Estimating Dynamic Characteristics of Longitudinal and Survival Data in Stochastic Process Models: Insights from Simulation Studies

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Abstract

The stochastic process model (SPM) provides a general framework for modeling the dynamics of repeatedly measured variables (represented by a stochastic process) in relation to time-to-event outcomes (modeled as the quadratic function of such stochastic covariates). Until recently, there were no publically available software tools implementing the SPM methodology. Recently we developed an R package *stpm* implementing different specifications of the SPM including discrete- and continuous-time multidimensional versions and a one-dimensional model with time-dependent components. In this work, we present simulation studies focusing on two aspects of applications of SPM currently underexplored in the literature: 1) behavior of estimation procedures in cases of small numbers of longitudinal observations per individual and 2) sensitivity to violations of assumption on independence of individuals. We consider here the one-dimensional model taking the recently developed measure of physiological dysregulation based on the statistical (Mahalanobis) distance of biomarker profiles as an example of a variable repeatedly measured in a longitudinal study. Simulations illustrated that the estimation algorithms produce reasonable estimates in case of small numbers of observations per individual. Simulations investigating the sensitivity of the estimation procedure to violations of independence assumption showed that only parameters of baseline hazard are affected in case of dependence in hazards induced by a gamma-distributed random variable. Development of SPM modifications that take into account dependence between individuals (both in hazard rates as well as in the dynamics of longitudinal variables) is necessary to accommodate such dependencies in analyses.

Key Words: stochastic process model, Mahalanobis distance, longitudinal data, mortality, simulations

1. Introduction

The stochastic process model (SPM) originates from the random walk model by Woodbury and Manton (1977). The theoretical background of SPM was presented in Yashin et al. (1985) and Yashin et al. (1989). This model provides a general framework for modeling the dynamics of repeatedly measured variables (represented by a stochastic process) in relation to time-to-event outcomes (modeled as the quadratic function of such stochastic covariates, hence its alternative name, the quadratic hazard model). Recently the approach has been further elaborated to address questions specifically relevant to research on aging

(Yashin et al., 2007) and SPM was extended in different ways, for example to work with latent classes and partially observed covariates (Arbeev et al., 2009; Arbeev et al., 2015; Yashin et al., 2008). Recent book *Biodemography of Aging* (Yashin et al., 2016) presents this methodological framework in more details, see Chapters 11-16. Arbeev et al. (2016b) provides description of the approach targeted at a non-technical audience.

Arbeev et al. (2016a) implemented the measure of multivariate distance (D_M) in the SPM framework. D_M is a composite measure constructed from multiple variables (e.g., biomarkers), see Cohen et al. (2013), and it is based on statistical distance (specifically, Mahalanobis distance, (De Maesschalck et al., 2000; Mahalanobis, 1936)). In case of biomarkers, it is interpreted as a measure of physiological dysregulation (Cohen et al., 2013) representing the deviation of a current physiological state of an organism from the "normal" physiological state. Such a combination (SPM and D_M) is important from the standpoint of applications as it allows one to work with multiple variables in a one-dimensional model while still permitting estimation and interpretation of all components of this one-dimensional SPM in the same way as in the original model (Arbeev et al., 2016a). This provides an opportunity to address relevant research questions still avoiding potential computational difficulties associated with estimation of multidimensional models.

Until recently, there were no publically available software tools implementing the SPM methodology. Recently we developed an R package *stpm* implementing different specifications of the SPM (stable version is available on CRAN: https://cran.r-project.org/web/packages/stpm/index.html; and the most recent version can be downloaded from GitHub: https://github.com/izhbannikov/spm/). The detailed description of the usage of this package will be presented elsewhere (Zhbannikov et al., submitted). In this work, we present simulation studies focusing on two aspects of applications of SPM currently underexplored in the literature: 1) behavior of estimation procedures in cases of small numbers of longitudinal observations per individual and 2) sensitivity to violations of assumption on independence of individuals. Although the general model is multidimensional, we focus on its one-dimensional form in this work (see Zhbannikov et al., submitted, presenting simulations in a multidimensional case) taking the measure of multivariate distance (D_M) as an example of a variable repeatedly measured in a longitudinal study.

2. Stochastic process model: General description and specifications for simulation studies

2.1 Description of model

The stochastic process model (Yashin et al., 2007) represents the dynamics of K variables (e.g., biomarkers) as a function of age (or time) t in the form of the stochastic process:
$$dY(t) = a(t)(Y(t) - f_1(t))\,dt + b(t)\,dW(t)\,, \tag{1}$$
with initial condition $Y(t_0)$. Here $Y(t)$ is a vector of variables at age t, $W(t)$ is a vector Wiener process with independent components ($W(t)$ is assumed to be independent of the initial vector $Y(t_0)$), $b(t)$ is a matrix of diffusion coefficients, $f_1(t)$ is the vector function representing the trajectory that $Y(t)$ tends to follow (i.e., the process has the "mean-reverting property" so that, in a long run, the process tends to drift towards its long-

term mean), and the matrix $a(t)$ is the (negative) feedback coefficient regulating how fast the trajectory of $Y(t)$ reverts to $f_1(t)$.

