\mathbf{Y}_i^1$ can be a longitudinal continuous response and $\mathbf{Y}_i^2$ can be a longitudinal binary response. Note that in the case of nonnormal responses, one must introduce link functions. However, in this paper, we focus on a model in which the two longitudinal responses are continuous.
2. Let $\mathcal{T}_i^k$ be the set of time points at which longitudinal response k ($k = 1, 2$) is observed for patient i ($i = 1, \dots, n$). Then, we can have
 - a. $\mathcal{T}_i^1 \equiv \mathcal{T}_i^2$. That is, both responses were observed at the same time points;
 - b. $\mathcal{T}_i^1 \cap \mathcal{T}_i^2 = \emptyset$, both responses were observed at completely different time points;
 - c. $\mathcal{T}_i^1 \cap \mathcal{T}_i^2 \neq \emptyset$, both responses were observed at least at some common time points.
3. Each response can have a different number of phases. That is, in general, we can have $L_1 \neq L_2$ for longitudinal responses $\mathbf{Y}^1$ and $\mathbf{Y}^2$.
4. We use the following approaches to link the bivariate responses together:
 - a. By the joint distribution of the random effects $\mathbf{b}_i = (b_i^1, b_i^2)^\top \sim \mathcal{N}_2(\mathbf{0}, \mathbf{G})$, with $\mathbf{G}$ is a 2×2 variance–covariance matrix of the random effects. Let $f(\mathbf{y}^1, \mathbf{y}^2)$ be the joint density of the two longitudinal outcomes. Then, under conditional independence assumption, we have $f(\mathbf{y}^1, \mathbf{y}^2) = \int_{\mathcal{R}^2} f(\mathbf{y}^1|\mathbf{b}) f(\mathbf{y}^2|\mathbf{b}) f(\mathbf{b}) d\mathbf{b}$, where $f(\mathbf{y}^1|\mathbf{b})$ and $f(\mathbf{y}^2|\mathbf{b})$ are conditional densities, and $f(\mathbf{b})$ is the joint density of $\mathbf{b}$. Further, measurement errors between the two longitudinal responses are also assumed to be

independent, $\varepsilon_i^1 \perp \varepsilon_i^2$. See Verbeke et al.¹⁰ for detailed discussion of this approach.

- b.** In addition to the joint distribution of the random effects, we also can use the joint distribution of the measurement errors of the two responses to link the two models. In this scenario, we assume that measurement errors for the two responses from the same subject are correlated. That is, $\varepsilon_i = (\varepsilon_i^1, \varepsilon_i^2) \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma} \otimes \mathbf{I}_{n_i})$, where $\otimes$ is the Kronecker product operator and $\mathbf{\Sigma}$ is the 2×2 variance-covariance matrix of the measurement errors for the two responses measured at a given time point for a given patient and are independent of random effects **b**. However, if the two responses are collected at a completely different set of time points, $\mathcal{T}_i^1 \cap \mathcal{T}_i^2 = \emptyset$, then the off diagonal term in $\mathbf{\Sigma}$ is not identifiable and the problem reduces to conditional independence case as in (a).

3.1 An approximation to association between two longitudinal continuous responses

We now derive an approximation to the marginal correlation between the two longitudinal continuous responses as a function of time and shaping parameters using the bivariate multiphase mixed effects model (4). Let $(Y_i^1(t), Y_i^2(t))$ be the bivariate longitudinal response at time point t for patient i . We now rewrite the model (4) for a bivariate response at time t as follows

$$Y_i^1(t) = \log \left(\sum_{l=1}^{L_1} \exp(\beta_{0l}^1 + \gamma_l^1 b_i^1) T_l(t, \boldsymbol{\Theta}_l^1) \right) + \varepsilon_i^1(t) \quad (5)$$

$$Y_i^2(t) = \log \left(\sum_{l=1}^{L_2} \exp(\beta_{0l}^2 + \gamma_l^2 b_i^2) T_l(t, \boldsymbol{\Theta}_l^2) \right) + \varepsilon_i^2(t)$$

with $\mathbf{b}_i = [b_i^1, b_i^2]^\top \sim \mathbf{N}_2(\mathbf{0}, \mathbf{G})$, with $\mathbf{G} = \begin{pmatrix} \tau_{11} & \tau_{12} \\ \tau_{12} & \tau_{22} \end{pmatrix}$, and $\varepsilon_i(t) = [\varepsilon_i^1(t), \varepsilon_i^2(t)]^\top \sim \mathbf{N}(\mathbf{0}, \mathbf{\Sigma})$ with

$$\mathbf{\Sigma} = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22} \end{pmatrix}.$$

