Journal of Statistical Research *https://doi.org/10.3329/jsr.v58i1.75415*
2024, Vol. 58, No. 1, pp. 97-110 *ISSN 0256 - 422 X*

MODELING INFORMATIVE DROPOUT IN LONGITUDINAL DATA: A JOINT MODEL APPROACH

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SUMMARY

In medical studies, a disease's progress is often monitored through indicators that signify the improved or worsened condition of the patient. These are known as longitudinal biomarkers, which are observed along with an event of importance. Together, they form the framework of joint modeling, which has a longitudinal process and an inherently associated time-to-event process. In clinical studies, the change in biomarkers is often monitored in the form of a change in the patient's plasma level after a drug is administered to the patient. Again, in such studies, patients also withdraw from the trials prematurely or at a later phase, thus giving rise to dropouts. In most cases, this dropout is not random (Missing Not at Random). A joint model has been considered to incorporate this informative dropout in longitudinal response. To demonstrate this approach, a one-compartmental pharmacokinetic (PK) nonlinear mixed-effects model consisting of time-dependent parameters has been used in this work. The dropout mechanism has been introduced using a proportional hazard model. A Bayesian model framework is adopted to study the model's performance through detailed simulation. A PK study on the drug Divalproex subject to an informative dropout model has been discussed.

Keywords and phrases: non-linear mixed effects model, MCMC convergence, Cox proportional hazard model, compartment model

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1 Introduction

Pharmacokinetic /Pharmacodynamics (PK/PD) studies have evolved out of the need to study the efficacy of a new drug on a patient's body or the efficacy of that drug over the other prevalent drugs in the market. An integral part of this study is monitoring the concentration of drugs in patients' blood over different time points. Hence, after a drug is administered to a patient's body, the drug concentration in blood over the follow-up visits over time serves as the longitudinal data in PK modeling. This also acts as a marker for disease progress in a patient's body, thus indicating whether the particular treatment is effective. This longitudinal trajectory acting as a biomarker can further be linear or nonlinear.

Again, in PK/PD studies, it is seen that patient dropout is a common feature. Patients under a study trial can become impatient or depressed due to the ineffectiveness or severe side effects of the drug administered to them and decide to leave or terminate the study. As a result, blood plasma concentrations become unavailable over subsequent time points. Dropout, in clinical studies, can be informative or non-informative. In PK modeling, it can be perceived that the likelihood of dropout in most cases is inherently related to the underlying observed data. This dropout is non-ignorable, and excluding this feature from the model may lead to gravely biased estimates. Thus, including the dropout mechanism in the model procedure is very significant. Since the past decade, this issue has been receiving much attention with the linear or generalized linear longitudinal submodel (Fitzmaurice and Laird, 2000).

Studies on modeling dropout in longitudinal processes can be found in the works of Verbeke et al. (2001), Yi and He (2009). Hogan et al. (2004) discussed regression-based modes for analyzing dropouts in longitudinal data in different clinical studies. Diggle and Kenward (1994) combined a multivariate linear model and a logistic regression model for modeling the dropout. Cuer et al. (2022) handled informative dropout in longitudinal esophageal cancer clinical study data.

Frequently, it is seen in many clinical studies that the disease progress in the patient's body follows a nonlinear pattern. Nonlinear models have been explored in the area of PK modeling by Sheiner et al. (1997), Wang et al. (2010), Hu et al. (2011), Bates (2005) and Owen and Fiedler-Kelly (2014). Usually, these studies are concerned with constant absorption rate, but they should consider a natural absorption process function and a disposition process function. The analysis of a nonlinear mixed-effects model having time-dependent covariates in the pharmacokinetic field was previously discussed by Lindstrom and Bates (1990) and Davidian and Giltinan (2003). Again, parametric modeling of drug concentration was considered by Lindsey et al. (2000) for a class of generalized nonlinear models. Further, mixed-effects modeling is considered relatable because there was a need for accommodation of the subject-specific random effects. A one-compartment model for time-varying covariates had been considered by Li et al. (2002) using a cubic spline. Again, Hu and Sale (2003) discussed joint modeling of nonlinear longitudinal data along with informative dropout using a shared random-effect model in the context of PK modeling on HIV and diabetic studies. The authors explored different types of dropout models, i.e., informative and non-informative, influencing the predictive ability of the joint model.