The conditional hazard rate at age t given the values of the longitudinal variables measured at respective age ($Y(t)$) is specified as:

$$\mu(t, Y(t)) = \mu_0(t) + (Y(t) - f_0(t))^T Q(t)(Y(t) - f_0(t)). \tag{2}$$

Here $\mu_0(t)$ is the baseline hazard that represents the risk which would remain if the variables in $Y(t)$ followed the "optimal trajectory" represented by the vector function $f_0(t)$. The positive-definite symmetric matrix $Q(t)$ regulates the quadratic shape of the hazard (as a function of variables $Y(t)$). T denotes transposition.

All components in the model can include dependence on observed (Yashin et al., 2012) and partially observed (Arbeev et al., 2009) variables. The components of the model have interpretations relevant in research on aging as discussed in the literature (see, e.g., Arbeev et al., 2011; Yashin et al., 2007; Yashin et al., 2012).

The SPM presented in Arbeev et al. (2016a) implemented the measure of physiological dysregulation (D_M) by Cohen et al. (2013) which is based on the multivariate statistical (Mahalanobis) distance (De Maesschalck et al., 2000; Mahalanobis, 1936) constructed for the joint distribution of multiple biomarkers. Such implementation allows working with multiple variables in a one-dimensional setting and interpreting all components of this one-dimensional SPM similarly to the original model. D_M is defined for a given set of variables measured in an individual at age t, $X(t)$, as:

$$D_M(X(t)) = \sqrt{(X(t) - \overline{X})^T S^{-1}(X(t) - \overline{X})}, \tag{3}$$

where $\overline{X}$ is a vector of means and S is the variance-covariance matrix for respective variables calculated from some population representing the "normal" state (which could be defined from the same population or some other "reference" population) (see more details and discussion on reference populations in Arbeev et al., 2016a; Cohen et al., 2015; Cohen et al., 2013). Then $Y(t) = D_M(X(t))$ can be modeled as the one-dimensional process in (1). The one-dimensional version of (2) is:

$$\mu(t, Y(t)) = \mu_0(t) + Q(t)(Y(t) - f_0(t))^2 \tag{4}$$

where $f_0(t)$ and $Q(t)$ are scalars.

In this work, we performed simulation studies in this one-dimensional version (1), (4). The D_M variable was taken as a prototype for $Y(t)$ in the model. The specific parameters were selected to mimic the dynamics observed in the real data applications, see Arbeev et al. (2016a).

2.2 Description of simulation studies

We considered two simulation scenarios to study designs comparable to data with a long follow-up period and more frequent exams (simulation scenario 1, "sim1") and a short follow-up with longer periods between exams (simulation scenario 2, "sim2"). The first scenario is similar to the original cohort of the Framingham Heart Study (FHS) and the second resembles the Long Life Family Study (LLFS). In each case, we simulated 100 datasets for different sample sizes and numbers of exams (i.e., time periods when measurements of biomarkers are collected for participants of the study). Sample sizes were

selected to be comparable to specific subgroups of respective datasets: 1) the total sample in LLFS or FHS (5,000); 2) sex-specific subsample in LLFS or FHS (2,500) and 3) the probands generation in LLFS (1,500). In sim1, the number of observations equals 1, 2, 3, or 30 (this last number is taken for comparison with the real data where currently 30 examinations are available for the original Framingham cohort) with a two-year period between exams (similar to the design of the original Framingham cohort). The age at the baseline in this case was generated as a uniformly distributed random variable over the interval [30, 60]. In sim2, the number of observations equals 1, 2 or 3 with seven-year periods between exams (like in LLFS) and the age at the baseline was generated from a uniform distribution over the range 50 to 100. The interval between observations for a specific individual was simulated as a sum of the number of years between observations specified above and the uniformly distributed random variable over the interval [-0.1, 0.1].

We used two specifications of the one-dimensional continuous-time model (1), (4):

Model 1: Gompertz baseline hazard: $\mu_0(t) = a_{\mu_0} e^{b_{\mu_0} t}$; constant parameters $Q(t) = a_Q$, $a(t) = a_Y$, $f_1(t) = a_{f_1}$, $f_0(t) = a_{f_0}$, $b(t) = \sigma_1$.

Model 2: Gompertz baseline hazard: $\mu_0(t) = a_{\mu_0} e^{b_{\mu_0} t}$; linear functions for $Q(t) = a_Q + b_Q t$, $a(t) = a_Y + b_Y t$, $f_1(t) = a_{f_1} + b_{f_1} t$, $f_0(t) = a_{f_0} + b_{f_0} t$; and constant $b(t) = \sigma_1$.

The parameters used in simulations were selected to provide realistic patterns of mortality observed in modern human populations and dynamics of D_M similar to that observed in analyses of FHS data in Arbeev et al. (2016a):

Model 1: $a_{\mu_0} = 10^{-4}$, $b_{\mu_0} = 0.08$, $a_Q = 8 \cdot 10^{-3}$, $a_Y = -0.2$, $a_{f_1} = 1.0$, $a_{f_0} = 0.0$, $\sigma_1 = 0.5$.