First, let us consider a first-order Taylor series approximation of the right side of the expression for Y_i^1 in equation (5) with respect to $\mathbf{b}_i$ at $\mathbf{b}_i = \mathbf{0}$. We have

$$Y_i^1(t) \approx \log \left(\sum_{l=1}^{L_1} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) \right) + \frac{\sum_{l=1}^{L_1} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) \gamma_l^1}{\sum_{l=1}^{L_1} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1)} b_i^1 + \varepsilon_i^1(t) \quad (6)$$

where $\mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) = e^{\beta_{0l}^1 T_l(t, \boldsymbol{\Theta}_l^1)}$ is a nonstochastic component (involving only fixed effect parameters). Hence, the approximate variance of Y^1 at time point t is given by

$$\text{var}\{Y_i^1(t)\} \approx \frac{\sum_{l=1}^{L_1} \mathcal{C}^2(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) (\gamma_l^1)^2}{\left\{ \sum_{l=1}^{L_1} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) \right\}^2} \tau_{11} + \sigma_{11} \quad (7)$$

We now derive the approximate covariance between Y^1 and Y^2 at time t . We know that

$$\text{cov}\{Y_i^1(t), Y_i^2(t)\} = E\{Y_i^1(t)Y_i^2(t)\} - E\{Y_i^1(t)\}E\{Y_i^2(t)\}$$

Now, using the approximation in equation (6) and the fact that $E(\varepsilon_i^k(t)) = 0, E(b_i^k) = 0$, and $\text{cov}(\varepsilon_i^k(t), b_i^k) = 0, \forall k \in \{1, 2\}$, we have

$$\text{cov}\{Y_i^1(t), Y_i^2(t)\} = \frac{\sum_{l=1}^{L_1} \sum_{l'=1}^{L_2} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) \mathcal{C}(t, \beta_{0l'}^2, \boldsymbol{\Theta}_{l'}^2) \gamma_l^1 \gamma_{l'}^2}{\sum_{l=1}^{L_1} \mathcal{C}(t, \beta_{0l}^1, \boldsymbol{\Theta}_l^1) \sum_{l'=1}^{L_2} \mathcal{C}(t, \beta_{0l'}^2, \boldsymbol{\Theta}_{l'}^2)} \tau_{12} + \sigma_{12} \quad (8)$$

Now, using equations (7) and (8) and the maximum likelihood estimates for the regression parameters and shaping parameters of the time function, we obtain an estimator of the approximate association between the bivariate longitudinal response $(Y^1(t), Y^2(t))$, as a function of time as follows

$$\hat{\rho}(Y^1(t), Y^2(t)) \approx \frac{\text{cov}\{\hat{Y}_i^1(t), \hat{Y}_i^2(t)\}}{\sqrt{\text{var}\{\hat{Y}_i^1(t)\} \text{var}\{\hat{Y}_i^2(t)\}}} \quad (9)$$

Note that, under the conditional independence assumption, the last term, σ_{12} , in equation (8) equals zero.

3.2 Estimation

When all the K responses are observed at the same time points for subject i ($i = 1, \dots, n$), that is, when the sets $\mathcal{T}_i^1 \equiv \mathcal{T}_i^2 \equiv \dots \equiv \mathcal{T}_i^K$ (thus, $n_i^1 = n_i^2 = \dots = n_i^K = n_i$), Faes et al.⁷ proposed a joint model that fits longitudinal outcomes of different type (e.g. continuous and binary)

under the assumption of conditional independence. Marshall et al.¹⁷ fitted a nonlinear random effects model for multivariate responses with missing data under the assumption of correlated measurement errors. However, if $\mathcal{T}_i^j \cap \mathcal{T}_i^k = \emptyset, \forall j \neq k$, then the off diagonal terms of Σ are not identifiable and hence cannot be estimated.

