Bayesian Semiparametric Multi-State Models

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Multi-State Models

- Multi-state models form a general class for the description of the evolution of discrete phenomena in continuous time.

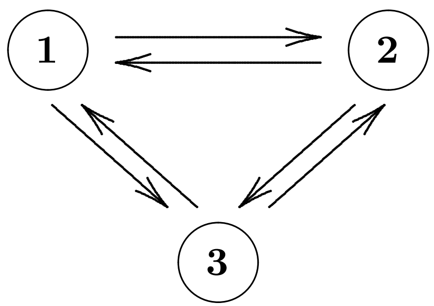
- We observe paths of a process

$$X = \{X(t), t \geq 0\} \quad \text{with} \quad X(t) \in \{1, \dots, q\}.$$

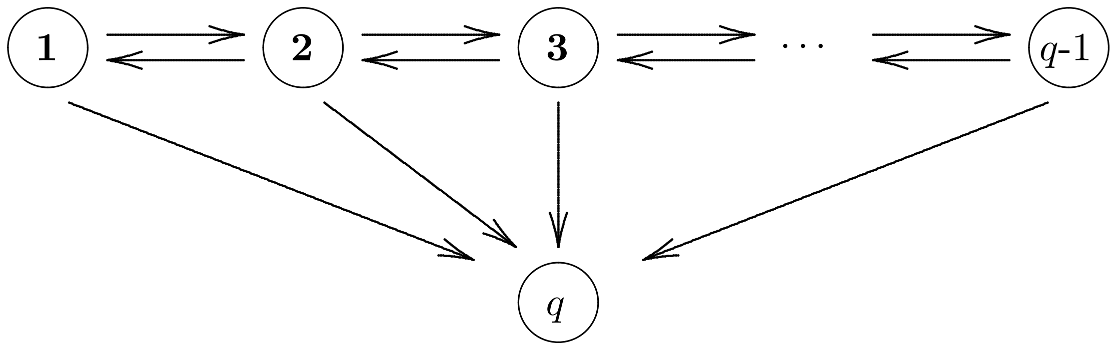
- Yields a similar data structure as for Markov processes.

- Examples:

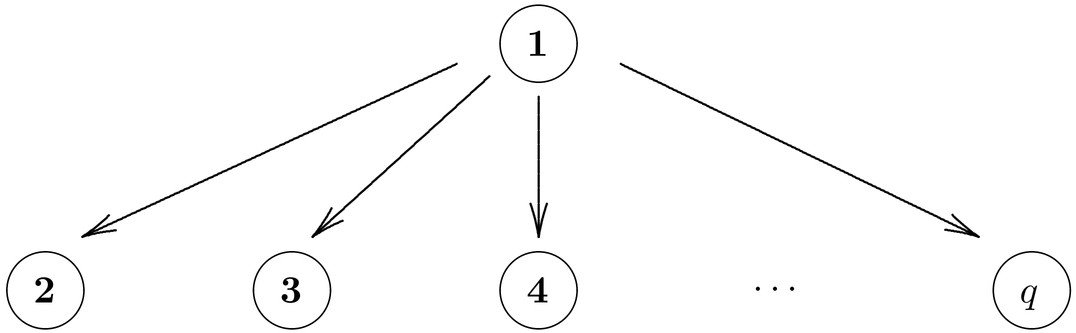
  – Recurrent events:



– Disease progression:



– Competing risks:



- (Homogenous) Markov processes can be compactly described in terms of the transition intensities

$$\lambda_{ij} = \lim_{\Delta t \to 0} \frac{P(X(t + \Delta t) = j | X(t) = i)}{\Delta t}$$

- Often not flexible enough in practice since
  - The transition intensities might vary over time.
  - The transition intensities might be related to covariates.
  - The Markov model implies independent and exponentially distributed waiting times.