Model 2: $a_{\mu_0} = 10^{-4}$, $b_{\mu_0} = 0.08$, $a_Q = 5 \cdot 10^{-4}$, $b_Q = 10^{-4}$, $a_Y = -0.2$, $b_Y = 10^{-3}$, $a_{f_1} = 0$, $b_{f_1} = 0.03$, $a_{f_0} = 0$, $b_{f_0} = 0$, $\sigma_1 = 0.5$.

We also simulated data for the scenario in which the assumption on the independence of individuals is violated. We assumed that the data consist of pairs of related individuals with hazards in the pair i given by

$$\mu_i(t, Y(t)) = Z_i(\mu_0(t) + Q(t)(Y(t) - f_0(t))^2), \tag{5}$$

where Z_i is a gamma-distributed random variable with mean 1 and variance s^2. We used different values of s^2 (0.1, 0.5, 1.0, 1.5) to test sensitivity of estimates in case of smaller and bigger variances of Z_i. For each value of s^2, we generated 100 datasets using the hazard rate (5) and dynamics of the longitudinal covariate given by (1) and estimated these data using the likelihood for the original model (1) and (4). Due to space limitation, we report only the results of Model 1 and sample size N=5000.

3. Results of simulation studies

Figure 1 illustrates components of the models (hazard rate and the quadratic term in the hazard) for Models 1 and 2. Fig. 1 (A) and 1 (C) show the hazard rate (4) in Models 1 and 2, respectively. Note the U-shape of the hazard as a function of $Y(t)$. This shape does not change with t in Model 1 but narrows with t in Model 2. The black lines denote function $f_0(t)$ corresponding to the minimal hazard rate given by $\mu_0(t)$. The blue line show function $f_1(t)$ to which the trajectories of $Y(t)$ tend to revert (see sample trajectories represented by red lines in Fig. 1 (B) and (D)). Note a constant $f_1(t)$ in Model 1 and its time-dependence in Model 2. Such dependence of model components on time t (e.g., age) can be relevant in different research areas. For example, it has biologically relevant interpretation in research on aging (see discussion in, e.g., Arbeev et al., 2016a) so it is important to have time-dependence represented and estimated in the models.

The results of simulations in scenarios sim1 and sim2 for models 1 and 2 are shown in Tables 1-4. The simulations indicate that the estimation procedure produces reasonably accurate results in cases with small number of longitudinal observations per individual in both scenarios sim1 and sim2 which differ in terms of the length of period between measurements and the age distribution at baseline (hence, the proportion of censored individuals). This observation is valid for both model 1 (with all constant parameters except the baseline hazard) as well as for model 2 (where some parameters are represented by linear functions).

The results for data generated assuming pairs of related individuals (i.e., the hazards given by (5)) and estimated using the procedure which ignores such dependence (i.e., using the equation for hazards (4)) in scenarios sim1 and sim2 for model 1 are given in Tables 5 and 6. The tables show that in such cases the estimates of parameters of the stochastic process $Y(t)$ remain largely unaffected even in case of big variances of the random variable Z_i (parameter s^2) and only the parameter of the baseline hazard (b_{μ_0}) shows substantial deviation from the true values starting with small s^2. We note here that these results illustrate only the situation when such dependence structure is introduced through the hazards. Additional studies are needed to investigate the sensitivity of the estimation procedure to violations of independence assumption induced also through specification of the process $Y(t)$.

3. Conclusions

The stochastic process model provides a general framework for modeling the dynamics of repeatedly measured variables (modeled by a stochastic process) in relation to time-to-event outcomes (modeled as the quadratic function of such stochastic covariates). Implementation of the measure of multivariate distance (D_M) in the SPM framework provides an opportunity to address relevant research questions avoiding potential computational difficulties associated with estimation of multidimensional models. We developed the R-package *stpm* which implements different specifications of SPM (both one-dimensional and multidimensional versions) and validated it in simulation studies. Simulations illustrated that the estimation algorithms produce reasonable estimates in case of small numbers of observations per individual. Simulations investigating the sensitivity of the estimation procedure to violations of independence assumption showed that only parameters of baseline hazard are affected in case of dependence in hazards induced by a

gamma-distributed random variable. Development of SPM modifications that take into account dependence between individuals (both in hazard rates as well as in the dynamics of longitudinal variables) is necessary to accommodate such dependencies in analyses.