We have bivariate continuous longitudinal responses (Y_i^1, Y_i^2) , with each observed at n_i number of time points for subject $i \in (1, \dots, n)$. Let Γ be the vector of all the fixed effect parameters and random effect coefficients in equation (5). We use the method of maximum likelihood to estimate Γ . In general, the estimation of joint models is carried out under the assumption of conditional independence. However, relaxing this conditional independence assumption by introducing joint distribution for measurement errors, in addition to the joint distribution of random effects, may provide a better fit for the evolution of marginal correlation.³ Therefore, we carried out the estimation using both approaches and selected a better model and then estimated the marginal correlation.

3.2.1 Conditional independent model—Under this scenario, off diagonal term σ_{12} in Σ is assumed to be 0, and the i th subject's contribution to the likelihood is given by

$$\begin{aligned} \mathcal{L}_i(\Gamma, G, \Sigma; y_i^1, y_i^2) &= \int_{\mathcal{R}^2} \prod_{j=1}^{n_i} f_{y^1, y^2 | \mathbf{b}}(y_{ij}^1, y_{ij}^2 | \mathbf{b}_i; \Gamma, \Sigma) f_{\mathbf{b}}(\mathbf{b}_i; G) d\mathbf{b}_i \quad (10) \\ &= \int_{\mathcal{R}^2} \prod_{j=1}^{n_i} f_{y^1 | \mathbf{b}}(y_{ij}^1 | \mathbf{b}_i; \Gamma, \Sigma) f_{y^2 | \mathbf{b}}(y_{ij}^2 | \mathbf{b}_i; \Gamma, \Sigma) f_{\mathbf{b}}(\mathbf{b}_i; G) d\mathbf{b}_i \end{aligned}$$

where $f_{y|\mathbf{b}}(\cdot|\cdot)$ is the conditional density of the longitudinal response, where in our model, it is a conditional normal density. $f_{\mathbf{b}}(\cdot)$ is the joint distribution of the random effects, assumed to be a bivariate normal.

Because of the ease in estimation and application, especially using readily available software, many have proposed different joint models under the assumption of conditional independence (e.g. Beckett et al.,² Pantazis et al.,¹⁸ Thiebaut et al.¹⁹). Further, under this assumption, for each subject, the time points at which the two responses were collected can be completely different for different responses, $\mathcal{T}_i^1 \cap \mathcal{T}_i^2 = \emptyset$.

3.2.2 Full joint model—Under this scenario, in addition to using the joint distribution of random effects, we also use a joint distribution of the measurement errors to link the two responses. The i th subject's contribution to the likelihood is given by

$$\mathcal{L}_i(\Gamma, G, \Sigma; y_i^1, y_i^2) = \int_{\mathcal{R}^2} \prod_{j=1}^{n_i} f_{y^1, y^2 | \mathbf{b}}(y_{ij}^1, y_{ij}^2 | \mathbf{b}_i; \Gamma, \Sigma) f_{\mathbf{b}}(\mathbf{b}_i; G) d\mathbf{b}_i \quad (11)$$

where $f_{y^1, y^2 | \mathbf{b}}(\cdot | \cdot)$ is the conditional joint density of the bivariate longitudinal response. When the conditional distribution is a bivariate normal, as in our model, one can rewrite the conditional distribution into the product of two univariate normals, $f_{y^1, y^2 | \mathbf{b}}(\cdot | \cdot) = f_{y^1 | \mathbf{b}}(\cdot | \cdot) f_{y^2 | y^1, \mathbf{b}}(\cdot | \cdot)$. These univariate representations can be easily implemented using commercially available software (e.g. SAS Software). That is, suppose

$$\begin{pmatrix} \mathbf{Y}^1 \\ \mathbf{Y}^2 \end{pmatrix} \sim N \left(\begin{pmatrix} \mathcal{M}_1(\mathbf{b}) \\ \mathcal{M}_2(\mathbf{b}) \end{pmatrix}, \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22} \end{pmatrix} \right) \quad (12)$$

where $\mathcal{M}_k(\mathbf{b}) = \log \left(\sum_{l=1}^{L_k} \exp(\beta_{0l}^k + \gamma_l^k b_i^k) T_l(t, \boldsymbol{\Theta}_l^k) \right)$, $k = 1, 2$. Then $\mathbf{Y}^1 \sim N(\mathcal{M}_1(\mathbf{b}), \sigma_{11})$ and $\mathbf{Y}^2 | \mathbf{Y}^1 \sim N(\mathcal{M}_2(\mathbf{b}) + \sigma_{12}(\mathbf{Y}^1 - \mathcal{M}_1(\mathbf{b}))/\sigma_{11}, \sigma_{22} - \sigma_{12}^2/\sigma_{11})$.

