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Mixed effect Poisson log-linear models for clinical and epidemiological sleep hypnogram data

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Bayesian Poisson log-linear multilevel models scalable to epidemiological studies are proposed to investigate population variability in sleep state transition rates. Hierarchical random effects are used to account for pairings of individuals and repeated measures within those individuals, as comparing diseased to non-diseased subjects while minimizing bias is of importance. Essentially, non-parametric piecewise constant hazards are estimated and smoothed, allowing for time-varying covariates and segment of the night comparisons. The Bayesian Poisson regression is justified through a re-derivation of a classical algebraic likelihood equivalence of Poisson regression with a log(time) offset and survival regression assuming exponentially distributed survival times. Such re-derivation allows synthesis of two methods currently used to analyze sleep transition phenomena: stratified multi-state proportional hazards models and log-linear models with GEE for transition counts. An example data set from the Sleep Heart Health Study is analyzed. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: multi-state models; recurrent event; competing risks; survival analysis; frailties; sleep; hypnogram

1. Introduction

Hypnograms are time series of an individual's sleep states from a single night's sleep. The primary focus of this manuscript is to describe methods for the analysis of hypnogram data, focusing on methods that scale to large cohort studies and complex covariance structures. Log-linear random effect models can be derived and used to synthesize existing methods for analyzing hypnogram transition data from large cohort studies and extended to multilevel settings, unearthing data features classical measures bury. In the following section, a motivating discussion of two subjects from a community based cohort study highlights how classical sleep measures may not capture transition and duration in state characteristics of the hypnogram, prompting this work to better describe and model the sleep hypnogram.

1.1. Motivating example

Summaries of the measurement of sleep for two subjects with intrinsically different sleep behavior can highlight or mask these differences. To illustrate, Subject A of Figure 1 has severe sleep-disordered breathing (SDB, discussed further

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below), as indicated by a respiratory disturbance index (RDI) of 52.28 events per hour, while Subject B does not (RDI 0.57 events/hour). Each subject was monitored overnight during sleep via a polysomnogram for eight hours. The classical summary of their sleep stages is similar across the two subjects: Subject A spent 69%, 16%, and 15% and Subject B spent 70%, 16%, and 14% of total sleep time in the Non-Rapid Eye Movement (NREM), Rapid Eye Movement (REM) and Wake states, respectively (Table 1). While overall sleep stage percentages are similar between these two subjects, the temporal evolution of their sleep may not be. Sleep for an individual is often visualized with hypnograms depicting states of sleep on the vertical axis and time from sleep onset on the horizontal axis. Subjects A and B have similar sleep stage amounts yet dissimilar hypnograms (see Figure 1). For example, in the zoomed-in portion around hour 7, we see a critical difference in the duration of REM sleep for each subject. Subject A's duration in REM sleep is fragmented, whereas Subject B's is non-fragmented. Degree of fragmentation is a feature that overall sleep stage percentages cannot capture.

Population variations of this phenomenon have been described more fully elsewhere [1, 2]. Despite severe sleep-related disease, sleep stage percentages remain consistent at the population level. Thus any statistical analysis of sleep stage percentages as a measure of sleep quality may not account for sleep fragmentation, even in extreme comparisons of severely diseased subjects to healthy ones.

Both scientific and methodological contributions are made in this paper. From a scientific perspective, 1) transition rates are developed and substantiated as an informative population measure for sleep comparisons, 2) population variations in transition rates for different segments of the night are reported, 3) a very large dataset of sleep hypnograms from $\sim$5600 subjects is utilized, and 4) bias in our results is reduced via matching. From a methods standpoint, 1) a framework is set forth to view the sleep of a population of individuals as a multi-state survival analysis problem with random effects, 2) a classical algebraic equivalence between survival analysis and Poisson regression is re-derived and employed within the framework, 3) piecewise constant hazards are smoothed, and 4) all of the aforementioned contributions are accomplished with relative computational ease for scalability to epidemiological studies.

1.2. Set up and challenges

The sleep transition rate data to be modeled is complex. Our proposed solution is a multi-state, recurrent event, competing risk, hierarchical, stratified survival model fit using Poisson hierarchical models. To elaborate, the model is *multi-state* because there are more than the traditional 2-states (i.e., alive/dead, wake/sleep, etc.) found in typical survival models. *Recurrent event* because no state is absorbing and all can recur. *Competing risk* because options exist for the state to which one will transition (from Non-REM to either Wake or REM). *Hierarchical* because of nesting of times-to-event within individuals and individuals nested within matched pairs. *Stratified* in such a way to render transition-type-specific fixed effects in different segments of the night. Our models are necessarily complex to capture the fine structure of the transition processes that are of interest. Oversimplification of data, as shown in our first example, may be misleading in many applications.

In cohort studies of sleep transitional phenomena, "time" has several meanings which can lead to considerable confusion. Three important distinctions aid in the discussion of time: duration in state (DIS) time, stopwatch accruing cumulative (SAC) time, and local wall clock (LWC) time. To elucidate, consider an example: a subject falls asleep when the alarm clock on her night stand displays 10:00PM. She goes through various states of sleep, and at 11:23pm enters REM sleep. At 11:30pm she exits REM sleep and enters NREM. Consequently, her DIS-time is 7 minutes, which simultaneously serves as the time-at-risk for both `REM` $\rightarrow$ `NREM` and `REM` $\rightarrow$ `Wake` transition-types. Her SAC-time was 83 minutes when she entered REM, 90 minutes upon exiting. The LWC-time of her entering into REM was 11:23PM; of her egress, 11:30PM. The distinction of each of these measurements of time is important, as DIS-times are the times-to-event and SAC-times help in the segmentation of the night which allows for inference for time-varying transition effects. LWC-time is useful to characterize diurnal effects as they are being increasingly recognized to have significance in defining the temporal variability in specific outcomes such as sudden cardiac death in people with SDB. [3].