Acknowledgements

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Figures:
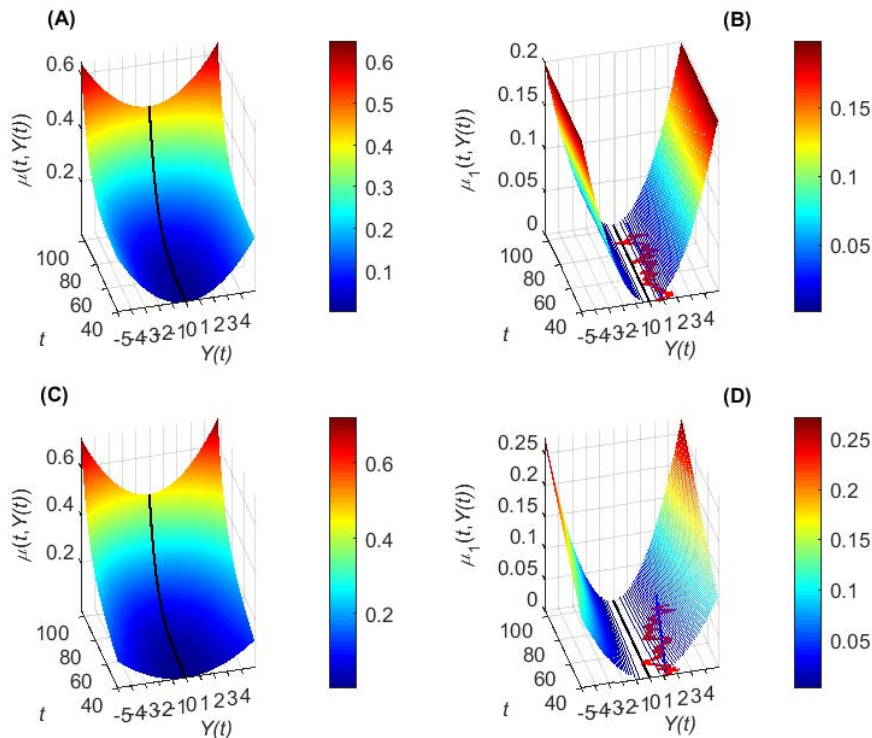
Figure 1: Illustration of stochastic process models (models 1 and 2): Hazard rate as a function of time (e.g., age) t and some variable $Y(t)$ (e.g., D_M, see the text), and other components of the model. (A) Hazard rate ($\mu(t,Y(t))$) in model 1. (B) The quadratic term in hazard ($\mu_1(t,Y(t)) = Q(t)(Y(t) - f_0(t))^2$) in model 1 (shown as contour lines for visibility). (C) Hazard rate ($\mu(t,Y(t))$) in model 2. (D) The quadratic term in hazard ($\mu_1(t,Y(t)) = Q(t)(Y(t) - f_0(t))^2$) in model 2. The blue

lines denote function $f_1(t)$. The black lines correspond to function $f_0(t)$. The red lines show a sample trajectory of $Y(t)$.

Tables:

Table 1: Results of simulation studies of model 1 in simulation scenario 1 (sim1). The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). $\mathbf{N_{ind}}$ denotes number of individuals in each dataset and $\mathbf{N_{obs}}$ is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

$\mathbf{N_{ind}}$	$\mathbf{N_{obs}}$	$a_{\mu_0} \cdot 10^3$	$b_{\mu_0} \cdot 10$	$a_Q \cdot 10^2$	$a_Y \cdot 10$	a_{f_1}	a_{f_0}	$\sigma_1 \cdot 10$
1500	1	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.60,0.95]	[0.60,1.00]	[-2.18,-1.77]	[0.87,1.13]	[-0.36,0.28]	[4.74,5.37]
	2	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.62,0.87]	[0.60,1.00]	[-2.14,-1.87]	[0.91,1.08]	[-0.25,0.20]	[4.76,5.18]
	3	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.69,0.87]	[0.64,1.00]	[-2.12,-1.89]	[0.94,1.07]	[-0.22,0.18]	[4.82,5.19]
	30	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.07,0.13]	[0.76,0.84]	[0.71,0.93]	[-2.05,-1.95]	[0.98,1.04]	[-0.09,0.12]	[4.91,5.08]
2500	1	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.60,0.88]	[0.60,1.00]	[-2.16,-1.83]	[0.92,1.08]	[-0.34,0.23]	[4.80,5.25]
	2	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.08,0.14]	[0.71,0.86]	[0.66,0.95]	[-2.09,-1.88]	[0.95,1.06]	[-0.19,0.16]	[4.84,5.16]
	3	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.08,0.14]	[0.71,0.86]	[0.64,0.94]	[-2.09,-1.91]	[0.95,1.05]	[-0.17,0.13]	[4.86,5.13]
	30	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.08,0.13]	[0.76,0.82]	[0.74,0.92]	[-2.04,-1.97]	[0.98,1.02]	[-0.06,0.12]	[4.95,5.07]
5000	1	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.09,0.14]	[0.66,0.85]	[0.62,0.98]	[-2.10,-1.88]	[0.94,1.06]	[-0.22,0.20]	[4.83,5.15]
	2	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.08,0.14]	[0.70,0.85]	[0.68,0.92]	[-2.08,-1.91]	[0.97,1.03]	[-0.14,0.12]	[4.89,5.11]
	3	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.08,0.14]	[0.72,0.83]	[0.70,0.92]	[-2.06,-1.95]	[0.96,1.03]	[-0.12,0.10]	[4.89,5.10]