The integrals in equations (10) and (11) were evaluated using Laplace approximations.^{20,21} Optimization of the approximate likelihood was implemented using the Quasi-Newton method. The whole estimation process was conveniently implemented using PROC NLMIXED (SAS, SAS Institute, Cary NC). The general implementation of this SAS Software procedure is based on Pinheiro and Bates.²⁰

4 Data analysis

Heart failure occurs when the heart loses the ability to pump enough blood through the body. Heart transplant (Htx) is the most effective treatment for selected patients with end-stage heart failure. Some of the initial indications for advanced heart failure are impaired renal and liver function. Low urine output and poor liver function are predictors of poor survival after mechanical circulatory support (MCS) device implantation.^{22,23} It is known that elevated serum creatinine and elevated bilirubin at the time of transplant are risk factors for long-term mortality after Htx.²⁴ Renal function can be evaluated using laboratory values such as creatinine, blood urea nitrogen, creatinine clearance, or GFR.²⁵ Liver (hepatic) function is evaluated using laboratory values such as aspartate transaminase, alanine transaminase, albumin, and total bilirubin. Evaluating the temporal trends of renal and liver functions and assessing the evolution of the association between these two organ functions are essential parts of patient management while waiting for HTx. With these objectives in mind, we focus on the following two continuous longitudinal responses, GFR and bilirubin.

Four hundred thirty-four patients who were transplant candidates (listed for transplant) and were bridged with MCS from December 1991 to July 2009 at Cleveland Clinic are considered in this data analysis. All had ventricular assist devices implanted to support their failing heart while awaiting transplant. A total of 9620 laboratory records on post-MCS bilirubin and GFR are available for these patients. Both bilirubin and GFR are available in all 9620 records. Among these, 43 (10%) patients had only one record, 38 (9%) had only two records, and the remaining had at least three records each. Mean follow-up time was 77 days (median=34 days, P_{25} =14 days, P_{75} =87 days).

The main objectives of this data analysis are to jointly model the temporal evolutions of renal function (GFR) and liver function (bilirubin) while on MCS and to estimate the evolution of the correlation between renal and liver functions. We define the joint model as follows

$$y_i^1 = \log \left(\sum_{l=1}^{L_1} \exp(\beta_{0l}^1 + \gamma_l^1 b_i^1) T_l(t_i, \Theta_l^1) \right) + \varepsilon_i^1 \quad (13)$$

$$y_i^2 = \log \left(\sum_{l=1}^{L_2} \exp(\beta_{0l}^2 + \gamma_l^2 b_i^2) T_l(t_i, \Theta_l^2) \right) + \varepsilon_i^2$$

where $\mathbf{b}_i = [b_{i1}^1, b_{i2}^2]^\top$ with $\mathbf{b}_i \sim \mathbf{N}(\mathbf{0}, \mathbf{G})$, where $\mathbf{G}$ is the 2×2 variance–covariance matrix of the random effects. We assume $\varepsilon_i = [\varepsilon_i^1, \varepsilon_i^2]^\top \sim \mathbf{N}(\mathbf{0}, \mathbf{\Sigma} \otimes \mathbf{I}_{n_i})$, where $\mathbf{\Sigma}$ is a 2×2 matrix that specifies the associations between the measurement errors between the two responses for a given subject i , n_i is the number of time points at which both responses are observed, and ε_i is independent of $\mathbf{b}_i$. We first performed temporal trend modeling for each response separately to identify the phases. We then used the resulting models as starting values in the joint modeling. The data suggested an early peaking and a late gradual decreasing phase for the temporal trend of bilirubin (Figure 1). Temporal trend analysis of GFR yielded an early peaking phase followed by a late constant phase (Figure 1). That is, we have $L_1 = L_2 = 2$ and have used these phases in the joint modeling. Based on different formations of $\mathbf{G}$ and $\mathbf{\Sigma}$, one can obtain different models that have different correlation structures as follows:

1. **Independent model:** Under this scenario, $\mathbf{G}$ and $\mathbf{\Sigma}$ are diagonal matrices. This is equivalent to fitting the two models in equation (13) separately.
2. **Joint model: Conditional independent model:** Under this scenario, the two responses are linked only through a joint distribution of random effects: $\mathbf{G}$ is an unstructured 2×2 matrix, and $\mathbf{\Sigma}$ is a diagonal matrix.
3. **Joint model: Full:** Under this scenario, the two responses are linked using joint distribution of random effects and conditional joint distribution of measurement errors: $\mathbf{G}$ is an unstructured 2×2 matrix and $\mathbf{\Sigma}$ is a 2×2 unstructured matrix.