2. Model and Implementation

An observation model is developed in the most general form for the Poisson representation of the hypnogram and implemented with priors via MCMC in `WinBUGS` to render a posterior likelihood [4, 5]. The representation of a classical survival likelihood with a piecewise constant hazard by a Poisson likelihood is well known in a setting without competing risks and recurrent events [6, 7, 8]. The pieces of the hazard are the result of applying a binning scheme on the true underlying hazard, as in an equally spaced grid or quantiles of survival times, and modeling the hazard as constant over each bin. With the binning in place, time at risk for a transition as well as whether a transition occurred within each bin is tallied. Thus, intuitively, the time-to-event data becomes a counting process of 0 events or 1 event occurring with an offset of the time experienced at risk for the event, within each bin. With multi-state models, there is more than one hazard because there is more than one type of transition, and thus each hazard is transition-type specific and can have distinct binning schemes applied. Competing risks and recurrent events introduce considerations on how to tally the number of transitions and calculate time at risk for those transitions within the bins of the transition-type specific scheme. Competing risks will have each observed transition tallied in one bin of one hazard yet the time at risk for the transition will be attributed to each possible transition, binned according to each transition-type's binning scheme. Recurrent events imply that multiple transitions of the same type contribute transition tallies and time at risk as per binning scheme in an additive fashion across the recurrent transition times. Therefore, a multi-state model of sleep with competing risks and recurrent events can be represented as a Poisson model relating the number of observed transitions during total time at risk spent in each bin.

A detailed derivation of the likelihood equivalence is in the appendix. We establish minimal notation to set up an intuitive derivation based on the classic survival-Poisson likelihood equivalence. For each transition-type h allow binning scheme $\{q_{hb}\}$ such that $0 < q_{h1} < \cdots < q_{hB_h}$ to represent the time grid over which B_h constant pieces α_{hb} will model the underlying log-baseline hazard. The time to transition for transition j of individual i is t_{ij}. Applying the transition-type-specific binning scheme to t_{ij} requires parsing the time among the bins:

$$d_{ijhb} = \begin{cases} q_{hb} - q_{h(b-1)} & \text{if } q_{hb} < t_{ij} \\ t_{ij} - q_{h(b-1)} & \text{if } q_{h(b-1)} < t_{ij} < q_{hb} \\ 0 & \text{if } q_{h(b-1)} > t_{ij} \end{cases}$$

where $\Sigma_b d_{ijhb} = t_{ij}$ for each h. Risk indicator $r_{ijhb} = 1$ denotes if t_{ij} is pertinent as time at risk of a transition-type h for transition j, and $r_{ijhb} = 0$ if transition-type h is not possible as transition j. With $r_{ijhb} = 1$, a transition is observed if $y_{ijhb} = 1$ and censored if $y_{ijhb} = 0$. Suppressing subscripts, the contribution to a survival log-likelihood for individual i with fixed and random effects in linear predictor η at transition j of type h in time bin b of B_h is

$$ry(\alpha + \eta) + \exp\{\alpha + \eta + \log(rd)\}$$

which is equivalent to a log-likelihood for a $y \sim$ Poisson(ϕ) log-linear model with $\phi = \exp\{\alpha + \eta + \log(d)\}$ and is the classic survival-Poisson likelihood equivalence where $y \in \{0, 1\}$. In our setting of competing risks and recurrent events, assuming the linear predictor η is not dependent on j, we can restate the log-likelihood by summing over the index j, yielding the contribution for an individual i, transition-type h, bin b of B_h:

$$n(\alpha + \eta) + \exp\{\alpha + \eta + \log(D)\}$$

where $n \in \{0, 1, \ldots, J_i\}$ is the total number of individual i's observed transitions of transition-type h in bin b of B_h as a result of being at risk for that transition in that bin for total duration D. Of course, the above likelihood is equivalent to a $n \sim$ Poisson(ϕ) log-linear model log-likelihood with $\phi = \exp\{\alpha + \eta + \log(D)\}$.

The linear predictor $\eta = \mathbf{X}_i\beta_{\mathbf{hk}} + \mathbf{Z}_i\mathbf{u}_i$ contains fixed effects $\beta_{\mathbf{hk}}$ of covariates $\mathbf{X}_i$ as well as cluster-specific effects

to account for hierarchical clustering. The vector $\mathbf{u}_i = (s_i, p_i)$, where s_i is a subject-specific random effect (individual-level log-frailty) and p_i is a pair-specific random effect (pair-level log-frailty). Design matrix $\mathbf{Z}_i$ is two columns wide and has the same number of rows as $\mathbf{X}_i$, one row if all covariates are constant through the night, or m rows for m total measurements of a time-varying covariate for the particular bin of the likelihood contribution. The time-varying case involves data augmentation of other parameters and is covered in the appendix. A segmented SAC-time analysis amounts to completing aforementioned aggregation of transition events and time at risk within segments of the night (1st and 2nd half, for example) defined as per individual and modeling fixed effects for each segment. Such segmented SAC-time analysis is a vast improvement over the past raw stratification approach of fitting separate models in different portions of the night [9, 1].

For a Bayesian analysis of the model, priors for β_{hk}, $\mathbf{u_i}$, and α_{hkb} of the observation model are selected as iid Gaussian distributions, with inverse Gamma hyperpriors for the variance components. Inference was attained via component-wise (as opposed to block-wise) Markov Chain Monte Carlo sampling in `WinBUGS` [4, 5].

3. Application and Results

The application makes use of hypnogram data from the Sleep Heart Health Study (SHHS), a multicenter study on SDB and cardiac outcomes [10]. Subjects for the SHHS were recruited from ongoing cohort studies on respiratory and cardiovascular disease. From the first SHHS cohort of over 6300 subjects, 5614 were identified as having reliable and high quality in-home polysomnograms. To assess the independent effects of SDB on sleep structure, a matched subset of the 5614 with and without SDB was selected for the current study. Subjects with severe SDB were identified as those with a RDI > 30 events/hour. Subjects without SDB were identified as those with an RDI < 5 events/hour. Other exclusion criteria included prevalent cardiovascular disease, hypertension, chronic obstructive pulmonary disease, asthma, coronary heart disease, history of stroke, and current smoking.

Matching is necessary as the data are observational and epidemologic confounding of the disease effect is of concern. The number of subjects in the SHHS dataset motivating this manuscript allow for well populated, well selected sub-groups for the desired comparisons. Propensity score matching was utilized to balance the groups on demographic factors and to minimize confounding [11]. SDB subjects were matched with no-SDB subjects on the factors of age, BMI, race, and sex. Race and sex were exactly matched, while age and BMI were matched using the nearest neighbor Mahalanobis technique so that matches had to be within a Mahalanobis distance (caliper) of 0.10, with multiple matches within the caliper being settled by random selection [12]. The resultant match was 51 pairs that met the strict inclusion criteria outlined above and exhibiting very low standardized biases, a vast improvement on the imbalance of BMI between diseased and non-diseased groups of past studies [1]. Polar opposites of SDB severity, isolated from comorbities, were used to increase the likelihood of finding 1) differences in sleep stage percentages (see Table 3) and 2) independent effects of SDB on sleep continuity.