N_{ind}	N_{obs}	$a_{\mu_0}\cdot10^3$	$b_{\mu_0}\cdot10$	$a_Q\cdot10^2$	$a_Y\cdot10$	a_{f_1}	a_{f_0}	$\sigma_1\cdot10$
30		0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.09,0.13]	[0.77,0.81]	[0.76,0.87]	[-2.03,-1.97]	[0.98,1.02]	[-0.04,0.08]	[4.95,5.04]
True		*0.1*	*0.8*	*0.8*	*-2.0*	*1.0*	*0.0*	*5.0*

Table 2: Results of simulation studies of model 1 in simulation scenario 2 (sim2). The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). N_{ind} denotes number of individuals in each dataset and N_{obs} is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

N_{ind}	N_{obs}	$a_{\mu_0}\cdot10^3$	$b_{\mu_0}\cdot10$	$a_Q\cdot10^2$	$a_Y\cdot10$	a_{f_1}	a_{f_0}	$\sigma_1\cdot10$
1500	1	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.76,0.86]	[0.60,1.00]	[-2.14,-1.85]	[0.93,1.07]	[-0.26,0.28]	[4.57,5.41]
	2	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.76,0.86]	[0.66,0.99]	[-2.10,-1.90]	[0.93,1.05]	[-0.25,0.21]	[4.70,5.31]
	3	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.06,0.14]	[0.76,0.85]	[0.68,0.98]	[-2.08,-1.93]	[0.95,1.03]	[-0.23,0.21]	[4.74,5.26]
2500	1	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.76,0.85]	[0.60,1.00]	[-2.10,-1.87]	[0.96,1.06]	[-0.21,0.26]	[4.74,5.26]
	2	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.07,0.14]	[0.76,0.84]	[0.66,0.97]	[-2.07,-1.91]	[0.96,1.04]	[-0.24,0.17]	[4.80,5.20]
	3	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.08,0.13]	[0.76,0.83]	[0.72,0.94]	[-2.06,-1.92]	[0.96,1.04]	[-0.16,0.17]	[4.76,5.19]
5000	1	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.07,0.14]	[0.77,0.85]	[0.66,0.98]	[-2.07,-1.92]	[0.96,1.04]	[-0.19,0.16]	[4.80,5.20]
	2	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.07,0.13]	[0.76,0.83]	[0.71,0.91]	[-2.04,-1.95]	[0.97,1.03]	[-0.13,0.12]	[4.83,5.17]
	3	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.07,0.12]	[0.78,0.83]	[0.73,0.89]	[-2.05,-1.95]	[0.97,1.03]	[-0.10,0.11]	[4.84,5.20]
True		*0.1*	*0.8*	*0.8*	*-2.0*	*1.0*	*0.0*	*5.0*

Table 3: Results of simulation studies of model 2 in simulation scenario 1 (sim1). The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). N_{ind} denotes number of individuals in each dataset and N_{obs} is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