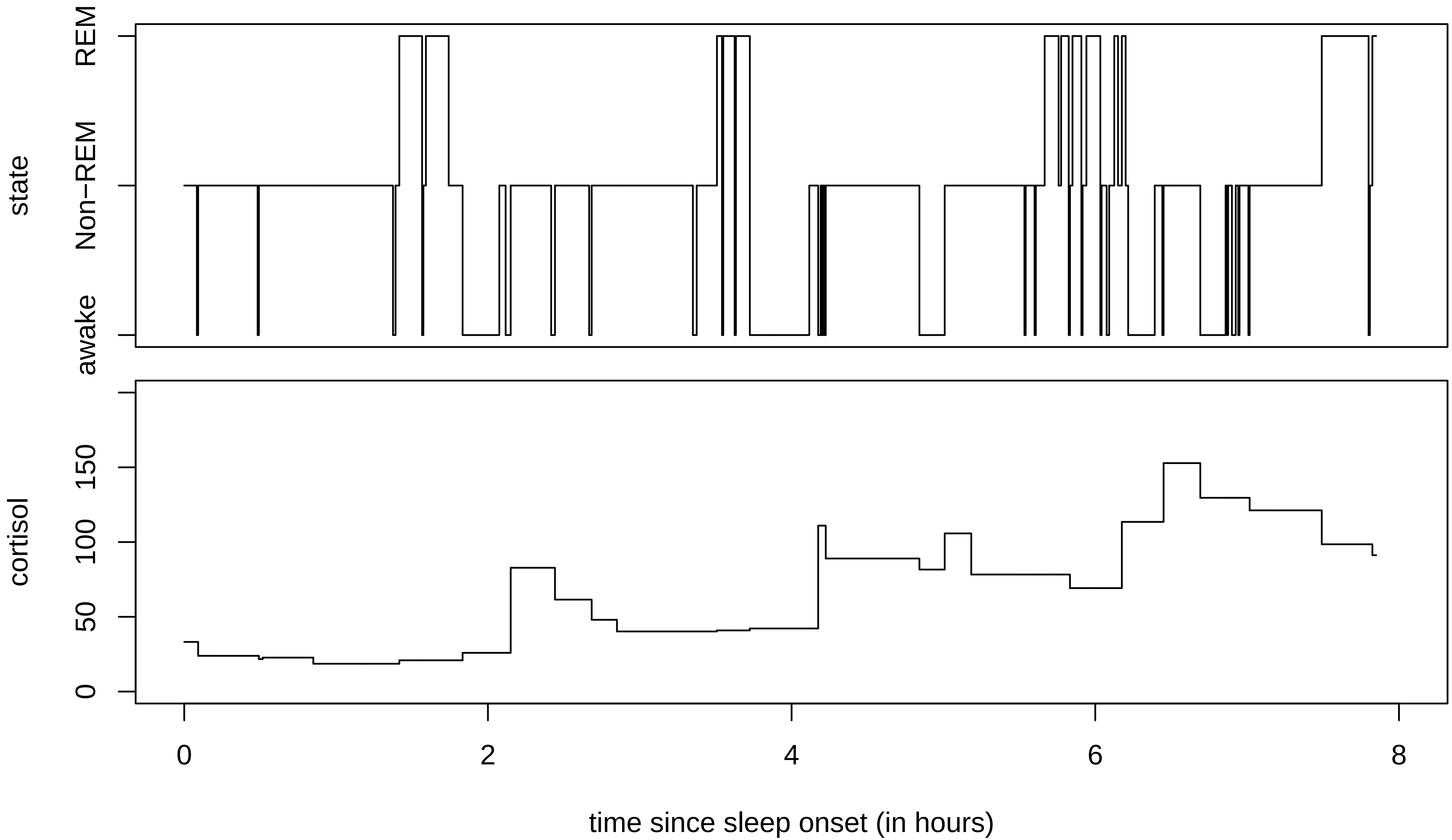
Human Sleep Data

- Human sleep can be considered an example of a recurrent event type multi-state model.

- State Space:

Awake	Phases of wakefulness
REM	Rapid eye movement phase (dream phase)
Non-REM	Non-REM phases (may be further differentiated)

- Aims of sleep research:
  - Describe the dynamics underlying the human sleep process.
  - Analyse associations between the sleep process and nocturnal hormonal secretion.
  - (Compare the sleep process of healthy and diseased persons.)