Conceptualizing sleep as a multi-state competing risks process, we focused only on three states of sleep, collapsing the four stages of non-REM into one state, “NREM”, leaving the traditional “Wake” and rapid eye movement “REM” states. From any of the three states one may transition into the others producing six possible transition types: Wake to NREM (WN), NREM to Wake (NW), NREM to REM (NR), REM to Wake (RW), REM to NREM (RN), and Wake to REM (WR).

In the context of the application, $i = 1, ..., 102$ indexes individual, $h = 1, ..., 6$ denotes the transition-type, $k = 1, 2$ segments the night, $(B_1, B_2, B_3, B_4, B_5, B_6) = (2, 6, 12, 12, 12, 1)$ are the number of bins for each transition-type specific hazard. The B_h were determined by the distinct quantiles of the duration in state times per transition-type h. Finding B_h was done iteratively, first attempting to have 12 bins with approximately the same number of transitions of type h in them for model stability. The number 12 was selected for its versatility: one pass through the data binning hazards into 12ths and one could easily construct 12, 6, 4, 3, 2, or 1 piece models by summing number of transtions and total duration in state

time, collapsing 1/12 bins into larger fraction binning. If the transition-type h did not yield distinct quanitles for 12 bins, then bin sizes of 6, 4, 3, 2, and 1 were sequentially tried. The quantiles are of times to transition but will be used to bin time at risk, which implies the final grid point for binning schemes of a competing risk set will need to be the maximum of the maximum times to transition for each transition-type of the competing risk set (Table 4).

The vector $\mathbf{u_i} = (s_i, p_i)$, is a vector of additive random effects for subject and pair, respectively. The vector $\mathbf{Z}_i = (1, 1)$ in models with individuals nested within matched pair, $(1, 0)$ for models not accounting for pairs. The vector $\mathbf{X}_i$ is composed of the design variables and (potentially) the demographic covariates. The design variables are the 3-way interaction of disease status, the k^{th} segment of the total SAC-time, and transition-type h. These design interaction variables require the data to be at the "cross-binned" $i - h - k - b$ level and enables the corresponding $\beta_{\mathbf{hk}}$ vector to have elements β_{hk} which quantify the average transition frequency of type h in the k^{th} segment of the total SAC-time for diseased versus non-diseased. In the case of $K = 2$, this allows sampling from the posterior distribution of the composite quanitity of the rate ratio between the two segments of night ($\frac{\exp(\beta_{h2})}{\exp(\beta_{h1})}$), enabling inference as to whether transition intensities change over the course of sleep. The multiple stratifications on transition-type, DIS and SAC-time interacted with disease status can easily make for high dimension parameterizations as well as binning combinations. Following recent research in smoothing [13, 14], we propose a fine level of binning and allow a smoothing/penalty to prevent over-parameterization via transition-type specific 1st order random walk priors, a strategy similar to the correlated pieces approach [15, 16, 17]. In the smoothing of the piecewise constant hazard across bins, the prior $\alpha_{hkb} \sim N(\mu_{hkb}, \sigma^2)$ is assigned for each α_{hkb}, where $\mu_{hkb} = 0$ if $b = 1$, $\mu_{hkb} = \alpha_{hk(b-1)}$ if $b > 1$. Thus, constant pieces from adjacent bins are "similar" to each other. The 1st order random walk prior just described is referenced hence forth as the "smoothed" model. Models with various combinations of bin smoothing, accounting for pair frailty, and number of included demographic covariates were fitted. All models were fitted with two segments of total SAC-time ($K = 2$) and the aforementioned number of bins B_h. For each model, we ran five chains for 1200 iterations and used the last 200 of each chain, yielding 1000 samples from each relevant full conditional of β_{hk}, $\mathbf{u}_i$ and α_{hkb}. Our hyper-parameter values were selected to favor small values but allow larger values of variances components, with $1/\sigma^2 \sim Gamma(1, .1)$ having a mean and standard deviation of 10 [17].

Upon visual inspection of trace plots, the chains were well mixed and the lag auto-correlation was acceptable (see Appendix). Convergence monitoring was conducted using the Brooks and Gelman diagnostic [18, 19] (acknowledging the limitations of such convergence diagnostic measures). A vast majority of these univariate diagnostics are greater than but close to 1, suggesting convergence and appropriately overdispersed starting values. From graphical inspection of the diagnostic over iterations, a vast majority not only narrow to 1, but also show the stabilization of the pooled and within interval widths.

All models exhibit SDB subjects transitioning significantly more of type `NREM` → `Wake` in both halves of the night, `Wake` → `REM` in the first half of the night, and significantly less of type `NREM` → `REM` for both segments of the night (Table 5). In other words, given a SDB subject is in NREM, he is more likely than a no-SDB subject to transition to Wake and less likely to transition to REM regardless of how long he has been asleep. These results elucidate findings of SDB subjects having higher all cause mortality [20] and increases in `NREM` → `Wake` and decreases in `NREM` → `REM` leading to higher all cause mortality [21].

Given a SDB subject is in Wake he is on average ~ 2.6 times as likely as his no-SDB counterpart to transition to REM in the 1st half of the night. However, there is no significant difference between the SDB groups for the WR transition in the second half of the night. The segmented SAC-time analysis of the 2nd half of the night to the 1st shows a reduction of 60% of the disparity between average transition frequencies of diseased and non-diseased for type WR (Table 6). This suggests the second half of the night has both groups getting to REM from Wake at more simliar rates than the first half.

Table 5 shows very little difference between models differing only by the accounting of pairs. In those comparisons, the magnitudes and directions mirror well, and the only difference in significant results are due to 95% credible intervals containing 1.00. It appears that in this analysis, the gain in parsimony would favor the omission of pairing information, echoing sentiments of not needing to account explicitly for pairing in models that utilized propensity score matching [22].