N_{ind}	N_{obs}	$a_{\mu_0} \cdot 10^3$	$b_{\mu_0} \cdot 10$	$a_Q \cdot 10^3$	$b_Q \cdot 10^3$	$a_Y \cdot 10$	$b_Y \cdot 10^2$	a_{f_1}	$b_{f_1} \cdot 10$	a_{f_0}	$b_{f_0} \cdot 10$	$\sigma_1 \cdot 10$
1500	1	0.1	0.8	0.5	0.1	-1.9	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.06,0.14]	[0.64,0.89]	[0.42,0.60]	[0.05,0.15]	[-2.42,-1.21]	[-0.05,0.20]	[-0.37,0.41]	[0.20,0.38]	[-0.49,0.50]	[-0.13,0.11]	[4.67,5.31]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.1	-0.0	5.0
		[0.07,0.14]	[0.66,0.87]	[0.41,0.60]	[0.06,0.14]	[-2.29,-1.63]	[0.01,0.16]	[-0.43,0.40]	[0.21,0.40]	[-0.47,0.49]	[-0.13,0.10]	[4.76,5.18]
	3	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.06,0.14]	[0.68,0.89]	[0.43,0.59]	[0.07,0.13]	[-2.34,-1.69]	[0.03,0.17]	[-0.25,0.35]	[0.23,0.35]	[-0.49,0.49]	[-0.11,0.09]	[4.87,5.20]
	30	0.1	0.8	0.5	0.1	-2.0	0.1	0.1	0.3	-0.0	0.0	5.0
		[0.08,0.13]	[0.76,0.83]	[0.45,0.57]	[0.09,0.12]	[-2.17,-1.80]	[0.07,0.12]	[-0.13,0.25]	[0.26,0.32]	[-0.33,0.29]	[-0.06,0.05]	[4.93,5.09]
2500	1	0.1	0.8	0.5	0.1	-1.9	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.06,0.14]	[0.66,0.89]	[0.43,0.60]	[0.06,0.14]	[-2.34,-1.58]	[0.01,0.18]	[-0.36,0.39]	[0.21,0.39]	[-0.50,0.50]	[-0.12,0.13]	[4.71,5.26]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.07,0.14]	[0.71,0.86]	[0.44,0.60]	[0.07,0.13]	[-2.31,-1.67]	[0.04,0.17]	[-0.31,0.35]	[0.21,0.37]	[-0.47,0.47]	[-0.11,0.09]	[4.81,5.19]
	3	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.08,0.13]	[0.70,0.85]	[0.45,0.59]	[0.08,0.13]	[-2.32,-1.78]	[0.05,0.15]	[-0.23,0.31]	[0.23,0.36]	[-0.45,0.46]	[-0.09,0.08]	[4.87,5.14]
	30	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.09,0.12]	[0.77,0.82]	[0.47,0.58]	[0.09,0.11]	[-2.14,-1.81]	[0.07,0.12]	[-0.14,0.27]	[0.26,0.33]	[-0.19,0.28]	[-0.06,0.03]	[4.93,5.08]
5000	1	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.07,0.14]	[0.68,0.86]	[0.43,0.60]	[0.06,0.14]	[-2.25,-1.65]	[0.03,0.15]	[-0.33,0.32]	[0.22,0.37]	[-0.47,0.49]	[-0.10,0.09]	[4.84,5.17]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	-0.0	0.0	5.0
		[0.07,0.13]	[0.73,0.87]	[0.45,0.59]	[0.08,0.12]	[-2.17,-1.73]	[0.05,0.14]	[-0.17,0.27]	[0.24,0.34]	[-0.47,0.44]	[-0.08,0.08]	[4.87,5.09]
	3	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	-0.0	0.0	5.0
		[0.09,0.13]	[0.73,0.83]	[0.45,0.59]	[0.08,0.11]	[-2.21,-1.77]	[0.05,0.14]	[-0.14,0.31]	[0.24,0.34]	[-0.44,0.36]	[-0.07,0.09]	[4.89,5.08]
	30	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	-0.0	-0.0	5.0
		[0.09,0.12]	[0.77,0.82]	[0.47,0.57]	[0.09,0.11]	[-2.16,-1.83]	[0.07,0.13]	[-0.08,0.18]	[0.27,0.31]	[-0.31,0.25]	[-0.04,0.05]	[4.96,5.04]
True		*0.1*	*0.8*	*0.5*	*0.1*	*-2.0*	*0.1*	*0.0*	*0.3*	*0.0*	*0.0*	*5.0*

Table 4: Results of simulation studies of model 2 in simulation scenario 1 (sim2). The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). **N**$_{ind}$ denotes number of individuals in each dataset and **N**$_{obs}$ is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

N$_{ind}$	**N**$_{obs}$	$a_{\mu_0} \cdot 10^3$	$b_{\mu_0} \cdot 10$	$a_Q \cdot 10^3$	$b_Q \cdot 10^3$	$a_Y \cdot 10$	$b_Y \cdot 10^2$	a_{f_1}	$b_{f_1} \cdot 10$	a_{f_0}	$b_{f_0} \cdot 10$	$\sigma_1 \cdot 10$
1500	1	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	0.0	-0.0	5.0
		[0.06,0.13]	[0.77,0.85]	[0.42,0.60]	[0.06,0.14]	[-2.31,-1.67]	[0.05,0.14]	[-0.37,0.41]	[0.23,0.36]	[-0.39,0.48]	[-0.09,0.08]	[4.60,5.40]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.0	0.3	-0.0	0.0	5.0
		[0.08,0.13]	[0.77,0.83]	[0.43,0.59]	[0.08,0.13]	[-2.28,-1.66]	[0.06,0.13]	[-0.39,0.39]	[0.23,0.36]	[-0.39,0.49]	[-0.07,0.05]	[4.70,5.25]
	3	0.1	0.8	0.5	0.1	-2.0	0.1	0.1	0.3	-0.0	-0.0	5.0
		[0.07,0.12]	[0.77,0.84]	[0.45,0.57]	[0.08,0.12]	[-2.20,-1.74]	[0.06,0.13]	[-0.16,0.34]	[0.25,0.33]	[-0.38,0.40]	[-0.06,0.05]	[4.72,5.27]
2500	1	0.1	0.8	0.5	0.1	-2.0	0.1	0.1	0.3	0.0	-0.0	5.0
		[0.07,0.13]	[0.77,0.84]	[0.43,0.59]	[0.07,0.13]	[-2.24,-1.71]	[0.06,0.13]	[-0.33,0.39]	[0.24,0.35]	[-0.34,0.48]	[-0.07,0.05]	[4.74,5.29]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.1	0.3	0.0	-0.0	5.0
		[0.08,0.12]	[0.77,0.82]	[0.45,0.58]	[0.08,0.12]	[-2.21,-1.69]	[0.06,0.13]	[-0.29,0.35]	[0.24,0.34]	[-0.35,0.32]	[-0.05,0.05]	[4.77,5.24]
	3	0.1	0.8	0.5	0.1	-1.9	0.1	0.1	0.3	-0.0	0.0	5.0
		[0.08,0.12]	[0.77,0.82]	[0.44,0.59]	[0.08,0.11]	[-2.25,-1.65]	[0.05,0.13]	[-0.23,0.36]	[0.24,0.33]	[-0.40,0.25]	[-0.04,0.04]	[4.80,5.19]
5000	1	0.1	0.8	0.5	0.1	-1.9	0.1	0.1	0.3	-0.0	-0.0	5.0
		[0.09,0.13]	[0.77,0.82]	[0.44,0.59]	[0.07,0.13]	[-2.21,-1.67]	[0.06,0.12]	[-0.22,0.36]	[0.24,0.34]	[-0.34,0.24]	[-0.04,0.05]	[4.78,5.17]
	2	0.1	0.8	0.5	0.1	-2.0	0.1	0.1	0.3	-0.0	0.0	5.0
		[0.08,0.13]	[0.77,0.82]	[0.46,0.59]	[0.09,0.11]	[-2.21,-1.72]	[0.06,0.13]	[-0.28,0.33]	[0.25,0.34]	[-0.34,0.29]	[-0.04,0.05]	[4.84,5.14]
	3	0.1	0.8	0.5	0.1	-1.9	0.1	0.1	0.3	0.0	-0.0	5.0
		[0.08,0.12]	[0.78,0.82]	[0.47,0.57]	[0.09,0.11]	[-2.16,-1.74]	[0.06,0.12]	[-0.17,0.42]	[0.24,0.33]	[-0.31,0.31]	[-0.05,0.04]	[4.82,5.19]
True		*0.1*	*0.8*	*0.5*	*0.1*	*-2.0*	*0.1*	*0.0*	*0.3*	*0.0*	*0.0*	*5.0*