In drug development, the mixed-effects analysis of pharmacokinetic data is commonly known as the population pharmacokinetic approach. This area includes the absorption, distribution, metabolism,

and elimination of a drug over time after it is administered in the body. The basis of Pharmacokinetics is how drugs move around the body and at which rate this movement occurs. After the drug is administered in the body, it may be assumed that it achieves instantaneous distribution throughout the body and instantaneously attains equilibrium between the body's tissues. So, it can be said that the body is depicted as a kinetically homogeneous unit (Gibaldi and Perrier, 1982) on which the drug acts.

Further, it can be noted that the drug concentration-time profile shows a monophasic response (monoexponential). This fact does not signify that the plasma drug concentration (C_p) is the same as the tissue drug concentration. However, plasma concentration change influences the changes in tissue concentration. Again, it is undeniable that the change in drug concentration holds significance as far as disease progression in concerned, and thus, it is monitored at every visit. For this reason, each patient is considered for an absorption and disposition process function to describe the absorption and disposition phases of the drug in the body.

In our work, we have considered a nonlinear longitudinal mixed-effects model along with patient dropout information and a dropout time-to-event submodel in the context of a pharmacokinetic study. As far as we know, not much work has been developed with applying pharmacokinetic data in the framework of joint modeling. Here, a nonlinear mixed pharmacokinetic model is proposed for monitoring the disease progression during 21 weeks. Pharmacokinetic parameters vary over time, and including the subject-specific random effects ensures the accommodation of correlation and variation in the data. Direct modeling of the disease progression would result in erroneous conclusions as some patients were untreated throughout the study. The dropout issue has been rationally incorporated into the joint model by developing the nonlinear mixed pharmacokinetic model, including the assumption of informative dropout and shared subject-specific random effects. The drug's pharmacokinetics focused on characterization while considering the effects of various covariates and the longitudinal model subject to dropout. In this work, joint longitudinal and time-to-event modeling and patient dropout information are proposed in the context of pharmacokinetic modeling. Here, the plasma drug concentration over time is considered the longitudinal observations, and the time-to-event process is modeled via the Cox proportional hazards (PH) model. Bayesian framework is adopted for the parametric estimation.

This work is organized as follows. Section 2 proposes joint modeling with one compartmental mixed PK model as the longitudinal submodel and time-to-event submodel with the patient dropout information. In Section 3, the proposed methodology is examined through a simulation study and is illustrated by a data set on PK study of Divalproex. Section 5 presents an overall discussion.

2 Methods

2.1 Pharmacokinetic mixed model

The current study asserts that the drug's pharmacokinetics resembles a one-compartment model. The usual choices are a one-compartment model with first-order absorption or a two-compartment model with zero-order absorption. Here, we can say that at the initial stage, when the drug is administered

orally, all the drug is in the gut before it enters the 'body'. Now, we let $A_1(t)$ and $A_2(t)$ signify the amount of drug in the gut and the body at time t, respectively. Here k_a and k_e are first-order absorption and elimination rates, respectively. Hence, we can express this under the differential equation setup:

$$\frac{dA_2(t)}{dt} = k_a A_1(t) - k_e A_2(t), \;\; A_2(0) = 0,$$
$$\frac{dA_1(t)}{dt} = -k_a A_1(t), \;\; A_1(0) = 1.$$

So, at time point t the concentration of drug in blood can be expressed by the relation $C_p(t) = A_2(t)/V$. Here, V signifies the apparent volume of the compartment, which is not a physiological volume. Some drugs are likely to have a higher value than the blood plasma but can be larger to a good extent than the body volume. These plasma concentrations are inherently regulated by the absorption and elimination rate of the drug. These rates are naturally time-dependent.