4. Discussion and Conclusion

The transition information of a sleep hypnogram is accounted for by the Poisson model and is eschewed by traditional sleep percentages, where only percent time in REM differed: SDB 17%, no-SDB 21% (Table 3). Showing the derivation of the Poisson representation provides motivation for a shift in the conceptualization of modeling sleep. The problem can be thought of as a multi-state, recurrent event, competing risk, hierarchical, stratified survival model or a Poisson process with the sufficent statistics of number of transitions arising from time at risk for those transitions. This shift makes concerns about tie handling of DIS-times inconsequential. The ability to piecewise model the hazard, segment the night, and account for transition-type allow for a very flexible model that can easily incorporate time-varying covariates. The Poisson model in `WinBUGS` is scalable, with an analysis of 5,614 unpaired individuals (6% SDB) taking five hours. A comparable multistate survival analysis in `bayesX` of 3,000 unpaired individuals (11% SDB) produced a conservative prediction of 14 hours to run [23, 24]. All analyses were conducted with the Windows operating system GUIs on a laptop with a 1.83 GHz processor.

Sleep hypnogram data ultimately comprise of six states and 30 transition-types. Although three states and six transition-types is a simplification, it is a closer repesentation of the competing risks structure of the data generating process than a hierarchy of transitions-types [25, 26, 27, 15]. The software `bayesX` and the work on structured additive regression (STAR) models that has fueled its development accommodates sample sizes typically generated by a clinical study and has the capability to fit the Poisson representation of the classical piecewise exponential survival model or a multistate survival model (with time-varying covariates and effects) [28, 29, 30, 15]. We acknowledge that our formulation of the Poisson model is a specific instance of a STAR model with zero-degree penalized splines modeling the baseline hazard. The proposed Poisson implementation of a multistate model of this specific instance may be beneficial in analyzing epidemiological studies because they typically are of a larger sample size and have constant subject-level covariates. Clinical studies up to moderate sample sizes with time-varying covariates are well-suited for STAR models in `bayesX`.

MCMC allowed us to account for the correlation induced by repeated measurements on the same individual nested within matched pairs and would facilitate the examination of the heterogeneity in our population through random intercepts. Heterogeneity of populations is a very crucial topic in epidemiological studies. Through the assumption of exponential survival times we gain a framework that potentially allows us to eschew/relax parametric assumptions about the hazard. These reasons plus the eloquence of jointly modeling the frequency of transitions and times to transition make the Bayesian Poisson regression framework a powerful and flexible tool in modeling sleep as represented by hypnograms.

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	Current state					
	Subject A			Subject B		
Previous state	N	R	W	N	R	W
Non-REM (N)	625	19	21	652	3	18
REM (R)	15	138	4	1	155	4
Wake (W)	24	0	119	19	2	111
Total epochs	664	157	144	672	160	133
Total in hours	5.54	1.31	1.91	5.61	1.33	1.10
Sleep Architecture (%)	69	16	15	70	16	14

Table 1. Cross Tabulation of Pairwise Contiguous Epochs for Subjects A and B.

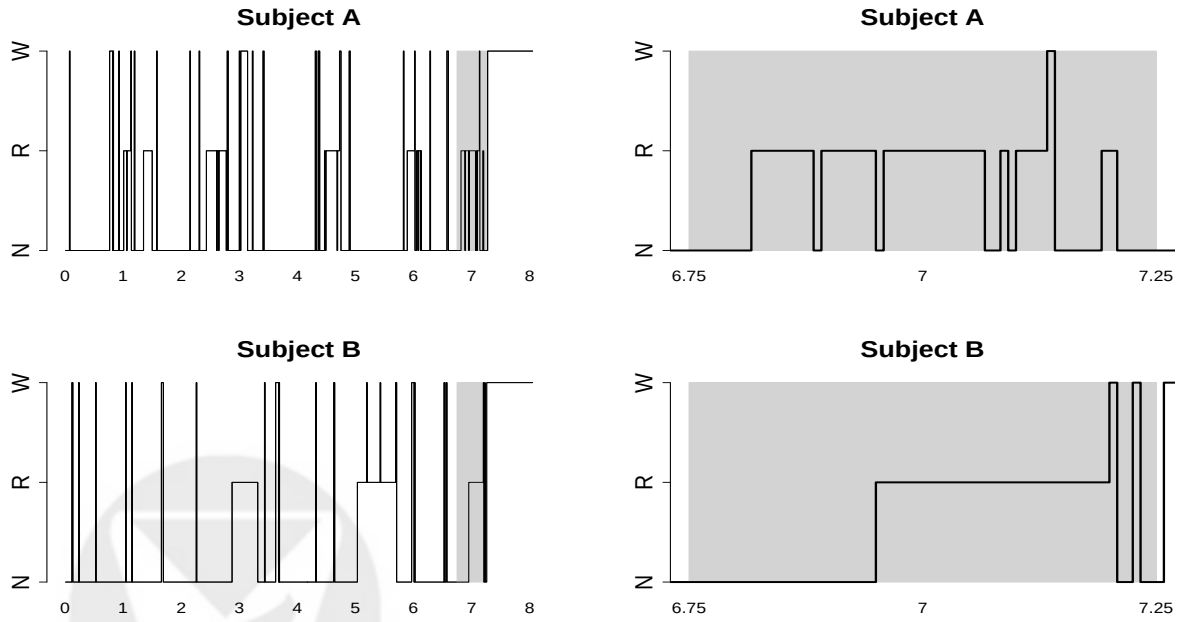

Figure 1. Left panels, 8 hour sleep hypnograms of Subjects A and B; Right panels, zoomed half-hour portions of the corresponding left panel. On all hypnograms, the vertical axis represents the states of sleep (N: Non-REM, R: REM, and W: Wake) a subject can occupy. The horizontal axis is time of night, with 0 being sleep onset, thus a hypnogram is a state-time graph, showing the trajectory of sleep for an individual.

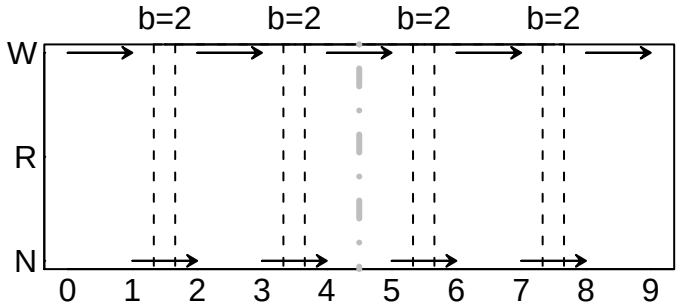

Figure 2. A sample hypnogram of three state sleep over 9 hours from sleep onset, illustrating binning for the 2nd bin of of the hazard of transition-type NR, as well as (potentially) a $K = 2$ analysis where SAC-time less than 4.5 hours is segment $k = 1$ and greater than 4.5 hours is segment $k = 2$. No time is spent in REM and each DIS-time is 60 minutes long. The different data formats of this graphic are in Table 2