Table 5: Results of simulation studies of model 1 in simulation scenario 1 (sim1) in case of data with dependence in hazards induced by a gamma-distributed random variable with different variances s^2. The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). $\mathbf{N_{ind}}$ denotes number of individuals in each dataset and $\mathbf{N_{obs}}$ is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

$\mathbf{N_{obs}}$	s^2	$a_{\mu_0} \cdot 10^3$	$b_{\mu_0} \cdot 10$	$a_Q \cdot 10^2$	$a_Y \cdot 10$	a_{f_1}	a_{f_0}	$\sigma_1 \cdot 10$
1	0.1	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.09,0.14]	[0.74,0.87]	[0.68,0.98]	[-2.08,-1.90]	[0.97,1.04]	[-0.16,0.14]	[4.91,5.09]
1	0.5	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.08,0.14]	[0.60,0.76]	[0.68,0.93]	[-2.07,-1.94]	[0.96,1.04]	[-0.11,0.14]	[4.90,5.12]
1	1.0	0.1	0.6	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.60,0.72]	[0.68,0.90]	[-2.08,-1.90]	[0.96,1.04]	[-0.12,0.11]	[4.88,5.12]
1	1.5	0.1	0.6	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.60,0.68]	[0.67,0.93]	[-2.08,-1.92]	[0.96,1.04]	[-0.12,0.13]	[4.89,5.10]
2	0.1	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.10,0.14]	[0.77,0.85]	[0.70,0.91]	[-2.04,-1.94]	[0.97,1.02]	[-0.11,0.10]	[4.93,5.08]
2	0.5	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.08,0.14]	[0.60,0.74]	[0.70,0.89]	[-2.06,-1.95]	[0.97,1.04]	[-0.09,0.10]	[4.92,5.09]
2	1.0	0.1	0.6	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.60,0.71]	[0.72,0.87]	[-2.06,-1.95]	[0.96,1.03]	[-0.08,0.10]	[4.90,5.07]
2	1.5	0.1	0.6	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.60,0.67]	[0.70,0.88]	[-2.04,-1.95]	[0.97,1.03]	[-0.07,0.12]	[4.91,5.08]
3	0.1	0.1	0.8	0.8	-2.0	1.0	-0.0	5.0
		[0.10,0.14]	[0.77,0.85]	[0.73,0.88]	[-2.05,-1.95]	[0.98,1.03]	[-0.09,0.09]	[4.92,5.06]
3	0.5	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.14]	[0.61,0.78]	[0.74,0.87]	[-2.04,-1.96]	[0.98,1.02]	[-0.07,0.07]	[4.93,5.06]
3	1.0	0.1	0.6	0.8	-2.0	1.0	0.0	5.0
		[0.07,0.14]	[0.60,0.69]	[0.73,0.86]	[-2.04,-1.95]	[0.98,1.03]	[-0.06,0.07]	[4.93,5.05]

