Multistate joint frailty models for interval censored data

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Abstract

Multistate survival models (MSMs) capture transitions through multiple health states over time or age. These models typically rely on the Markov assumption, which implies that transition intensities depend only on the current state and observed covariates. In practice, this assumption is frequently violated because transition hazards depends on unobserved heterogeneity, sojourn time, or unobserved transitions in the intervals between interviews or observations, i.e. interval censoring. This paper extends MSMs for interval-censored data by introducing a joint frailty model that captures unobserved heterogeneity across several transitions simultaneously. Whereas existing joint frailty models have primarily been used to link dependence between two transitions to a health event and death, the proposed joint frailty models generalize this concept to multiple transitions within a unified and computationally efficient structure. The model accommodates different baseline hazard specifications (e.g., Gompertz or Weibull) and alternative frailty distributions (commonly Gamma or Normal). By allowing transition-specific loadings of the same frailty term, the joint frailty model provides a flexible solution to represent the effect of latent characteristics on multiple health transitions. A preliminary empirical application using data on German women from SHARE illustrates the feasibility and empirical relevance of the approach. The results confirm that including a frailty term improves model fit and mitigates bias caused by violations of the Markov assumption. The proposed models offer a theoretically coherent and computationally tractable extension of multistate models for interval-censored data.

1 Topic

Multistate survival models (MSM) capture transitions through multiple health states over time (age). MSM are based on the Markov assumptions, which means that an individual's probability of transitioning between health states is a function of their current health status and selected individual characteristics. For the current health status and given characteristics, the Markov assumption implies homogeneity in transition hazards (Commenges, 1999). Nonetheless, it is widely recognized that these hazard values reflect not only the inherent risk of death within homogeneous subgroups but also the overall composition of the population. The composition of the population does not remain constant but changes with time (or age) and hence needs to be accounted for in the models. As all sources of heterogeneity are not and cannot be captured by observed covariates, frailty terms are introduced to represent the unobserved differences between individuals (Van Den Hout, 2016). Adding frailty parameters to multistate survival models improves the fit of the model. First,

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frailty terms capture unobserved susceptibility and distinguish between individuals who progress rapidly through states and those who transition more slowly (Van Den Hout, 2016). The fact that individual-level differences in the propensity for ill health contribute significantly to the variation in the length of life was demonstrated as early as the 1980s by Vaupel et al. (1979) and Manton et al. (1981, 1986). Frailty has also been shown to be a crucial determinant of observed health status (Contoyannis et al., 2004; Halliday, 2008; Heiss et al., 2009; Hernandez-Quevedo et al., 2008). Taking the classical mover-stayer model as an example, where stayers only leave the healthy state through death (e.g., (Singer and Spilerman, 1976)). The episodes of decreased health occupancy for movers cannot be accurately derived from average transition rates, as they represent an average between rates for stayers and movers. Consequently, the duration of these episodes is incorrect.

The second violation of Markov assumption of MSM is related to the fact that, in epidemiological, demographic, but also clinical studies, the exact time of transition is not observed because individuals are only assessed at discrete follow-up times, i.e. the data is *interval censored*. In such cases, especially in the case of long intervals between observations as in panel data from surveys, transitions may occur between observation times but remain unobserved, and for the observed transitions the time of the transition remain unknown. This characteristic of the data violates the Markov assumption of the MSM, as transition probabilities depend on the current health state but the relevant state information is partially missing. Multistate models for interval-censored data address this challenge by integrating the likelihood over the unobserved transition intervals, calculating the probability of all possible transition paths that could have occurred between two observation times (Lievre et al., 2003; Van Den Hout, 2016).

This study extends multistate survival models for interval-censored data by introducing a joint frailty framework that links unobserved heterogeneity across multiple health transitions. While joint frailty models have previously been applied mainly to capture dependence between two transitions to a health event and death in progressive or recurring health events, they have not been generalized to modeling in parallel several transitions. We test several combinations of specification of hazard functions and frailty distributions. We show that incorporating frailty in this way substantially improves model fit relative to interval-censored models without frailty and corrects bias arising from violations of the Markov assumption.