Survival format						Poisson format (K=1)						Poisson format (K=2)					
j	type	h	t	r	y	type	h	k	b	n	D	type	h	k	b	n	D
1	WN	1	60	1	1	WN	1	1	1	0	75	WN	1	1	1	0	30
1	WR	6	60	1	0	WN	1	1	2	4	225	WN	1	1	2	2	90
2	NW	2	60	1	1	WR	6	1	1	0	300	WR	6	1	1	0	120
2	NR	3	60	1	0	NW	2	1	1	0	20	NW	2	1	1	0	10
3	WN	1	60	1	1	NW	2	1	2	0	200	NW	2	1	2	0	100
3	WR	6	60	1	0	NW	2	1	3	4	20	NW	2	1	3	2	10
4	NW	2	60	1	1	NR	3	1	1	0	80	NR	3	1	1	0	40
4	NR	3	60	1	0	NR	3	1	2	0	80	NR	3	1	2	0	40
5	WN	1	60	1	1	NR	3	1	3	0	80	NR	3	1	3	0	40
5	WR	6	60	1	0							WN	1	2	1	0	45
6	NW	2	60	1	1							WN	1	2	2	2	135
6	NR	3	60	1	0							WR	6	2	1	0	180
7	WN	1	60	1	1							NW	2	2	1	0	10
7	WR	6	60	1	0							NW	2	2	2	0	100
8	NW	2	60	1	1							NW	2	2	3	2	10
8	NR	3	60	1	0							NR	3	2	1	0	40
9	WN	1	60	1	0							NR	3	2	2	0	40
9	WR	6	60	1	0							NR	3	2	3	0	40

Table 2. (Accompanies Figure 2): Multistate survival data of times-to-transition t in minutes represented as a Poisson process without $(K = 1)$ and with $(K = 2)$ SAC-time segmenting. The Poisson formats assume binning schemes $\{q_{hb}\}$: for WN $\{q_{1b}\} = (0, 15, 60)$, for WR $\{q_{6b}\} = (0, 60)$, for NW $\{q_{2b}\} = (0, 5, 55, 60)$, for NR $\{q_{3b}\} = (0, 20, 40, 60)$. All duration in state times are 60 minutes and no time is spent in REM, therefore transition-types RW and RN are not possible (Figure 2). The total time spent in NREM is 240 minutes, which implies that 240 minutes were simultaneously the total time at risk for NW and NR transitions. Each transition-type has a different binning scheme, thus when survival data is converted to unsegmented $(K = 1)$ Poisson data, the 240 minutes are parsed differently: for NW, three bins of dissimilar sizes, and for NR three bins of equal sizes. For the $(K = 2)$ Poisson data, the times and transitions are aggregated within each segment, thus the 240 minutes in NREM gets split into 120 minutes in $k = 1$ and 120 minutes spent in $k = 2$. Once appropriated to the correct segment, the binning scheme is applied. For bin $b = 2$ of the NR binning scheme, transition tallies and time at risk between 20 and 40 minutes are summed over the duration in state times. No transitions happen in the four durations, so 0 tallies are recorded and 80 minutes total time at risk are attributed to bin $b = 2$ of the hazard of NR of the unsegmented Poisson model. Note the last transition $(j = 9)$ is censored, so there is no transition tally contributed, but time at risk is. Also note that the transition from Wake to NREM that crosses the segmenting line at SAC-time 4.5 hours is attributed in total to segment $(k = 2)$ because the transition took place in segment $k = 2$.

Variable	SDB	no-SDB	p-value
RDI ($events/hour$)	40.532	2.114	0.000
BMI (kg/m^2)	30.275	30.247	0.972
Age ($years$)	61.804	61.804	1.000
Race ($\%\ white$)	92.160	92.160	1.000
Sex ($\%\ male$)	66.667	66.667	1.000
Total Sleep Time ($min.$)	351.397	357.466	0.593
% Total Sleep Time asleep	81.941	83.364	0.743
% Night in Stage 1	5.750	5.577	0.815
% Night in Stage 2	62.693	59.109	0.121
% Night in Stage 3 or 4	13.647	13.908	0.904
% Night in REM	17.909	21.406	0.002

Table 3. Demographic Covariates and Sleep Variables, means of the two groups. All measures are not significantly different except for % Night in REM (RDI is different by design).

Type	B_h	Scheme	Binning Grid											
			q_{h0}	q_{h1}	q_{h2}	q_{h3}	q_{h4}	q_{h5}	q_{h6}	q_{h7}	q_{h8}	q_{h9}	q_{h10}	q_{h11}	q_{h12}
WR	1	$\{q_{6b}\}$	0.0	*317.0											
WN	2	$\{q_{1b}\}$	0.0	0.5	317.0										
NW	6	$\{q_{2b}\}$	0.0	0.5	1.5	3.5	7.5	18.5	*163.5						
NR	12	$\{q_{3b}\}$	0.0	0.5	1.0	1.5	2.0	3.0	4.5	6.0	8.5	14.0	25.5	41.5	163.5
RN	12	$\{q_{4b}\}$	0.0	1.0	1.5	2.5	3.0	4.5	5.5	7.0	8.5	11.0	14.0	19.5	*77.5
RW	12	$\{q_{5b}\}$	0.0	0.5	1.0	1.5	2.5	3.5	5.0	7.0	10.0	13.5	18.0	25.0	77.5

Table 4. Transition-type specific binning schemes, (in minutes): The distinct quantiles are calculated on the times to transition, not the time at risk. This nuance has implications for the final grid point, where the maximum grid point for transition-type specific binning schemes of the same competing risk set will be the maximum time to transition of the competing risk set, not necessarily the maximum time to transition for the transition-type. Therefore, the asterisk denotes where this substitution is made; the actual maximum time to transition follows accordingly:
*317.0=166.0, *163.5=140, *77.5=62.5