We have compared the model performance using Akaike's information criteria²⁶ (AICc—corrected version) and using a concordance statistic (r_c) proposed by Vonesh et al.²⁷ Concordance statistic and the observed versus predicted profiles depicted in Figure 2 are appeared to be similar for all three models. One of the reasons for not observing any marked differences among the three different models based on the r_c and observed versus expected profile graphs may be that computation of r_c and predicted profiles are based only on the shaping and scaling parameter, not on association parameters $\mathbf{G}$ and $\mathbf{\Sigma}$. In this data analysis, estimates of shaping and scaling parameters are almost similar across the three models.

However, because AICc clearly shows that the *joint-full model* is better than the other two models (Table 1), we choose the *joint-full model* in this data analysis. Further note that if the objective is to assess the evolution of association, then the choice has to be made between joint-conditional and joint-full model; complete independent model, which has no association parameters, has no use. However, on the other hand, if the objective is to assess the temporal trend, we could compare all three models. Further, in terms of computational time and difficulties, independent model is the simplest to implement and the joint-full model is the most complex. Even though the joint-full model has only two parameters more than that in joint-conditional model, because of bivariate assumption in the measurement error, the full model is computationally complex. SAS Software code for the joint-full model is given in Appendix 1.

Under the joint-full model, estimation of variance–covariance matrices, $\mathbf{G}$ and $\mathbf{\Sigma}$, is

$$\hat{\mathbf{G}} = \begin{pmatrix} 1.3 & -0.18 \\ -0.18 & 0.68 \end{pmatrix}, \text{ and } \hat{\mathbf{\Sigma}} = \begin{pmatrix} 0.36 & -0.048 \\ -0.048 & 0.37 \end{pmatrix}$$

4.1 Evolution of association between the renal and liver functions

We now estimate the evolution of association between the renal function (GFR) and liver function (bilirubin) using the joint-full model. As a crude verification of this evolution, we have employed an ad hoc procedure proposed by Fieuws and Verbeke³ to estimate “observed” marginal correlation. Following their “moving window” approach, we have estimated the observed correlation coefficient for a subset of data within a time window of three weeks. We then moved this window by an increment of seven days and obtained the coefficient estimates as a function of time. Note that this is a very crude marginal estimate, because a window can have repeated responses for the same patient. This crude estimation also does not take into account the fact that repeated responses from the same subject are correlated. We have discarded “moving windows” that have fewer than 50 pairs of observations. Figure 3 shows the parametric estimation of the marginal correlation based on the joint-full model. In general, there is a negative correlation between GFR (renal) and bilirubin (liver) throughout the follow-up period. That is, lower GFR is associated with higher bilirubin. It is known that lower GFR values are a marker for poor renal function, and higher bilirubin values are a marker for poor liver function. Hence, negative association points to the fact that throughout the follow-up period, poor renal function is associated with poor liver function and vice versa. That is, both organs simultaneously either performed better or worse. It is noted, however, that the association changed over time from mild to very mild by month 3. Figure 4 shows the contour plots between the two responses at different time points. It can be clearly seen that the association gets milder as time on MCS increases.

5 Simulation study

We have performed a focused simulation study to assess the performance of approximate estimator of the marginal correlation derived in Section 3.1 (equation (9)). Following the model estimates for shaping and scaling parameters in the data analysis in Section 4 as

closely as possible, we simulated a bivariate normal response from the nonlinear mixed effects joint-full model with two phases as follows: For the longitudinal response $\mathbf{Y}^1$ we have used an early decreasing phase ($\beta_{01}^1 = -2$, $t_{1/2} = 0.042$, $m = 0$, and $\nu = -0.75$) and a late increasing phase that plateaued by three months ($\beta_{02}^1 = 0$, $t_{1/2} = 1.5$, $m = 0$, and $\nu = 1.5$); for the longitudinal response $\mathbf{Y}^2$, we have used an early peaking phase ($\beta_{01}^2 = -0.6$, $t_{1/2} = 0.25$, $m = 0$, and $\nu = -0.75$) and a late increasing phase ($\beta_{02}^2 = 0$, $t_{1/2} = 1.5$, $m = 0$, and $\nu = 0.8$). The shapes of the phases and the mean response curve for a typical subject (where $\mathbf{b} = \mathbf{0}$) are given in Figure 5. We have generated longitudinal responses at nine time points over a 12-month period at one day, two weeks, one, two, three, six, nine, and at 12 months. We have simulated 500 datasets each with 500 subjects.