2 Theoretical focus

In a pure Markov specification of MSM, the hazard of leaving a state depends only on the current state and observed covariates, not on how long an individual has been in that state or on the path taken to reach it. In practice, however, transition hazards often depend on sojourn time or previous events—for example, the risk of death increases with the duration of illness, or the probability of leaving unemployment depends on prior unemployment spells. Frailty terms absorb part of this dependence by capturing unobserved susceptibility that jointly influences both the time spent in a state and the likelihood of transition. Therefore, when the strict Markov assumption is violated, frailty models provide a practical alternative to semi-Markov specifications, which are typically more computationally demanding (Bijwaard, 2014; Van Den Hout, 2016; Wang, 2022). Frailty terms can compensate for violations of the conditional Markov property by representing dependencies between duration of stay and transition hazards within the model. As shown by Van Den Hout (2016), including a frailty term improves model fit, yielding lower deviance and more favorable information criteria compared to fixed-effects specifications. As a result, these models provide a more robust basis for inference and prediction of individual life-course trajectories than standard multistate models (Balan and Putter, 2020). Moreover, Bijwaard (2014) demonstrated that ignoring heterogeneity in frailty not only biases duration dependence toward a more rapidly declining shape but can also distort covariate effects, sometimes even reversing their sign.

Multistate survival models for interval-censored data with frailty depend on specific assumptions about the hazard functions and the functional form of the frailty parameter. Because each individual can experience multiple transitions between health states, we treat individuals as clusters, with transitions nested within them. The frailty parameter can be introduced in several ways: one shared frailty per individual across all transitions (shared frailty models); separate frailty terms for each transition but with a correlated distribution between them (correlated frailty models); or a single frailty with transition-specific coefficients (joint frailty models). Shared frailty models impose the same multiplicative frailty effect on selected transitions, offering a parsimonious but restrictive formulation when different transitions respond differently to the same latent susceptibility. Correlated frailty models allow multiple frailty terms with a parameterized covariance structure across transitions. While flexible, such models are often difficult to identify in multistate settings with limited recurrent events, and they may suffer from numerical instability and wide uncertainty in covariance estimates.

joint frailty preserves parsimony of the shared frailty models (one frailty variable) but adds transition-specific loadings, allowing for different effect of the frailty parameter on different types of transitions for an individual. Similar to correlated frailty models, joint frailty models provide information on interdependence between the effect of frailty between different transitions, but with fewer parameters. This fact improves the differentiability, computation, and substantive interpretability of the models. Moreover, when we interpret the frailty parameter as susceptibility to poor health, or robustness, joint frailty is often the most defensible specification (Hens et al., 2009; Martins et al., 2019; Wienke et al., 2005). In joint frailty models, transition from $r \to s$ is specified as $\lambda_{rs,i}(t \mid Z_i) = \lambda_{rs,0}(t)\exp\{x_i^\top \beta_{rs}\}\, g(Z_i; \alpha_{rs})$, where $g(\cdot)$ multiplicatively modulates risk and α_{rs} scales how strongly the same latent propensity Z_i expresses itself on each transition. Choices include $g(Z;\alpha) = Z^\alpha$ for Gamma/PVF frailty on the multiplicative scale or $g(Z;\alpha) = \exp(\alpha Z)$ for log-normal frailty.

3 Methods

We set up our model defining the likelihood contribution for a single individual i with observation times $t_1, ..., t_J$. Let $\boldsymbol{y}_i$ be the trajectory of the observed states of the subject i, $\boldsymbol{y}_i = (y_{i1}, ..., y_{iJ_i})$ at times $t_1, ..., t_{J_i}$. We collect in the vector $\boldsymbol{\theta} = \{\lambda_{11}, \ldots, \lambda_{rs}, \xi_{11}, \ldots, \xi_{rs}\}$ the parameters of Gompertz distributions for all transitions.