Model				Rate Ratios by Transition Type h					
	Pair	No.	Night						
Smoothed	Frailty	Covariates	Segment	WN	NW	NR	RW	RN	WR
Yes	Yes	4	1	$_{0.99}1.12_{1.28}$	$_{1.10}1.25_{1.42}$	$_{0.56}0.72_{0.92}$	$_{1.02}1.32_{1.73}$	$_{0.67}0.93_{1.24}$	$_{1.57}2.66_{4.95}$
			2	$_{0.87}0.98_{1.11}$	$_{1.11}1.26_{1.42}$	$_{0.54}0.66_{0.81}$	$_{0.87}1.07_{1.31}$	$_{0.74}0.98_{1.3}$	$_{0.78}1.01_{1.32}$
Yes	Yes	2	1	$_{0.99}1.12_{1.29}$	$_{1.10}1.26_{1.43}$	$_{0.55}0.71_{0.92}$	$_{1.01}1.31_{1.72}$	$_{0.67}0.90_{1.23}$	$_{1.59}2.69_{4.55}$
			2	$_{0.87}0.98_{1.10}$	$_{1.11}1.27_{1.43}$	$_{0.53}0.66_{0.81}$	$_{0.87}1.08_{1.33}$	$_{0.76}1.00_{1.31}$	$_{0.78}1.03_{1.38}$
Yes	Yes	0	1	$_{1.00}1.13_{1.27}$	$_{1.11}1.27_{1.43}$	$_{0.56}0.73_{0.93}$	$_{0.98}1.30_{1.70}$	$_{0.70}0.93_{1.29}$	$_{1.57}2.65_{4.36}$
			2	$_{0.88}0.98_{1.11}$	$_{1.12}1.27_{1.43}$	$_{0.53}0.66_{0.81}$	$_{0.89}1.08_{1.31}$	$_{0.75}0.99_{1.32}$	$_{0.77}1.03_{1.36}$
Yes	No	0	1	$_{0.97}1.12_{1.29}$	$_{1.10}1.24_{1.39}$	$_{0.55}0.71_{0.91}$	$_{1.00}1.31_{1.69}$	$_{0.67}0.91_{1.26}$	$_{1.62}2.71_{4.43}$
			2	$_{0.86}0.97_{1.09}$	$_{1.10}1.25_{1.41}$	$_{0.53}0.66_{0.82}$	$_{0.88}1.07_{1.28}$	$_{0.75}0.98_{1.28}$	$_{0.78}1.02_{1.35}$
No	No	0	1	$_{0.98}1.12_{1.26}$	$_{1.07}1.22_{1.39}$	$_{0.53}0.68_{0.86}$	$_{0.96}1.25_{1.61}$	$_{0.64}0.87_{1.14}$	$_{1.57}2.56_{4.42}$
			2	$_{0.85}0.96_{1.09}$	$_{1.10}1.24_{1.42}$	$_{0.50}0.63_{0.78}$	$_{0.87}1.05_{1.29}$	$_{0.72}0.95_{1.25}$	$_{0.77}1.01_{1.33}$
No	Yes	0	1	$_{0.98}1.11_{1.26}$	$_{1.09}1.24_{1.40}$	$_{0.53}0.68_{0.87}$	$_{0.98}1.25_{1.66}$	$_{0.65}0.87_{1.18}$	$_{1.51}2.48_{4.24}$
			2	$_{0.86}0.97_{1.10}$	$_{1.10}1.26_{1.41}$	$_{0.51}0.64_{0.81}$	$_{0.86}1.05_{1.29}$	$_{0.72}0.95_{1.24}$	$_{0.76}1.01_{1.32}$

Table 5. Rate Ratios for SDB vs. no-SDB by Transition Type. Blue indicates diseased transition significantly more than non-diseased. Red indicates diseased transition significantly less than non-diseased. The tables are in a format where the elements are the triplet with credible intervals as the left and right subscripts and the center number as the rate ratio estimate [31].

Model			Relative Rate Ratios of segment 2 vs segment 1 by Transition Type h					
	Pair	No.						
Smoothed	Frailty	Covariates	WN	NW	NR	RW	RN	WR
Yes	Yes	4	$_{0.75}0.87_{1.01}$	$_{0.57}0.82_{1.15}$	$_{0.87}1.01_{1.18}$	$_{0.72}1.08_{1.64}$	$_{0.66}0.92_{1.24}$	$_{0.20}0.40_{0.71}$
Yes	Yes	2	$_{0.75}0.87_{1.02}$	$_{0.59}0.84_{1.14}$	$_{0.86}1.01_{1.18}$	$_{0.74}1.14_{1.72}$	$_{0.69}0.94_{1.27}$	$_{0.21}0.40_{0.72}$
Yes	Yes	0	$_{0.75}0.87_{1.01}$	$_{0.62}0.84_{1.14}$	$_{0.86}1.01_{1.18}$	$_{0.70}1.08_{1.59}$	$_{0.67}0.92_{1.24}$	$_{0.22}0.41_{0.70}$
Yes	No	0	$_{0.75}0.87_{1.02}$	$_{0.60}0.82_{1.11}$	$_{0.86}1.01_{1.18}$	$_{0.71}1.10_{1.62}$	$_{0.68}0.94_{1.28}$	$_{0.21}0.39_{0.64}$
No	No	0	$_{0.74}0.86_{1.00}$	$_{0.61}0.85_{1.12}$	$_{0.86}1.02_{1.19}$	$_{0.73}1.11_{1.64}$	$_{0.67}0.94_{1.29}$	$_{0.22}0.41_{0.67}$
No	Yes	0	$_{0.75}0.88_{1.02}$	$_{0.61}0.85_{1.15}$	$_{0.87}1.02_{1.19}$	$_{0.74}1.11_{1.66}$	$_{0.67}0.96_{1.33}$	$_{0.23}0.43_{0.69}$

Table 6. Comparisons of beta coefficients, 2nd segment of night to 1st segment. Blue indicates the relative rate of 2nd segment of night for diseased transitioning compared to the non-diseased is significantly more than that of the 1st segment. Red indicates the relative rate of 2nd segment of night for diseased transitioning compared to the non-diseased is significantly less than that of the 1st segment. The tables are in a format where the elements are the triplet with credible intervals as the left and right subscripts and the center number as the relative rate ratio estimate [31].