Here, we consider a one-compartment PK model with a first-order absorption rate and consider the differential equation, which can be expressed by

$$\begin{pmatrix} \frac{dA_{1,i}(t)}{dt} \\ \frac{dA_{2,i}(t)}{dt} \end{pmatrix} = \begin{pmatrix} -k_{a_i}(t) & 0 \\ k_{a_i}(t) & -k_{e_i}(t) \end{pmatrix} \begin{pmatrix} A_{1,i}(t) \\ A_{2,i}(t) \end{pmatrix}.$$

Taking the idea from Li et al. (2002) the expression can be put as

$$\frac{dA(t)}{dt} = G(\psi(t))A(t), \tag{2.1}$$

Here, $A(t) = (A_1(t), A_2(t))'$, $\psi(t) = (k_a(t), k_e(t))'$ and G is a function of $\psi(t)$.

Next, we consider a mixed-effects regression model for the longitudinal response

$$y_{ij} = g(\boldsymbol{x}'_{ij}\boldsymbol{\beta}_i, t_{ij}) + e_{ij}.$$

Here, $\boldsymbol{x}_{ij}$ denotes the covariate vector for y_{ij} which is the longitudinal response for the i^{th} individual at the j^{th} time point where $i = 1, 2, \ldots, n$ and $j = 1, 2, \ldots, m_i$. Here, $g(\cdot)$ denotes a nonlinear smooth function of $\boldsymbol{x}'_{ij}\boldsymbol{\beta}$. Following Davidian and Giltinan (2003), the mean function can be expressed as

$$g(\boldsymbol{x}'_{ij}\boldsymbol{\beta}_i, t) = \log \frac{[A_{2i}\{k_{a_i}(t), k_{e_i}(t), t\}]}{V_i}.$$

Here, V_i denotes i^{th} individual's apparent volume of the compartment. $e_{ij} \sim N(0, \sigma_0^2)$. Again, we can write

$$\boldsymbol{\beta}_i = \boldsymbol{Q}(\boldsymbol{\alpha}, \boldsymbol{b}_i),$$

where $\boldsymbol{\beta}_i$ is the PK parameter for the i^{th} individual having $\boldsymbol{b}_i$ as the subject-specific random effects which can be expressed by the three dimensional functional $\boldsymbol{Q}$. Again, $\boldsymbol{\beta}_i = (k_{a_i}(t), k_{e_i}(t), V_i)'$

and it is reasonably assumed that the subject-specific volume of an individual is independent of time. Further, the components of $\boldsymbol{Q}$ can be expressed as

$$\begin{aligned}\log\ k_{a_i} &= \boldsymbol{x}'_{1i}\boldsymbol{\alpha}_1 + \boldsymbol{z}'_{1i}\boldsymbol{b}_{1i},\\ \log\ k_{e_i} &= \boldsymbol{x}'_{2i}\boldsymbol{\alpha}_2 + \boldsymbol{z}'_{2i}\boldsymbol{b}_{2i},\\ \log\ V_i &= \boldsymbol{x}'_{3i}\boldsymbol{\alpha}_3 + \boldsymbol{z}'_{3i}\boldsymbol{b}_{3i},\end{aligned}$$

where $\boldsymbol{x}_i$ and $\boldsymbol{z}_i$ respectively denote the design matrices for the fixed-effects and random-effects respectively for the i^{th} patient. Here, for the sake of computational convenience, the absorption rate $k_{ai}(t)$ and elimination rate $k_{ei}(t)$ are assumed to be independent of time. Hence, in that situation, equation (**??**) can be solved analytically where the amount of drug present in the body at time t may be expressed as

$$A_{2,i}(t) = \frac{k_{ai}}{k_{ai} - k_{ei}}[(e^{-k_{ei}t} - e^{-k_{ai}t})].$$

We can clearly see that the expression above is a difference between two exponential terms where the former is slower and the latter has a faster rate due to obvious reasons related to the mechanism of bodily functions.