Then, using the Markov assumption, the likelihood contribution of individual i is given as

$$L_i(\boldsymbol{\theta},\mathbf{b}_i|\boldsymbol{y}_i) = P(Y_{iJ_i} = y_{iJ_i},...,Y_{i2} = y_{i2}|Y_{i1} = y_{i1},\boldsymbol{\theta},\mathbf{b}_i).$$

Integrating out the frailty $\mathbf{b}_i$ yields the marginal likelihood

$$L_i(\boldsymbol{\theta}|\boldsymbol{y}_i) = \int_{\Theta_{\mathbf{b}_i}} P(Y_{iJ_i} = y_{ij_i},...,Y_{i2} = y_{i2}|Y_{i1} = y_{i1},\boldsymbol{\theta},\mathbf{b}_i) f(\mathbf{b}_i) d\mathbf{b}_i.$$

For N subjects $i = 1,\ldots,n$, the overall likelihood is the product of all the individual likelihood contributions $L(\boldsymbol{\theta}) = \prod_{i=1}^{n} L_i(\boldsymbol{\theta}|\boldsymbol{y_i})$. This model accounts for left-truncation in the data as the likelihood function is defined conditional on the first observed state. We further adopt methodology proposed by Van Den Hout (2016). As is common in multistate survival modeling, we specify the baseline hazard using either a Gompertz or Weibull distribution, and the frailty term using either a Gamma or Normal distribution.. We fit the frailty model by maximizing the marginal log-likelihood function, integrating out the frailty.

4 Data

Data comes from the Survey of Health and Ageing in Europe (SHARE) (Börsch-Supan, 2020) waves 1-3 and 5-7. We will focus on four widely used self-assessed health measures: (i) presence of chronic diseases, (ii) functional limitations (GALI), (iii) poor self-rated health (SRH), and (iv) limitations in activities of daily living (ADL), and clinical measure of gerontological frailty. Gerontological frailty is a state of increased physiological vulnerability, and it will be measured according to the definition of *frailty phenotype* by Fried et al. (2001), which is based on the following five dimensions of frailty: weakness (grip strength), slow walking speed, low level of physical activity, low energy or self-reported exhaustion and unintentional weight loss. We will follow the adaptation of the gerontological frailty index of Fried et al. (2001) to the SHARE data as proposed by Santos-Eggimann et al. (2009).

4.1 Preliminary results

Log-likelihood values at the maximum for the multistate models for health states across ADL and GALI for German women are presented in Table 1. As it takes longer for the models to converge, we have not managed to estimate all the possible models yet. For ADL, the best fitting model is the model with frailty parameter in transitions from healthy to unhealthy, and from unhealthy to healthy. For this model frailty term for transition $1 \to 2$ at age 50 is Gamma distributed with the mean=1 and variance=0.84, for the recovery the effect of individual frailty on transition are about twice as strong as for the reference transition. For GALI, the best fitting model is the model with frailty parameter in transitions from healthy to unhealthy, and from

Table 1: Log-likelihood values at the maximum for the multistate models for health states across ADL and GALI for German women

	$-2\log(L_{\max})$	
Model	ADL	GALI
Fixed effects only	8183.0	11616.1
With frailty for transitions		
$1 \rightarrow 2$	8189.5	11636.5
$1 \rightarrow 2$ and $1 \rightarrow 3$	8170.8	11636.3
$1 \rightarrow 2$ and $2 \rightarrow 1$	8146.6	11507.3
$1 \rightarrow 2$ and $2 \rightarrow 3$		11635.2
$1 \rightarrow 2$, $1 \rightarrow 3$, $2 \rightarrow 1$	8165.6	
$1 \rightarrow 2$, $1 \rightarrow 3$, $2 \rightarrow 1$	8150.9	
$1 \rightarrow 2$, $2 \rightarrow 1$, $2 \rightarrow 3$,		11505.9
$1 \rightarrow 2$, $1 \rightarrow 3$, $2 \rightarrow 1$, $2 \rightarrow 3$	8147.6	

States: 1=healthy, 2=unhealthy, 3=dead;
Data source: SHARE waves 1-2, 4-7

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