state
REM
Non−REM
awake
cortisol
0
50
100
150
0
2
4
6
8
time since sleep onset (in hours)

- Data generation:
  - Sleep recording based on electroencephalographic (EEG) measures every 30 seconds (afterwards classified into the three sleep stages).
  - Measurement of hormonal secretion based on blood samples taken every 10 minutes.
  - A training night familiarises the participants of the study with the experimental environment.

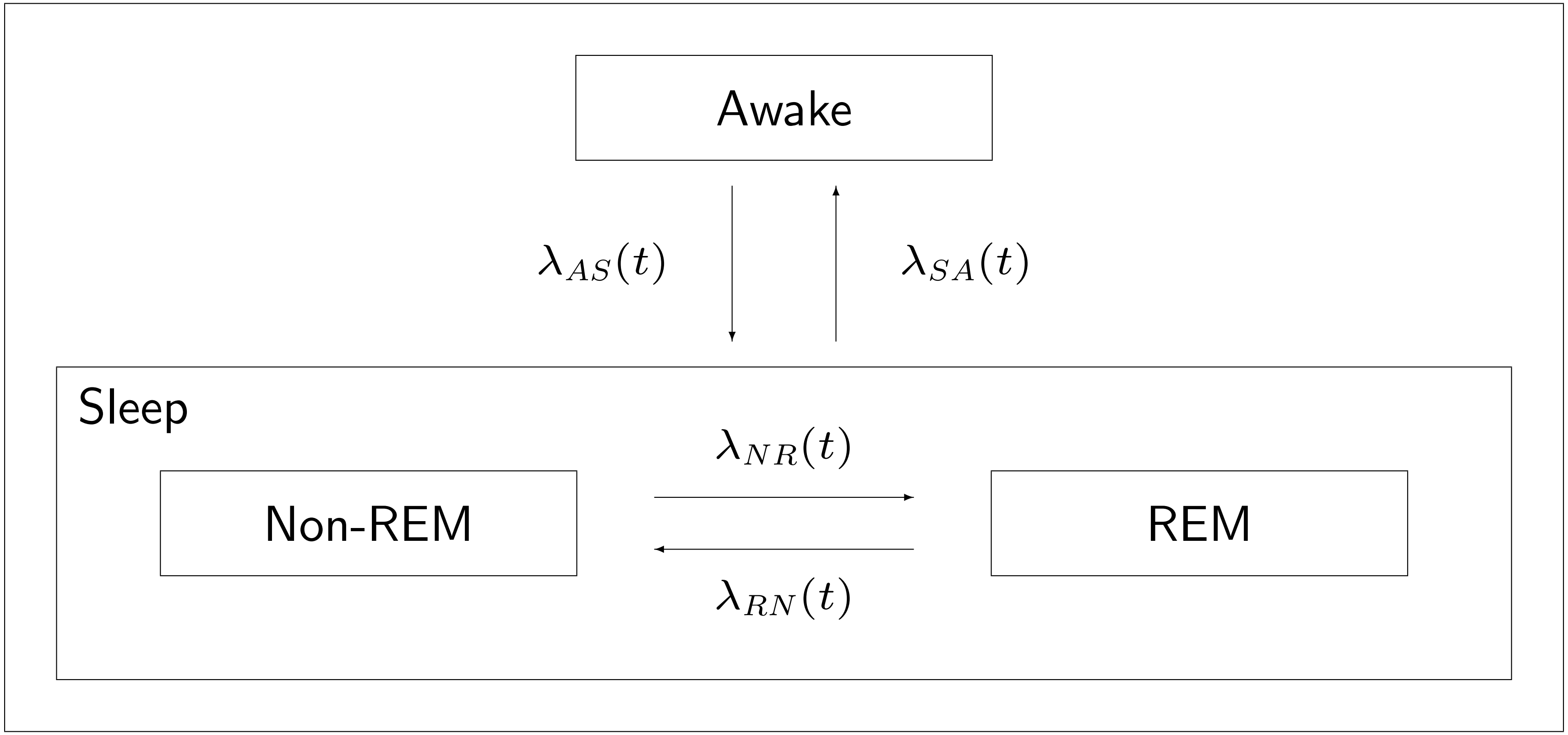
  $\Rightarrow$ Sleep processes of 70 participants.