2.2 Dropout model

Dropouts arise in studies when an individual decides to leave or discontinue the treatment due to dissatisfaction or restlessness due to perceived ineffectiveness. Wu and Carroll (1988) was the pioneer in bringing into light the issue of informative dropout, i.e., where the dropout mechanism depends completely or partially on the observed or unobserved outcomes. A summary of this mechanism can be found in Hogan and Laird (1997), and a classification can be found in Rubin (1976). The dropout mechanism can be broadly classified into three categories, i.e., Missing Completely At Random (MCAR), Missing At Random (MAR), and Missing Not At Random (MNAR). MCAR occurs when the dropout mechanism is independent on both observed and unobserved outcomes, MAR occurs when the mechanism depends on observed but not on unobserved outcomes, and MNAR occurs when the dropout mechanism depends on both observed and unobserved data (informative). Hence, it is very evident that ignoring these kinds of dropouts where the reason is inherently linked to the study or process leads to bias in inference.

To model the informative dropout, the Cox proportional hazards model has been used. We let T_i be the dropout time for patient i since the start of the study and δ_i the censoring indicator, which attains value 1 if the patient does not drop out of the study and 0 otherwise. Diggle and Kenward (1994) in their work had proposed considering the dropout time as a survival variable. So we can write

$$h(t) = lim_{\Delta t \longrightarrow 0}\frac{Prob(T < t + \Delta t | T > t)}{\Delta t},$$

where T signifies the dropout time and $h(t)$ signifies the hazard function at time $T = t$. According to the Cox model, we can formulate the hazard function at time T_i as

$$h(T_i) = h_0(T_i)\exp\{\nu_1 b_{1i} + \nu_2 b_{i2} + \nu_3 b_{i3}\}.$$

Here, $h_0(T_i)$ is the baseline hazard function and b_{i1}, b_{i2} and b_{i3} are the components of the subject-specific random-effects responsible for keeping the longitudinal and survival processes correlated. Here, $\boldsymbol{\nu} = (\nu_1, \nu_2, \nu_3)'$ reflects the strength of association between the two processes. Further, if the patient remains in the study until time T_j, the survival probability is

$$S(T_j) = \exp(-\int_0^{T_j} h(u)du).$$

A piecewise constant baseline hazard function is adopted for approximating the baseline hazard function $h_0(T_i)$ by adopting a series of fixed cut points $0 = \tau_0 = \tau_1 < \cdots < \tau_m$ equivalent to the number of clinic visits over all patients. Here, the baseline hazard is assumed to be constant in each interval where $\boldsymbol{h}_0 = (h_{0,1}, h_{0,2}, \ldots, h_{0,m-1})$ where the last point in the interval, i.e., τ_m signifies the maximum observation time in the dataset. The two submodels (longitudinal response and time-to-dropout) are independent if $\boldsymbol{b}_i$ is given.

The unknown parameter vector is say, $\Psi = (\boldsymbol{\alpha}, \sigma_0^2, \rho, \boldsymbol{\nu}, \boldsymbol{h_0})$. Hence, we can write the full likelihood function for the joint model for the i^{th} individual as:

$$\begin{aligned} L_\Psi(\boldsymbol{y}_i, T_i, \delta_i, \boldsymbol{b}_i) &= L_y(\boldsymbol{y}_i|\boldsymbol{b}_i) L_s(T_i, \delta_i|\boldsymbol{b}_i) L(\boldsymbol{b}_i|\rho) \\ &= \prod_{j=1}^{m_i} f(y_{ij}) h(T_i)^{\delta_i} S(T_i) f(\boldsymbol{b}_i|\rho), \end{aligned}$$

where L_y and L_s signifies the likelihood contribution for the longitudinal and time-to-event whereas $L(\boldsymbol{b}_i|\rho)$ signifies the density function for the subject-specific random-effects for the i^{th} individual.

2.3 Bayesian inference

The unknown parameters are inferred using Bayesian inference based on Markov chain Monte Carlo (MCMC) simulations. The results are analyzed by looking at the posterior means and 95% credible intervals (CI). For all the parameters, priors were selected to ensure non-informativeness. Standard priors were chosen for all the parameters. The model is fitted by implementing **BUGS** programming language where we specify the full likelihood and prior distributions for all the parameters. We run multiple chains with overdispersed initial values, and the trace plots and autocorrelation function indicate good convergence (Gelman et al., 1995). Priors with other distribution choices were also considered to ensure the robustness of the results to prior specifications. The likelihood function

along with the priors take the following form for the posterior distribution:

$$\begin{aligned} L(\Psi|\boldsymbol{y}_i, T_i, \delta_i, \boldsymbol{b}_i), &= L(\boldsymbol{y}_i, T_i, \delta_i, \boldsymbol{b}_i|\Psi)L(\Psi), \\ &= L(\boldsymbol{y}_i|\boldsymbol{b}_i)L_s(T_i, \delta_i|\boldsymbol{b}_i)L(\boldsymbol{b}_i|\rho)L(\Psi), \\ &= \Big(\prod_{j=1}^{m_i} f(y_{ij})h(T_i)^{\delta_i}S(T_i)f(\boldsymbol{b}_i|\rho)\Big)f(\boldsymbol{\alpha})f(\sigma_0^2)f(\boldsymbol{\nu})f(\rho)f(\boldsymbol{h}_0), \\ &= \Big(\prod_{j=1}^{m_i} f(y_{ij})h(T_i)^{\delta_i}S(T_i)f(\boldsymbol{b}_i|\rho)\Big)\times \\ &\qquad f(\alpha_1)f(\alpha_2)f(\alpha_3)f(\sigma_0^2)f(\nu_1)f(\nu_2)f(\nu_3)f(\rho)f(h_0), \end{aligned}$$

where $\boldsymbol{\alpha}_i^{'}s$ are taken from normal distribution, $\boldsymbol{\nu}^{'}s$, ρ and h_0 taken from Uniform distribution and σ_0^2 from inverse gamma distribution. The posterior distribution is not a standard one from which samples can be drawn easily. Gibbs sampling is implemented through OpenBugs which works on the full likelihood and prior distributions thus specified. The software uses Metropolis algorithm to generate a Markov chain by sampling from full conditional distributions. This includes probabilistically choosing or throwing away samples at each step dependent on the data and parameter values given at the previous step. The unknown parameters are thus inferred and the results are analyzed looking at the posterior means and 95% credible intervals (CI). For all the parameters priors were selected in a way to ensure non-informativeness.

We run multiple chains with overdispersed initial values and the trace plots and autocorrelation function indicate good convergence (Gelman et al., 2004). Priors with other distribution choices were also considered to ensure the robustness of the results to prior specification.

3 Simulation Study

A simulation study is conducted to investigate the performance of the model. We have generated three data sets with $n = 50, 200$ and 500 individuals under two different sets of parameters. For each individual, a varying number of observations are generated from Uniform(7, 10). True values are assumed to be

$$\text{Set I} : \boldsymbol{\alpha} = (0.3, 0.4, 0.3)', \boldsymbol{r} = (0.5, 0.4, 0.5)', \rho = 0.4, \sigma_b = 0.5$$

$$\text{Set II} : \boldsymbol{\alpha} = (0.8, 0.1, 0.8)', \boldsymbol{r} = (0.7, 0.8, 0.7)', \rho = 0.1, \sigma_b = 0.9$$

A nonlinear mixed-effects model is considered for the longitudinal submodel. Continuous covariates for fixed effects were generated from normal distribution, i.e., $x_{1i} \sim N(1.2, 0.1)$, $x_{2i} \sim N(1.2, 0.2)$ and $x_{3i} \sim N(1.1, 0.1)$. Continuous covariates for random effects were generated from a normal distribution, i.e., $z_{1i} \sim N(1.1, 0.1)$, $z_{2i} \sim N(1.1, 0.2)$ and $z_{3i} \sim N(1.1, 0.1)$. Again, the subject-specific random effects for each individual have been assumed to follow a trivariate normal with $\boldsymbol{b}_i \sim N(\boldsymbol{0}, \boldsymbol{\Sigma})$ where $\boldsymbol{\Sigma}$ follows AR(1) structure i.e. $\boldsymbol{\Sigma} = \sigma_b^2((\rho^{|i-j|}))$. Here, the longitudinal

observations can be expressed as follows

$$\boldsymbol{y}_i = [\frac{k_{a_i}}{k_{a_i} - k_{e_i}}(e^{-\boldsymbol{k}_{e_i}} - e^{-\boldsymbol{k}_{a_i}})]/\boldsymbol{V}_i + \boldsymbol{e}_i.$$