Variance–covariance matrices, $\mathbf{G}$ and $\mathbf{\Sigma}$, are set as follows

$$\hat{\mathbf{G}} = \begin{pmatrix} 1.3 & -0.2 \\ -0.2 & 0.75 \end{pmatrix} \quad \hat{\mathbf{\Sigma}} = \begin{pmatrix} 0.4 & -0.05 \\ -0.05 & 0.4 \end{pmatrix}$$

Since there is no closed form solution to calculate the population (“true”) marginal correlation using the nonlinear model, we have “empirically” calculated the “true” marginal correlation using the simulated bivariate longitudinal response at the given nine time points for 50,000 subjects. Since the sample size is very large and the bivariate response was simulated at time t , we speculate that the correlation estimated using the bivariate longitudinal response ($\mathbf{Y}^1(t)$, $\mathbf{Y}^2(t)$) can be regarded as a “true” representation of population value at time t .

Figure 6 shows the simulation results compared to the “true” marginal correlation. It can be noted that “true” value is within the distribution of simulated approximate value with some deviation between the values in the last three time points. Overall, it appears that the simulated values are closer to the “true” values.

6 Conclusion

We have presented a system of nonlinear multiphase mixed effects models to analyze bivariate continuous longitudinal data. That is, we have extended the nonlinear multiphase mixed effects model¹³ for a single continuous longitudinal response to accommodate bivariate longitudinal responses. Extension to accommodate more than two longitudinal responses is straightforward. We further, using the nonlinear bivariate mixed effects model, provide an estimate for evolution of marginal correlation between two continuous longitudinal responses. It appears that the association between renal and liver function in patients on MCS awaiting Htx evolved nonlinearly over time. This nonlinearity is easily captured by using the nonlinear bivariate mixed effects model.

One of the advantages, in terms of applicability, is that we have implemented the bivariate model using readily available software. By changing a bivariate problem into a univariate problem, we have implemented the bivariate model using PROC NLMIXED (SAS). When there are more than two longitudinal responses, one can follow the approach proposed by

Fieuws and Verbeke²⁸ to reduce the problem into a series of bivariate models. In principle, by changing the link function from identity to another function, for example, logit, in one of the models in equation (4), one can accommodate responses of different types. For example, a normal response and a binary response. However, it should be noted that when modeling different types of responses, care should be given to the interpretation of the association (see, for example, Faes et al.⁷). Further, when the random effects enter the model nonlinearly, especially for nonnormal response models, estimation procedures that use Laplace approximations for numerical integration may not be efficient.²⁹ In this case, one can use numerical integration methods, such as Gaussian-Quadrature, to obtain the marginal likelihood.

In the bivariate model (4), we have joined the different responses using joint distributions of random effects and measurement error. However, we have assumed i.i.d. for measurement error for a given response within a patient. This assumption can be relaxed, so that one can introduce correlation structure, for example, auto-regressive of order 1, for a response. Further, these correlation structures can be different for different responses if data warrants. In our data analysis, as the protocol requires, patients listed for HTx were monitored rigorously such that both longitudinal responses were observed simultaneously at every time point; hence, there was no need to consider missing data. But in most observational studies, we encounter missing data, where not all the longitudinal responses are observed at all time points. This problem can be handled as outlined by Marshall et al.¹⁷