- Simple parametric approaches are not appropriate in this application due to
  - Changing dynamics of human sleep over night.
  - The time-varying influence of the hormonal concentration on the transition intensities.
  - Unobserved heterogeneity.

$\Rightarrow$ Model transition intensities nonparametrically.

Specification of Transition Intensities

- To reduce complexity, we consider a simplified transition space:



- Model specification:

$$
\begin{aligned}
\lambda_{AS,i}(t) &= \exp\left[\gamma_0^{(AS)}(t) + b_i^{(AS)}\right] \\
\lambda_{SA,i}(t) &= \exp\left[\gamma_0^{(SA)}(t) + b_i^{(SA)}\right] \\
\lambda_{NR,i}(t) &= \exp\left[\gamma_0^{(NR)}(t) + c_i(t)\gamma_1^{(NR)}(t) + b_i^{(NR)}\right] \\
\lambda_{RN,i}(t) &= \exp\left[\gamma_0^{(RN)}(t) + c_i(t)\gamma_1^{(RN)}(t) + b_i^{(RN)}\right]
\end{aligned}
$$

where

$$
\begin{aligned}
c_i(t) &= \begin{cases} 1 & \text{cortisol} > 60 \text{ n mol/l at time } t \\ 0 & \text{cortisol} \leq 60 \text{ n mol/l at time } t, \end{cases} \\
b_i^{(j)} \sim N(0, \tau_j^2) &= \text{transition- and individual-specific frailty terms.}
\end{aligned}
$$

- Penalised splines for the baselines and time-varying effects:
  - Approximate $\gamma(t)$ by a weighted sum of B-spline basis functions

$$\gamma(t) = \sum_j \xi_j B_j(t).$$

  - Employ a large number of basis functions to enable flexibility.
  - Penalise k-th order differences between parameters of adjacent basis functions to ensure smoothness:

$$Pen(\xi|\tau^2) = \frac{1}{2\tau^2} \sum_j (\Delta_k \xi_j)^2.$$

  - Bayesian interpretation: Assume a k-th order random walk prior for ξ_j, e.g.

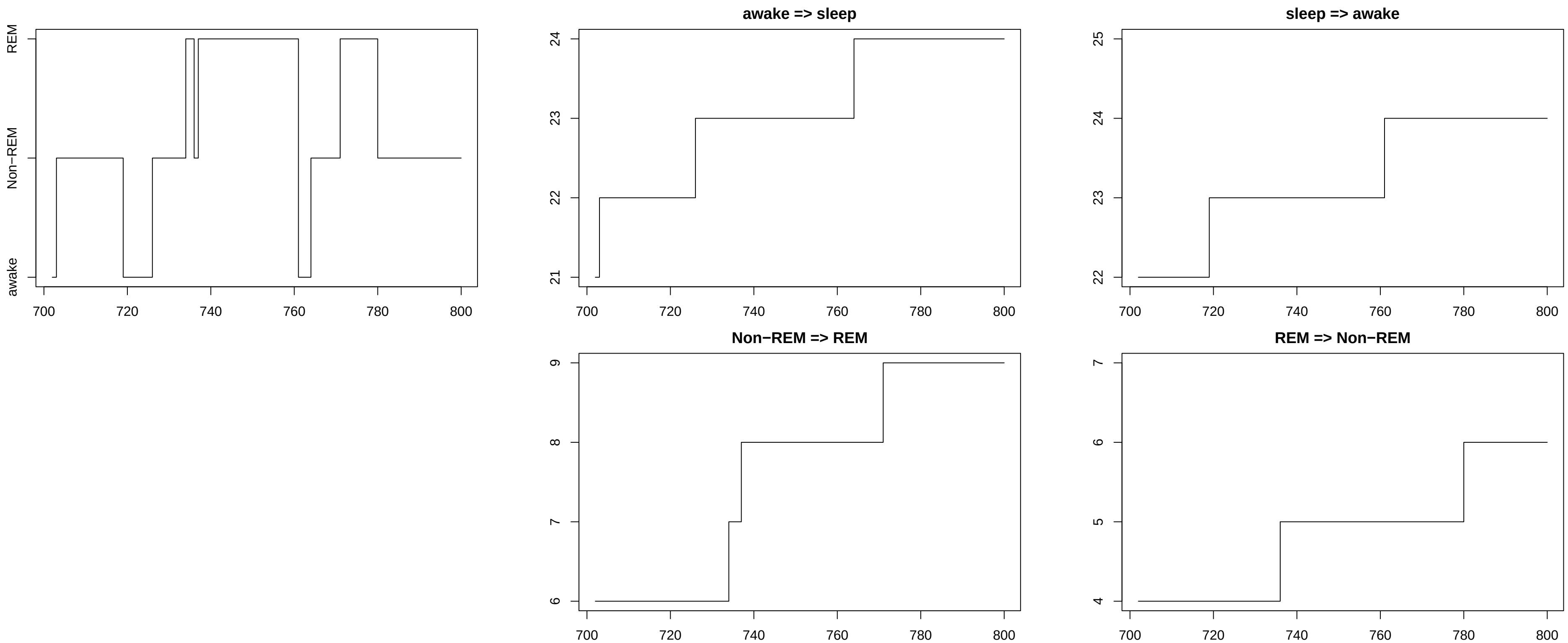
$$\xi_j = 2\xi_{j-1} - \xi_{j-2} + u_j, \quad u_j \sim N(0, \tau^2) \qquad \text{(RW2)}.$$

  - This yields the prior distribution:

$$p(\xi|\tau^2) \propto \exp\left(-\frac{1}{2\tau^2}\xi' K \xi\right).$$

Counting Process Representation

- A multi-state model with k different types of transitions can be equivalently expressed in terms of k counting processes $N_h(t)$, $h = 1, \dots, k$ counting these transitions.