Here $\boldsymbol{e}_i \sim N_{n_i}(\boldsymbol{0}, \sigma_0^2 \boldsymbol{I})$ where $\sigma_0^2 = 0.3$. Here, the censoring information δ_i is taken as 1 if the i^{th} patient dropped out of the study and 0 if the patient remained until the end. Again, the time-to-event submodel is modeled by a Cox proportional hazards model where the hazard is taken as

$$h(T_i) = ke^{\nu_1 b_{i1} + \nu_2 b_{i2} + nu_3 b_{i3}},$$

where $k \sim Uniform(0.01, 10)$. Again $\nu_1 \sim N(0, 0.001)$, $\nu_2 \sim N(0, 0.001)$ and $\nu_3 \sim N(0, 0.001)$. The data $(\boldsymbol{y}_i, x_{1i}, x_{2i}, x_{3i}, z_{1i}, z_{2i}, z_{3i}, T_i, \delta)$ is thus generated from these assumptions.

Bayesian framework is implemented for obtaining inference. Bayesian trace plots and autocorrelation plots were examined from the **OpenBUGS** summary output and the appropriate number of burn-in iterations was set as 5000. MCMC convergence and the mixing of the chains were examined. Three parallel MCMC chains with overdispersed initial values were taken and the final inference was based on 10000 iterations. All the parameters exhibited rapid convergence with $\widehat{R}$ (Gelman Rubin diagnostic) to be within 1.1. The estimation results are reported in Tables below, which display the True value, estimates, Bias, standard deviation, median and 95% equal-tailed credible intervals. From the results under the two sets of parameters vector, it can be seen that the estimates have low bias and standard deviation with tight confidence intervals.

Table 1: Summary Statistics parameter estimates under Set I for $n = 50$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.3	0.5801	0.2801	0.2737	0.1197	0.6065	0.9848
α_2	0.4	0.2309	0.1691	0.1192	0.1034	0.1969	0.5449
α_3	0.3	0.188	0.112	0.07951	0.1024	0.1654	0.3867
r_1	0.5	0.5488	0.0488	0.2593	0.1227	0.5452	0.976
r_2	0.4	0.551	0.151	0.2602	0.1225	0.5503	0.978
r_3	0.5	0.5498	0.0498	0.2594	0.1219	0.5507	0.976
ρ	0.4	0.2506	0.1494	0.1357	0.0169	0.2513	0.4832
σ_b	0.5	0.9952	0.4952	0.004649	0.9818	0.9966	1.005

4 An Application: Divalproex Study

A drug is often characterized by some fundamental parameters related to pharmacokinetics (Gibaldi and Perrier (1982)), i.e., k_a, k_e, V, and also in terms of some derived parameters, i.e., the area

Table 2: Summary Statistics parameter estimates under Set I for $n = 200$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.3	0.7346	0.4346	0.2798	0.189	0.8767	0.9955
α_2	0.4	0.311	0.089	0.1155	0.1197	0.3052	0.5679
α_3	0.3	0.1846	0.1154	0.07786	0.1022	0.1618	0.3866
r_1	0.5	0.5506	0.0506	0.2586	0.1239	0.5499	0.9775
r_2	0.4	0.5509	0.1509	0.2608	0.1226	0.5506	0.9783
r_3	0.5	0.551	0.051	0.2597	0.122	0.551	0.9778
ρ	0.4	0.04114	0.35886	0.03912	5.583×10^{-4}	0.0294	0.14515
σ_b	0.5	0.9999	0.4999	9.34×10^{-5}	0.994	0.9999	1.0068

Table 3: Summary Statistics parameter estimates under Set I for $n = 500$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.3	0.6986	0.3986	0.221	0.2023	0.744	0.9892
α_2	0.4	0.2917	0.1083	0.1608	0.1059	0.2508	0.6952
α_3	0.3	0.3408	0.0408	0.1461	0.1176	0.3228	0.632
r_1	0.5	0.5507	0.0507	0.2584	0.1242	0.5515	0.97585
r_2	0.4	0.5506	0.1506	0.2598	0.1226	0.5489	0.9786
r_3	0.5	0.5501	0.0501	0.2604	0.1232	0.5512	0.9778
ρ	0.4	0.2523	0.1477	0.1429	0.01374	0.2546	0.487
σ_b	0.5	0.9989	0.4989	0.001054	0.9922	0.9993	1.006