Appendix: Likelihood equivalence with SAC-time constant covariates

For each transition-type $h = 1, \ldots, H$ allow binning scheme $\{q_{hb}\}$ such that $0 < q_{h1} < \cdots < q_{hB_{(h)}}$ to represent the time grid over which B_h constant pieces α_{khb} will model the underlying log baseline hazard within the segment $k = 1, \ldots, K$ of SAC-time. For transition $j = 1, \ldots, J_i$ of individual $i = 1, \ldots, I$ the time to transition is t_{ij}. Applying the transition-type-specific binning scheme to t_{ij} requires parsing the DIS-time among the bins on the hazard within the segment k of SAC-time:

$$d_{ijhkb} = \begin{cases} q_{hb} - q_{h(b-1)} & \text{if } q_{hb} < t_{ij} \\ t_{ij} - q_{h(b-1)} & \text{if } q_{h(b-1)} < t_{ij} < q_{hb} \\ 0 & \text{if } q_{h(b-1)} > t_{ij} \end{cases}$$

where $\Sigma_b d_{ijhkb} = t_{ij}$ for each h for the transition j that takes place in segment k. Risk indicator $r_{ijhkb} = 1$ denotes if d_{ijhkb} is pertinent as time at risk of a transition-type h for transition j in segment k, and $r_{ijhkb} = 0$ if transition-type h is not possible as transition j. With $r_{ijhkb} = 1$, a transition is observed if $y_{ijhkb} = 1$ and censored if $y_{ijhkb} = 0$. In the case of SAC-time constant covariates, row vector $\mathbf{X}_i$ contains the values of the covariates and column vector $\beta_{\mathbf{hk}}$ are the fixed effects of those covariates. The column vector $\mathbf{u}_i = (s_i, p_i)$ accounts for within-subject and within-pair correlation, respectively. Design row vector $\mathbf{Z}_i = (1, 1)$ for models accounting for pairing, $\mathbf{Z}_i = (1, 0)$ for ignoring pairing. Note that the definition of "segment" of total SAC-time is subject-specific and "ragged" in a sense. If a t_{ij} started in segment $k-1$ and ends in segment k, it is assigned in its entirety to segment k. With that stated, the segmenting of SAC-time supersedes binning the DIS-time: total SAC-time is divided into K segments (i.e. K=2 implies 1st half and 2nd half of night) on an individual basis. Then the DIS-times are assigned in their entirety to one of the segments. Then the DIS-times are partitioned among the $b = 1, ..., B_h$ bins within the segment of SAC-time.

Now, the established relation between survival data and the Poisson likelihood will be reanimated in the outlined framework [6, 7, 8]. Let the hazard for transition-type h, segment k and bin b be $\lambda_{hkb}(d_{ijhkb} \mid \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i) = \lambda_{0hkb}(d_{ijhkb}) e^{\mathbf{x}_i \beta_{hk} + \mathbf{z}_i \mathbf{u}_i}$.

The hazard is defined as

$$\lambda_{hkb}(d_{ijhkb} \mid \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i) = \frac{f_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)}{S_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)} = \frac{f_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)}{1 - F_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)},$$

where $f_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)$, $S_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)$, and $F_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)$ are the density, survivor, and distribution functions associated with the survival (DIS) times. Suppressing subscripts for the three most recently mentioned entities, the conditional likelihood is:

$$\begin{aligned} & \prod_{i=1}^{I} \prod_{j=1}^{J} \prod_{h=1}^{H} \prod_{k=1}^{K} \prod_{b=1}^{B_h} \left[f(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)^{y_{ijhkb}} \{1 - F(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)\}^{1 - y_{ijhkb}} \right]^{r_{ijhkb}} \\ = & \prod_{i=1}^{I} \prod_{j=1}^{J} \prod_{h=1}^{H} \prod_{k=1}^{K} \prod_{b=1}^{B_h} \left[\lambda_{hkb}(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)^{y_{ijhkb}} \{S(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i)\} \right]^{r_{ijhkb}} \end{aligned} \quad (1)$$

Consider the instance where $\log \lambda_{0hkb}(d_{ijhkb}) = \alpha_{hkb}$; hence the strata-specific hazard does not depend on time (d_{ijhkb}) and thus f is the exponential density. Utilizing $S(d_{ijhkb}; \mathbf{x}_i, \mathbf{z}_i, \mathbf{u}_i) = \exp\{\int_0^{\mathrm{d_{ijhkb}}} \lambda_{\mathrm{hkb}}(\mathrm{t}; \mathbf{x}_\mathrm{i}, \mathbf{z}_\mathrm{i}, \mathbf{u}_\mathrm{i}) \mathrm{dt}\}$, the conditional likelihood simplifies to

$$\prod_{i=1}^{I} \prod_{j=1}^{J} \prod_{h=1}^{H} \prod_{k=1}^{K} \prod_{b=1}^{B_h} \{\exp(\alpha_{hkb} + \mathbf{x}_i \beta_{hk} + \mathbf{z}_i \mathbf{u}_i)\}^{y_{ijhkb} r_{ijhkb}} \exp\{-r_{ijhkb} d_{ijhkb} e^{\alpha_{hkb} + x_{ijhkb} \beta_{hk} + z_{ijhkb} \mathbf{u}_i}\}$$

Taking the log and summing over j,

$$= \sum_{i=1}^{I}\sum_{h=1}^{H}\sum_{k=1}^{K}\sum_{b=1}^{B_h} n_{ihkb}(\alpha_{hkb} + \mathbf{x}_i\beta_{hk} + \mathbf{z}_i\mathbf{u}_i) - e^{\alpha_{hkb}+\mathbf{x}_i\beta_{hk}+\mathbf{z}_i\mathbf{u}_i+\log(D_{ihkb})} \quad (2)$$

Noting the general form of the log likelihood for $n \sim$ Poisson(ϕ) is proportional to $nlog(\phi) - \phi$, (2) could arise from a Poisson log-linear model with $\phi = \exp\{\alpha_{hkb} + \mathbf{x}_i\beta_{hk} + \mathbf{z}_i\mathbf{u}_i + \log(D_{ihkb})\}$. Formally written, the conditional model is:

$$n_{ihkb} \mid \alpha_{hkb}, \mathbf{x}_i, \beta_{hk}, \mathbf{z}_i, \mathbf{u}_i, D_{ihkb} \sim \text{Poisson}[e^{\alpha_{hkb}+\mathbf{x}_i\beta_{hk}+\mathbf{z}_i\mathbf{u}_i+\log(D_{ihkb})}]$$

Above, n_{ihkb} is the count of the number of observed transitions committed during D_{ihkb}, the total time at risk for person i committing a transition of type h, occuring in segment k and bin b. Accounting for D_{ihkb} is crucial when modeling relative counts, for if a subject makes twice as many transitions as another but had twice as long to do so the rate of transitioning is not truly elevated. If $B_h = 1, \forall h$ and $K = 1$ then (2) is equivalent to an exponential survival model. As $B_h \to \infty$, the model approaches having a completely non-parametric piecewise constant hazard for transition-type h.