- From the counting process representation we can derive the likelihood contributions for individual i:

$$
\begin{aligned}
l_i &= \sum_{h=1}^{k} \left[\int_0^{T_i} \log(\lambda_{hi}(t)) dN_{hi}(t) - \int_0^{T_i} \lambda_{hi}(t) Y_{hi}(t) dt \right] \\
&= \sum_{j=1}^{n_i} \sum_{h=1}^{k} \left[\delta_{hi}(t_{ij}) \log(\lambda_{hi}(t_{ij})) - Y_{hi}(t_{ij}) \int_{t_{i,j-1}}^{t_{ij}} \lambda_{hi}(t) dt \right].
\end{aligned}
$$

k	number of possible transitions.
$N_{hi}(t)$	counting process for type h event and individual i.
$Y_{hi}(t)$	at risk indicator for type h event and individual i.
t_{ij}	event times of individual i.
n_i	number of events for individual i.
$\delta_{hi}(t_{ij})$	transition indicator for type h transition.

- The counting process representation also provides a possibility for model validation based on martingale residuals.
- Every counting process is a submartingale and can therefore (Doob-Meyer-) decomposed as

$$\begin{aligned} N_{hi}(t) &= A_{hi}(t) + M_{hi}(t) \\ &= \int_0^t \lambda_{hi}(t) Y_{hi}(t) du + M_{hi}(t), \end{aligned}$$

  where $M_{hi}(t)$ is a martingale and $A_{hi}(t)$ is the (predictable) compensator process of $N_{hi}(t)$.

- The martingales $M_{hi}(t)$ can be interpreted as continuous-time residuals.
- Plots of $M_{hi}(t)$ against t can be used to compare models, evaluate the model fit, etc.

Bayesian Inference

- In principle, a multi-state model consists of several duration time models

  ⇒ Adopt methodology developed for nonparametric hazard regression.

- Fully Bayesian inference based on Markov Chain Monte Carlo simulation techniques (Hennerfeind, Brezger & Fahrmeir, 2006):
  - Assign inverse gamma priors to the variance and smoothing parameters.
  - Metropolis-Hastings update for the regression coefficients (based on IWLS-proposals).
  - Gibbs sampler for the variances (inverse gamma with updated parameters).
  - Efficient algorithms make use of the sparse matrix structure of the matrices involved.

- Mixed model based empirical Bayes inference (Kneib & Fahrmeir, 2006):
  - Consider the variances and smoothing parameters as unknown constants to be estimated by mixed model methodology.
  - Problem: The P-spline priors are partially improper.
  - Mixed model representation: Decompose the vector of regression coefficients as

$$\xi = X\beta + Zb,$$

    where

$$p(\beta) \propto const \qquad \text{and} \qquad b \sim N(0, \tau^2 I).$$

    $\Rightarrow$ β is a fixed effect and b is an i.i.d. random effect.
  - Penalised likelihood estimation of the regression coefficients in the mixed model (posterior modes).
  - Marginal likelihood estimation of the variance and smoothing parameters (Laplace approximation).

Software

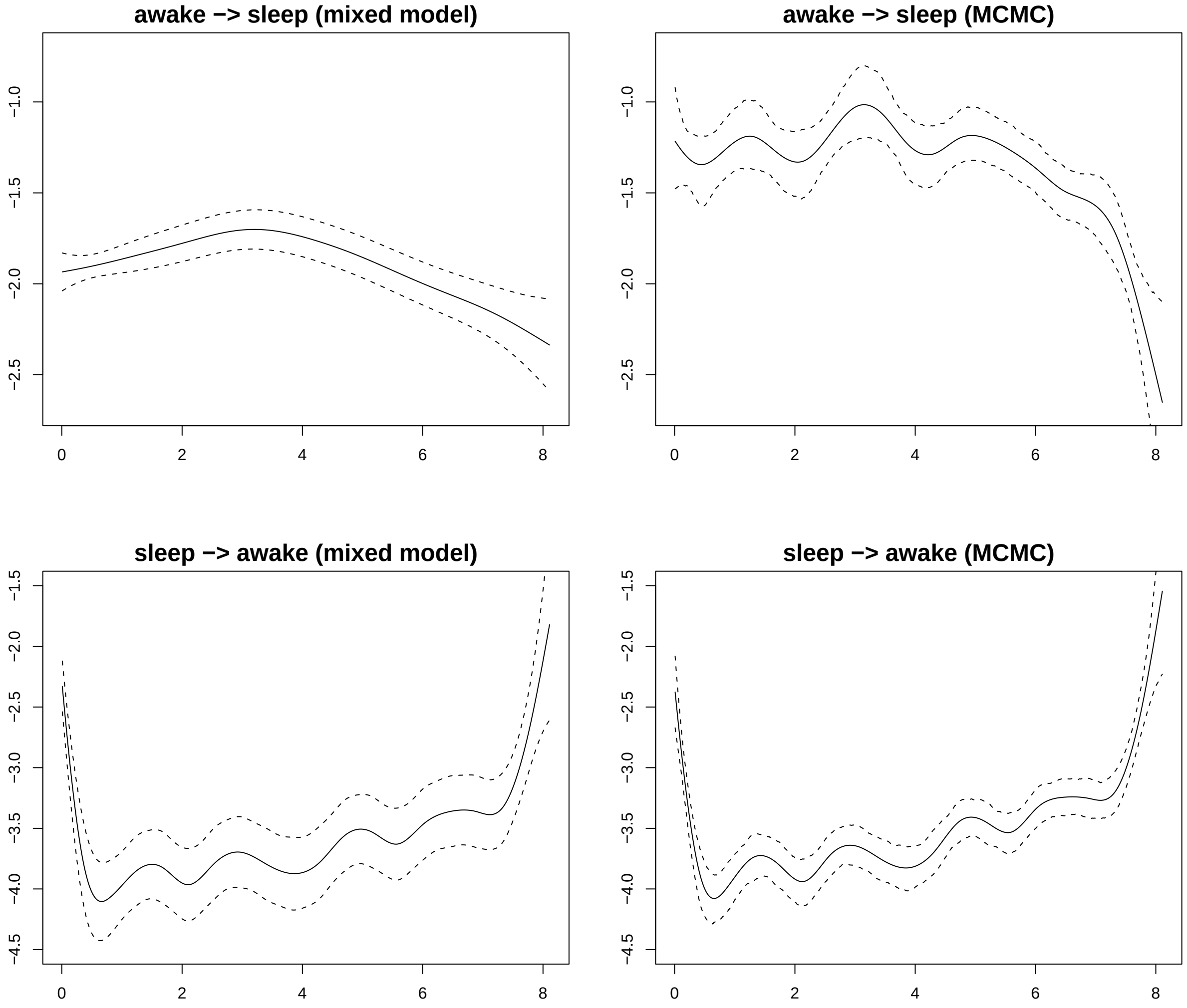
- Implemented in BayesX.
- Public domain software package for Bayesian inference in geoadditive and related models.