Table 4: Summary Statistics parameter estimates under Set II for $n = 50$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.8	0.5449	0.2551	0.2557	0.1246	0.5427	0.9754
α_2	0.1	0.444	0.344	0.2354	0.114	0.4077	0.9358
α_3	0.8	0.4714	0.3286	0.2262	0.1214	0.45	0.9329
r_1	0.7	0.549	0.251	0.259	0.1226	0.5445	0.9774
r_2	0.8	0.5472	0.4472	0.2597	0.1211	0.5453	0.9775
r_3	0.7	0.5518	0.3482	0.2601	0.1224	0.5535	0.9768
ρ	0.1	0.2344	0.5656	0.1453	0.009969	0.2266	0.4856
σ_b	0.9	0.9536	0.0536	0.03204	0.8805	0.9588	0.998

Table 5: Summary Statistics parameter estimates under Set II for $n = 200$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.8	0.5134	0.2866	0.26	0.1179	0.495	0.9725
α_2	0.1	0.5805	0.4805	0.2444	0.1348	0.5946	0.9753
α_3	0.8	0.7999	0.0001	0.1667	0.3806	0.8431	0.9936
r_1	0.7	0.6456	0.0544	0.2603	0.1219	0.5445	0.9767
r_2	0.8	0.5917	0.2083	0.2598	0.1236	0.5527	0.9795
r_3	0.7	0.6496	0.0504	0.2598	0.1229	0.5511	0.9788
ρ	0.1	0.2127	0.1127	0.1424	0.007724	0.1944	0.4797
σ_b	0.9	0.9878	0.0878	0.0095	0.9643	0.9899	1.003

Table 6: Summary Statistics parameter estimates under Set II for $n = 500$

Parameter	True Value	Estimate	Bias	SD	2.5%	Median	97.5%
α_1	0.8	0.5376	0.2624	0.2564	0.1221	0.531	0.9746
α_2	0.1	0.4027	0.3027	0.2048	0.1134	0.3705	0.8356
α_3	0.8	0.2304	0.5696	0.1075	0.1043	0.2046	0.4961
r_1	0.7	0.5493	0.1507	0.2604	0.1219	0.5505	0.9782
r_2	0.8	0.5501	0.2499	0.2599	0.1223	0.5509	0.9775
r_3	0.7	0.5489	0.1511	0.2598	0.123	0.5494	0.9771
ρ	0.1	0.2042	0.1042	0.1427	0.007239	0.1798	0.4787
σ_b	0.9	0.996	0.096	0.00359	0.9849	0.9971	1.005

under the curve (AUC) and terminal half-life $t_{\frac{1}{2}}$. The half-life is the time taken by the plasma concentration of the drug to fall to half of its original value. Again, V converts the entire drug dose in the compartment into the measured concentration. The drug that has a higher volume binds itself strongly to protein, whereas the one having a smaller volume associates itself with the tissue outside the vascular area. k_a and k_e for a drug indicate the speed with which the absorption and elimination processes operate. The relative efficiency of different drug products is evaluated in terms of AUC value (continuous setup) defined as

$$\text{AUC} = \frac{1}{V(t)} \frac{k_a(t)}{k_a(t) - k_e(t)} \int_0^\infty \left(e^{-k_a(t)t} - e^{-k_e(t)t} \right) dt.$$

In the case where the parameters are assumed to be independent of time, $AUC = 1/Vk_e$.

An active ingredient of the drug Depakote is Divalproex sodium, which is basically a compound of Sodium valproate and Valproic acid. This drug is responsible for intensifying gamma-aminobutyric acid in the patient's brain. This acid produced by the body naturally, acts as a neurotransmitter thus enabling the nerves to communicate. There is lack of transparency in the fact about how this drug (Depakote) affects the body of the patient consuming it. It is a matter of investigation whether the drug is effective in reducing the adverse effects, thus increasing the concentration of plasma in patients suffering from epileptic seizures. A study was carried out over 21 weeks on patients orally receiving this drug, and measurements of the actual plasma concentration were recorded over the time points of 1st, 3rd, 8th, 14th, and 21st weeks. Here, patients were permitted to leave the study whenever they desired due to ethical reasons. Progress in the disease was thus observed for a patient at every visit.