Appendix: Likelihood equivalence with SAC-time-varying covariates

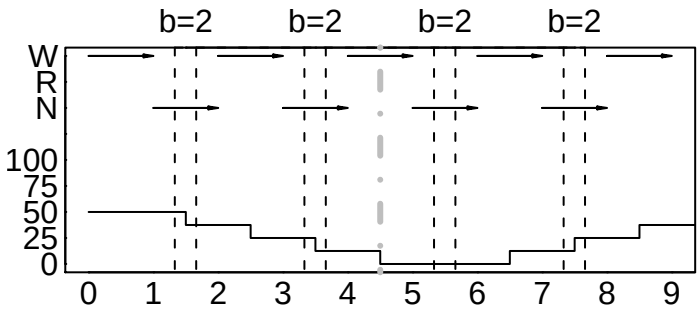

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Figure 3. The sample hypnogram of three state sleep (as in Figure 2 and Table 2) over hours from sleep onset, superimposed on a SAC-time-varying covariate. Binning for the 2nd bin of the hazard of transition-type NR is illustrated, as well as (potentially) a $K = 2$ analysis where SAC-time less than 4.5 hours is segment $k = 1$ and greater than 4.5 hours is segment $k = 2$. With SAC-time-varying covariates, X_i in the likelihood becomes a matrix comprised of stacked row vectors of values occurring in a particular bin b and segment k.

As Figure 3 implies, SAC-time-varying covariates will necessitate data augmentation for the M measurements taking place in bin b and segment k, where M is the total number of epochs (the finest and uniform time grid for all subjects) taking place in bin b and segment k of the SAC-time. Then X_i of the previous section is a matrix of rows X_{im} and the likelihood is:

$$= \sum_{i=1}^{I}\sum_{h=1}^{H}\sum_{k=1}^{K}\sum_{b=1}^{B_h}\sum_{m=1}^{M_{kb}} n_{ihkb}(\alpha_{hkb} + \mathbf{x}_{im}\beta_{hk} + \mathbf{z}_i\mathbf{u}_i) - e^{\alpha_{hkb}+\mathbf{x}_{im}\beta_{hk}+\mathbf{z}_i\mathbf{u}_i+\log(D_{ihkb})} \quad (3)$$

Appendix: Subset of Chains from MCMC Sampling

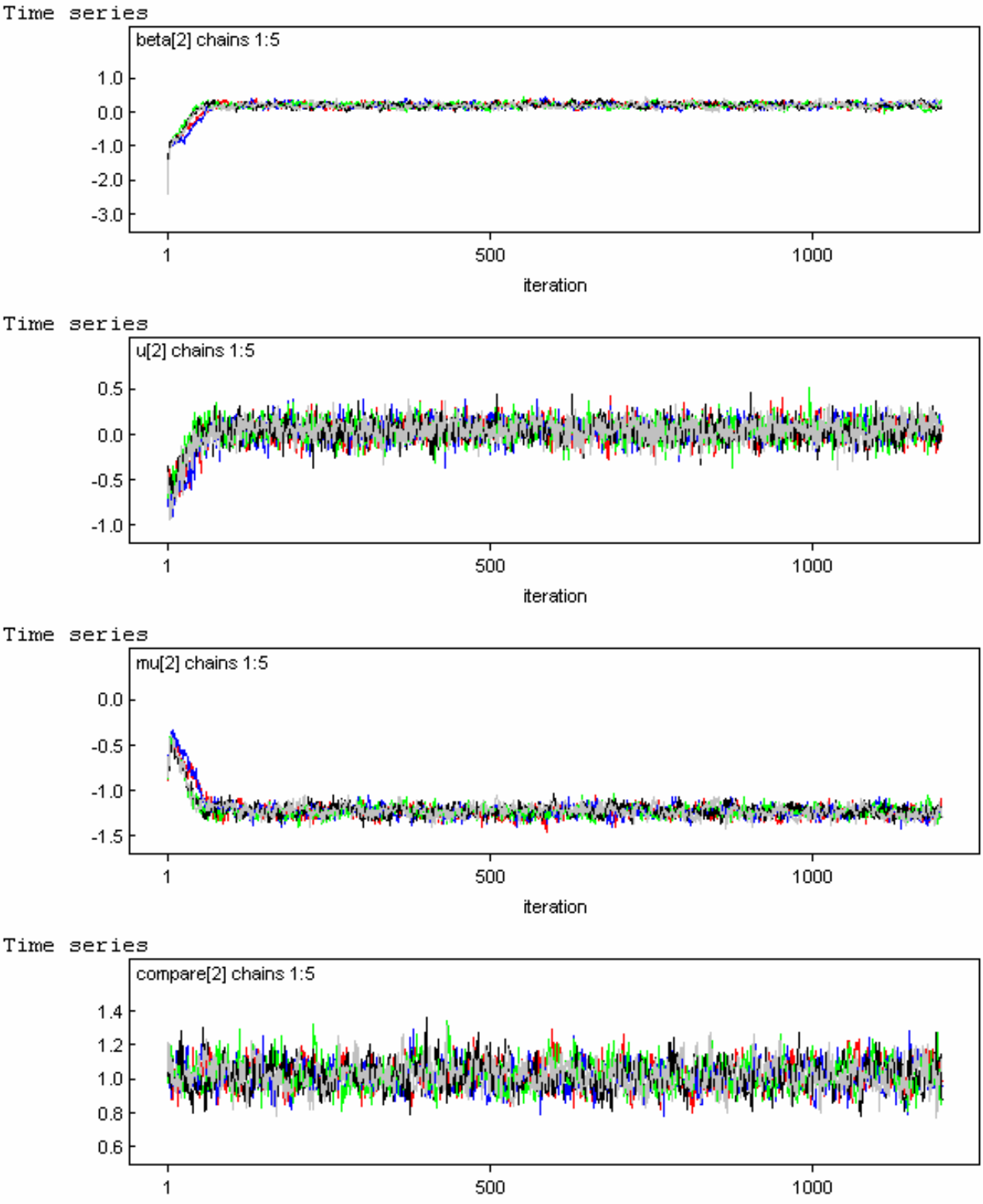

Figure 4. Each plot is 5 chains of a component draw. Each chain is 1200 samples long with a burn-in of 1000 used for each chain. From top panel to bottom, the chains of fixed effect $beta[2] = \beta_{21}$, individual log-frailty $u[2] = s_i = s_2$, $mu[2] = \alpha_{hkb} = \alpha_{112}$ and $compare[2] = \exp(\beta_{22})/\exp(\beta_{21})$, respectively.