N_obs	s^2	$a_{\mu_0}\cdot 10^3$	$b_{\mu_0}\cdot 10$	$a_Q\cdot 10^2$	$a_Y\cdot 10$	a_{f_1}	a_{f_0}	$\sigma_1\cdot 10$
3	1.5	0.1 [0.06,0.14]	0.6 [0.60,0.66]	0.8 [0.74,0.88]	-2.0 [-2.05,-1.96]	1.0 [0.98,1.02]	0.0 [-0.05,0.08]	5.0 [4.92,5.08]
30	0.1	0.1 [0.10,0.13]	0.8 [0.80,0.83]	0.8 [0.76,0.92]	-2.0 [-2.02,-1.98]	1.0 [0.99,1.01]	0.0 [-0.06,0.07]	5.0 [4.97,5.03]
30	0.5	0.1 [0.06,0.12]	0.7 [0.71,0.79]	0.8 [0.75,0.85]	-2.0 [-2.02,-1.98]	1.0 [0.99,1.01]	0.0 [-0.04,0.07]	5.0 [4.97,5.03]
30	1.0	0.1 [0.06,0.11]	0.7 [0.67,0.75]	0.8 [0.73,0.83]	-2.0 [-2.02,-1.98]	1.0 [0.99,1.01]	0.0 [-0.05,0.06]	5.0 [4.97,5.03]
30	1.5	0.1 [0.06,0.12]	0.7 [0.64,0.72]	0.8 [0.73,0.84]	-2.0 [-2.02,-1.98]	1.0 [0.99,1.01]	0.0 [-0.05,0.07]	5.0 [4.96,5.03]
True		*0.1*	*0.8*	*0.8*	*-2.0*	*1.0*	*0.0*	*5.0*

Table 6: Results of simulation studies of model 1 in simulation scenario 2 (sim2) in case of data with dependence in hazards induced by a gamma-distributed random variable with different variances s^2. The numbers show mean values of parameter estimates in 100 simulated datasets (lower 2.5% and upper 97.5% values are in brackets). **N_ind** denotes number of individuals in each dataset and **N_obs** is maximal number of longitudinal observations (exams) per individual. Some parameters are scaled for better visibility. True values used in simulations are shown in the last row.

N_obs	s^2	$a_{\mu_0}\cdot 10^3$	$b_{\mu_0}\cdot 10$	$a_Q\cdot 10^2$	$a_Y\cdot 10$	a_{f_1}	a_{f_0}	$\sigma_1\cdot 10$
1	0.1	0.1 [0.10,0.14]	0.8 [0.79,0.83]	0.8 [0.68,0.98]	-2.0 [-2.06,-1.94]	1.0 [0.97,1.03]	0.0 [-0.14,0.16]	5.0 [4.85,5.14]
1	0.5	0.1 [0.06,0.11]	0.8 [0.72,0.79]	0.8 [0.64,0.93]	-2.0 [-2.06,-1.95]	1.0 [0.98,1.03]	0.0 [-0.13,0.13]	5.0 [4.87,5.13]
1	1.0	0.1 [0.06,0.11]	0.7 [0.68,0.75]	0.8 [0.66,0.90]	-2.0 [-2.06,-1.95]	1.0 [0.97,1.03]	0.0 [-0.11,0.12]	5.0 [4.86,5.14]
1	1.5	0.1 [0.06,0.14]	0.7 [0.63,0.72]	0.8 [0.67,0.96]	-2.0 [-2.05,-1.93]	1.0 [0.97,1.03]	0.0 [-0.10,0.19]	5.0 [4.84,5.14]
2	0.1	0.1 [0.09,0.14]	0.8 [0.79,0.84]	0.8 [0.74,0.91]	-2.0 [-2.03,-1.96]	1.0 [0.98,1.02]	0.0 [-0.10,0.10]	5.0 [4.84,5.11]

2	0.5	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.11]	[0.72,0.79]	[0.73,0.87]	[-2.04,-1.97]	[0.98,1.02]	[-0.08,0.09]	[4.91,5.11]
2	1.0	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.10]	[0.69,0.75]	[0.69,0.89]	[-2.04,-1.97]	[0.98,1.02]	[-0.10,0.10]	[4.90,5.12]
2	1.5	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.12]	[0.65,0.72]	[0.70,0.87]	[-2.03,-1.97]	[0.97,1.02]	[-0.10,0.11]	[4.89,5.12]
3	0.1	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.09,0.14]	[0.79,0.84]	[0.74,0.95]	[-2.03,-1.97]	[0.98,1.03]	[-0.10,0.10]	[4.86,5.13]
3	0.5	0.1	0.8	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.11]	[0.73,0.79]	[0.73,0.87]	[-2.03,-1.98]	[0.97,1.02]	[-0.06,0.09]	[4.91,5.11]
3	1.0	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.12]	[0.68,0.75]	[0.72,0.85]	[-2.03,-1.98]	[0.98,1.02]	[-0.04,0.09]	[4.89,5.09]
3	1.5	0.1	0.7	0.8	-2.0	1.0	0.0	5.0
		[0.06,0.11]	[0.65,0.73]	[0.72,0.85]	[-2.03,-1.97]	[0.98,1.02]	[-0.07,0.10]	[4.89,5.10]
True		*0.1*	*0.8*	*0.8*	*-2.0*	*1.0*	*0.0*	*5.0*