In our Divalproex data study, we have patients ranging from 14-73 years with a median age of 47. The vital signs of the patients were observed to be normal at the baseline level and after the treatment, which indicates no significant change until the end of the study period. These signs include mean pulse rate, respiratory rate, weight, body temperature, and blood pressure. Missing

Table 7: Data Study. Divalproex Data.

Parameter	Estimate	SD	Upper	Lower
α_1	0.9559	0.0534	0.8160	1.0020
α_2	0.1000	0.0100	0.0907	0.1092
α_3	0.1000	0.0100	0.0907	0.1093
ν_1	0.5499	0.2577	0.1225	0.9787
ν_2	0.5471	0.2598	0.1206	0.9783
ν_3	0.5511	0.2593	0.1228	0.9788
ρ	0.3027	0.0215	0.2655	0.3411
σ_b	1.0000	0.0100	0.9907	1.0090

data in the form of patient dropouts were considered where dropouts may have occurred due to the wariness of the patient due to the perceived ineffectiveness of the treatment. We denote by y_{ij} the plasma concentration of the drug for the i^{th} patient at the j^{th} time point and then model it as:

$$\begin{aligned} y_{ij} &= \log \frac{[A_{2_i}\{k_{aij}, k_{eij}\}]}{V_{ij}} + e_{ij} \\ \log k_{aij} &= \alpha_1 + z_{1ij} b_{i1} \\ \log k_{eij} &= \alpha_2 + z_{2ij} b_{i2} \\ \log V_i &= \alpha_3 + z_{2ij} b_{i3}. \end{aligned}$$

Here, $e_{ij} \overset{iid}{\sim} N(0, \sigma_e^2)$ and $\boldsymbol{b}_i = (b_{i1}, b_{i2}, b_{i3})' \overset{iid}{\sim} N(\mathbf{0}, \boldsymbol{\Sigma})$. The structure of $\boldsymbol{\Sigma}$ is taken as AR(1) in order to take into account the longitudinal variation. The time-to-event submodel is modelled by Cox proportional hazards model where the dropout time for the i^{th} patient is denoted as T_i and piecewise hazards is applied to the hazard function of each patient. For the Bayesian analysis three parallel MCMC chains with varying initial values are considered and initial 5000 were excluded as burn-in. This has been identified by examining the trace plots and autocorrrelation plots from the output summary. The inference is based on the next 5000 iteration values and they exhibited rapid convergence with $\hat{R}$ within 1.1. The results displayed in Table 7 display the estimates, standard deviation and 95% credible intervals for all the parameters in the data study. It is to be noted that derived PK parameters like absorption rate, elimination rate or apparent volume are patient as well as time-dependent. From Table 7 it can be seen that 95% credible interval are very close for the parameters α_1, α_2, α_3 and sd. SD values are also within acceptable range for all the parameters.

5 Discussion

Here, in this work, pharmacokinetic mixed model, along with patient dropout (informative) is jointly modelled. The drug concentration in blood over time is modeled as mixed-effects pharmacokinetic model with time-varying covariates. For modeling dropout, we have used a time-to-event submodel. However, instead of a Cox PH model, a modified Kaplan-Meier or Kaplan-Meier estimator can also be used in place of Cox proportional hazards if the non-parametric approach is desired. Here, the absorption and elimination rate of a drug from the body is considered time-independent for computational ease. In reality, they might be time-dependent. Thus it can also be taken as time-varying parameters which might enhance computational challenge. An efficient algorithm is also required to handle this complexity. Again, a sensitivity analysis can be done using different choice of priors.

Acknowledgement

The corresponding author (A.C.) would like to express gratitude to Prof. Kalyan Das who introduced and taught joint modelling to him. The authors are also thankful to the anonymous reviewer who contributed a lot to enhance the quality of the manuscript.

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Received: February 13, 2024

Accepted: June 27, 2024