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Appendix 1: Sample SAS code for joint-full model

```
*****Codes are for equation (13) in Section 4*****;
* built - sas dataset;
* ID - patient ID;
* bilip_z - response variable - bilirubin - longitudinal continuous;
* gfrp_z - response variable - GFR - longitudinal continuous;
* iv_lab - time interval from transplant to response measurement;
*****;
* %decompos is a sas macro for the time function;
*****;
proc sort data = built; by id iv_lab; run;
ods trace on;
ods output parameterestimates = est.peMLgfrbli_uvalberr;
proc nlmixed data = built gconv = 1E-8 qpoints = 1;
  parms
    /*****For bilirubin *****/
    /* Early */
    e01 = -2.0506 thalf1l1 = -3.2789 null = -0.8213
    /* Late */
    thalf1l2 = 0.2348 nu12 = 1.3879
    /* Conditional Normal model variance */
    logsig1 = -0.5174
    /* Random effect variace */
    logsigu = 0.1523 a12 = -0.02058
    /*****For GFR *****/
    /* Early */
    e02 = -0.5905 thalf2l1 = -1.3229 nu21 = -0.7712
    /* Late */
    thalf2l2 = 0.5158 nu22 = 0.7248
    /* Conditional Normal model variance */
    logsig2 = -0.4997
    /* Random effect variance*/
    logsigv = -0.3920 a22 = 0.6177
    /*****Random effects covariance between bilirubin and
GFR*****/
    suv = -0.320
    /***** Measurement error covariance between bilirubin and GFR
*****/
    sig12 = 0.05
  ;
```

```

/* Early */
mue = exp(e01 + u); m11 = 0;
thalf11 = exp(thalf111);
%decompos(_complet = 0, _time = iv_lab, _thalf = thalf11, _nu = null, _m
= m11);
g11 = _hazard;
/* Late */
mul = exp(a12*u); m12 = 0;
thalf12 = exp(thalf112);
%decompos(_complet = 1, _time = iv_lab, _thalf = thalf12, _nu = nul2, _m
= m12);
g12 = _hazard;
eta = (mue*g11 + mul*g12);
l_etal = log(eta);
MNZ = l_etal;
s11 = exp(2*logsig1);
sigmasq = s11;
resid = (bilip_z - MNZ);
if (abs(resid) > 1.3E100) or (sigmasq < 1E-12) then do;
  llvar1 = -1e20;
end; else do;
  llvar1 = -0.5*(1.837876 + resid**2 / sigmasq + log(sigmasq));
end;
/*****/
/* Early */
mue = exp(e02 + v); m21 = 0;
thalf21 = exp(thalf211);
%decompos(_complet = 0, _time = iv_lab, _thalf = thalf21, _nu =
nu21, _m = m21);
g21 = _hazard;
/* Late */
m22 = 0; mul = exp(a22*v);
thalf22 = exp(thalf212);
%decompos(_complet = 1, _time = iv_lab, _thalf = thalf22, _nu = nu22,
_m = m22);
g22 = _hazard;
eta = (mue*g21 + mul*g22);
l_etal2 = log(eta);
MNZ = l_etal2 + sig12*(bilip_z-l_etal)/s11;
s22 = exp(2*logsig2);
sigmasq = s22 - (sig12*sig12/s11);
resid = (gfrp_z - MNZ);
if (abs(resid) > 1.3E100) or (sigmasq < 1E-12) then do;
  llvar2 = -1e20;

```



```
end; else do;
  llvar2 = -0.5*(1.837876 + resid**2 / sigmasq + log(sigmasq));
end;
model gfrp_z ~ general(llvar1 + llvar2);
su = exp(2*logsigu);
sv = exp(2*logsigv);
random u v ~ normal([0, 0], [su, suv, sv]) subject = id out = rand_out;
run;
```

Figure 1. Temporal trends of bilirubin and GFR for a “typical patient” ($\mathbf{b}_I = (0,0)^T$). GFR: glomerular filtration rate.

Figure 2. Goodness of fit: Observed versus predicted profiles for each response under three different scenario. r_c depicts the concordance statistic—value closer to 1, better the model fit.

Figure 3.
Evolution of association between renal and liver function. Solid line is the approximate association estimated using the joint-full model. The symbols are crude “observed” correlation estimates based on the “moving window” approach.

Figure 4.

Evolution of association between renal and liver function. Contour plot of the two responses at six different time points while on MCS. MCS: mechanical circulatory support.

Figure 5.
Shapes of phases and temporal trends used in simulating a bivariate normal response.

Figure 6.

Simulation results: large circle symbols depict the "true" marginal correlation and boxplots depict the distribution of estimated approximate marginal correlation based on simulated data.

Table 1

Model selection: $AICc$ for three different models for bivariate longitudinal model (13). is the difference in the $AICc$ between the joint-full model and the other two models.

Model	$AICc$	
Joint-full model	35,753	0
Joint model: Conditional model	35,875	122
Independent model	35,892	139

AIC: Akaike's information criteria.