- Available from

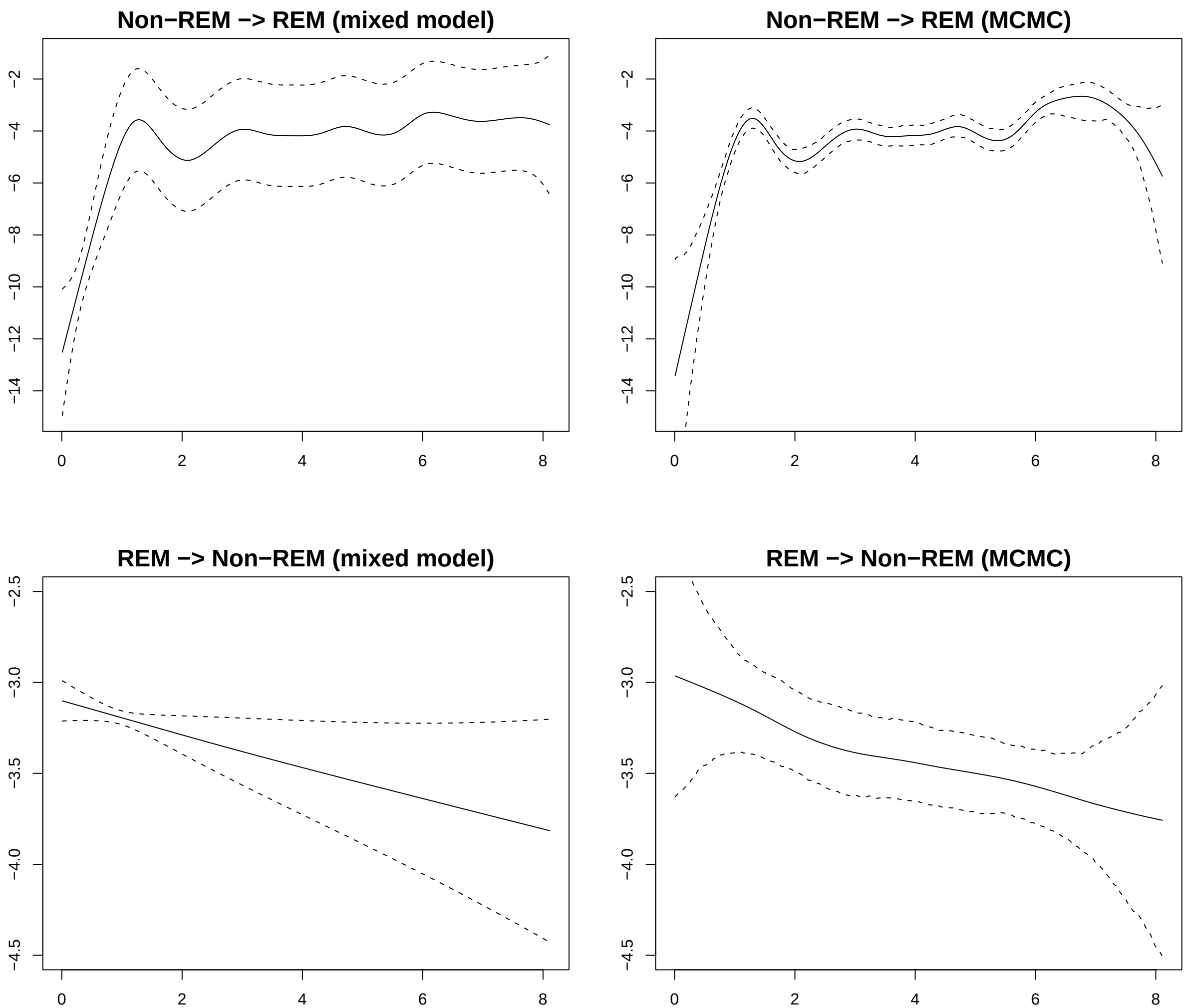
http://www.stat.uni-muenchen.de/~bayesx

Human Sleep Data II

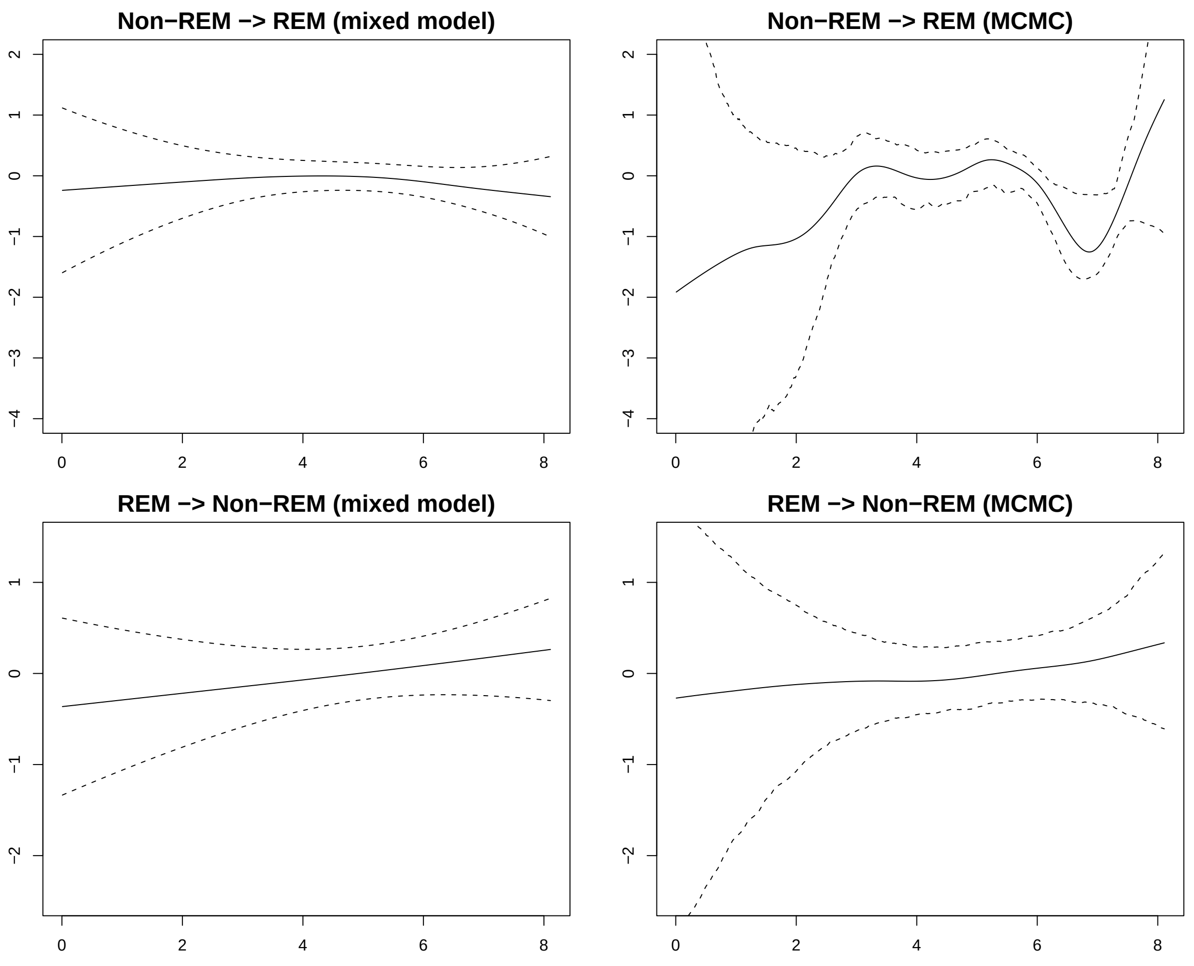
- Baseline effects I:



- Baseline effects II:

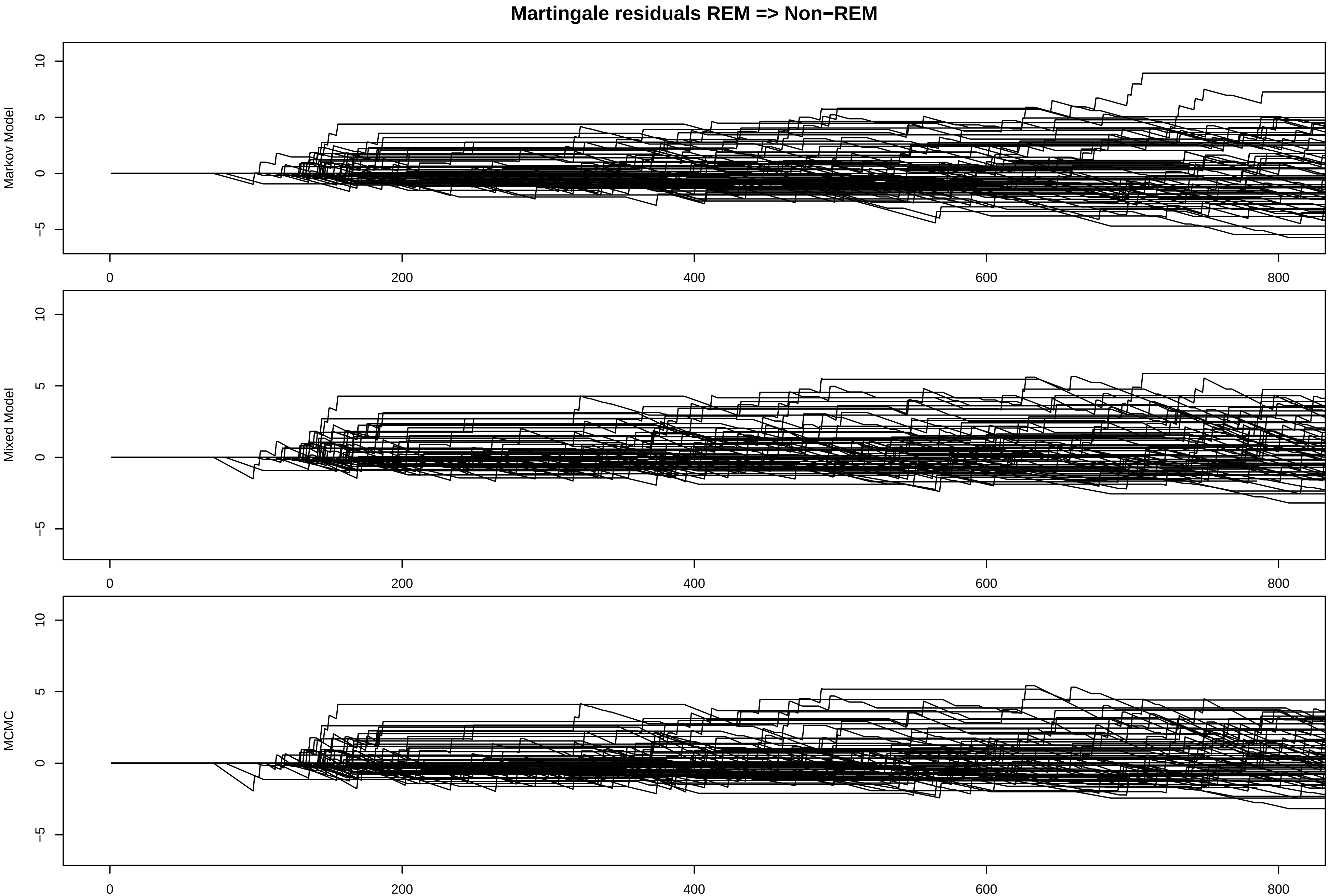


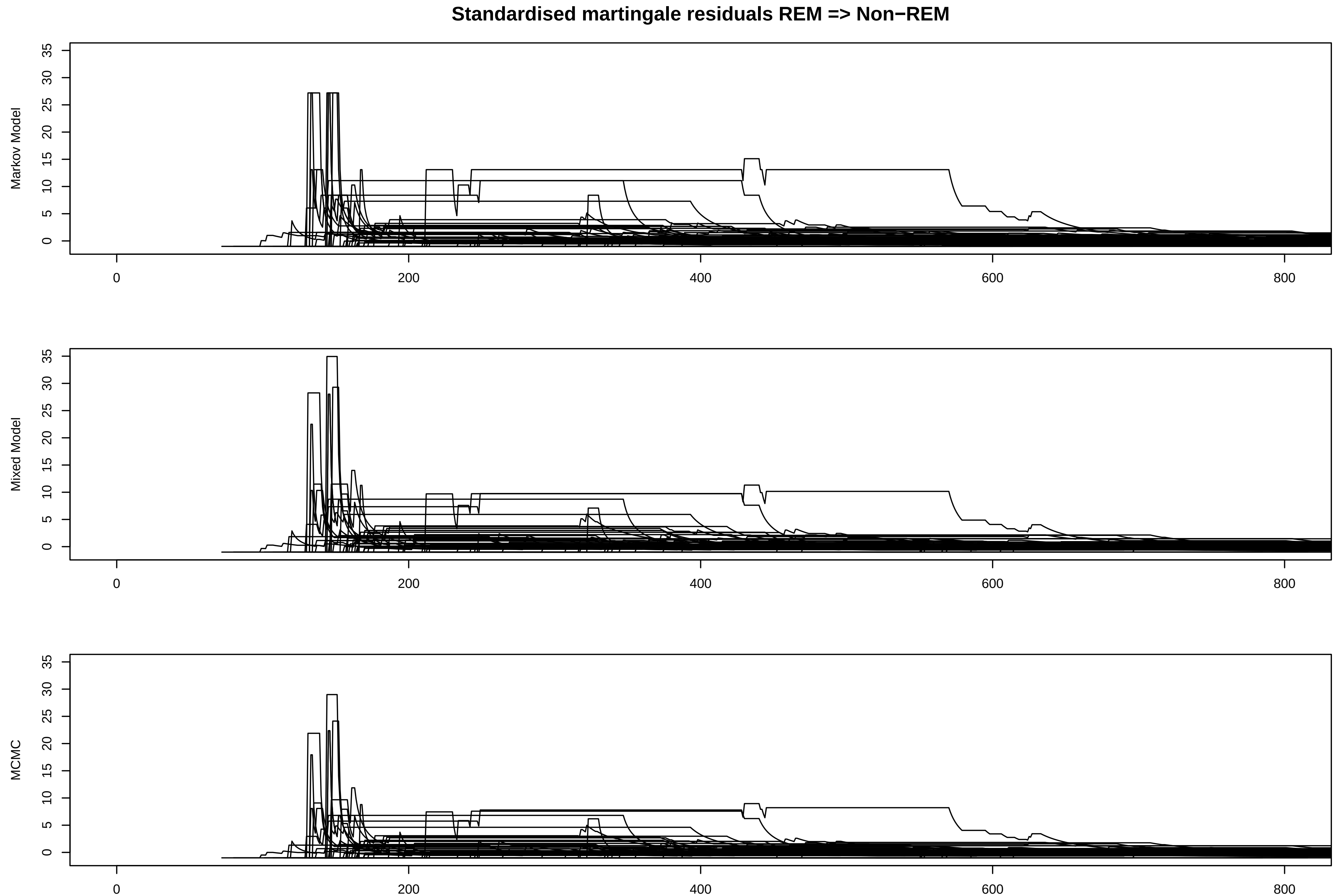
- Time-varying effects for a high level of cortisol:

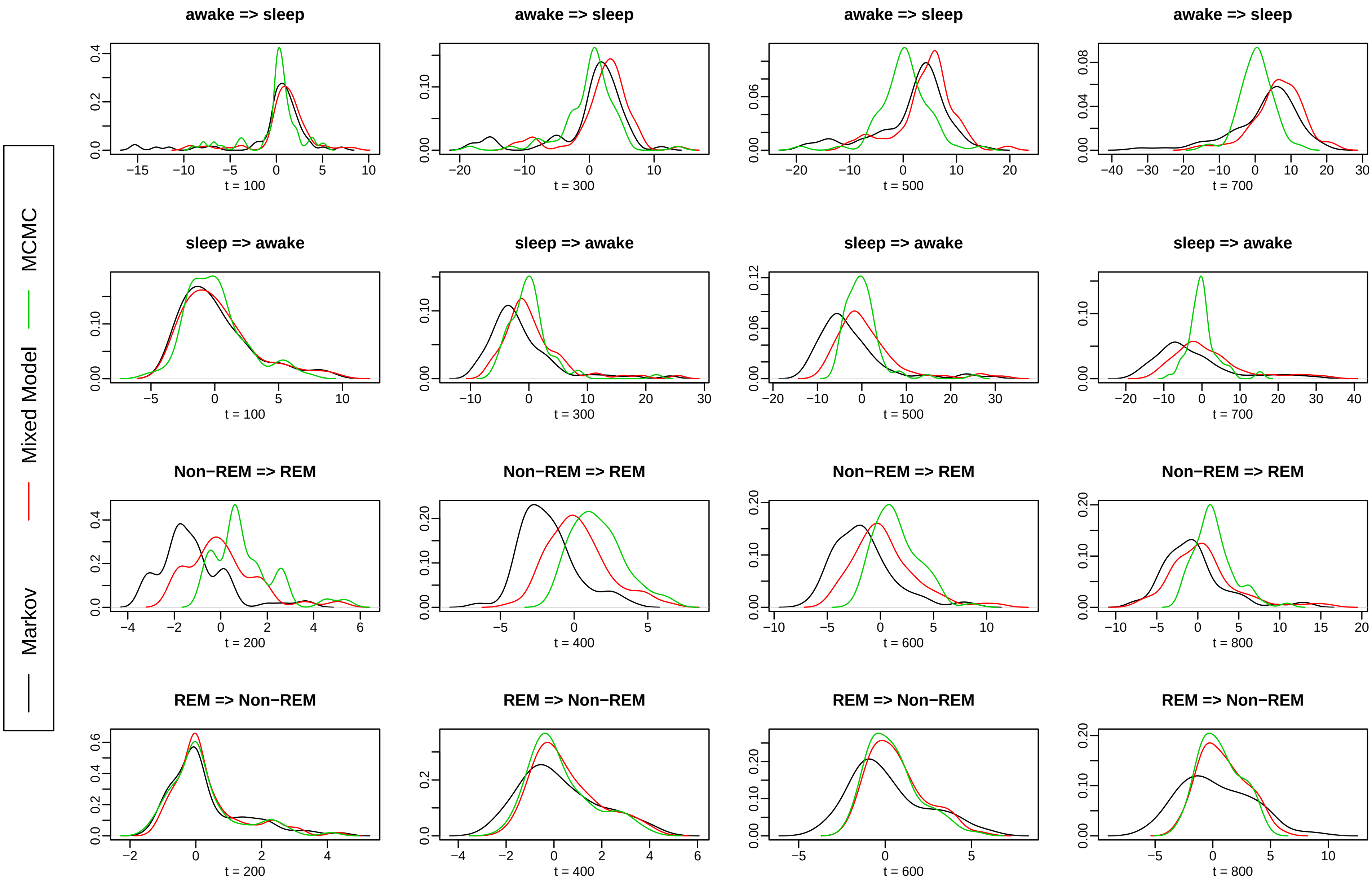


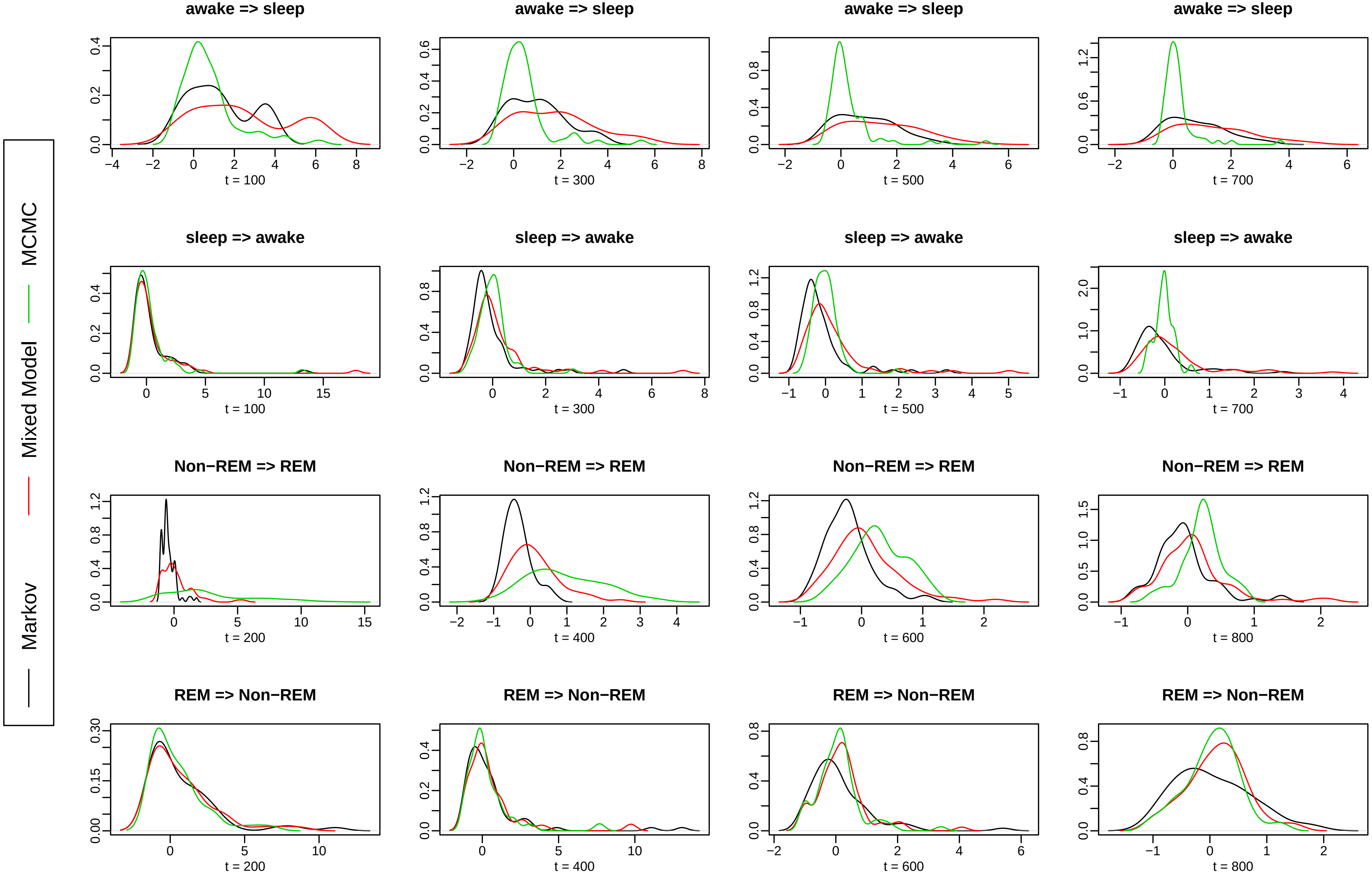
- The fully Bayesian approach detects individual-specific variation for all transitions.

- The empirical Bayes approach only detects individual-specific variation for the transition between REM and Non-REM.


Martingale residuals REM => Non−REM
Markov Model
Mixed Model
MCMC
10
5
0
−5
0
200
400
600
800


Standardised martingale residuals REM => Non−REM
Markov Model
Mixed Model
MCMC
0
5
10
15
20
25
30
35
0
200
400
600
800


Markov
Mixed Model
MCMC
awake => sleep
t = 100
t = 300
t = 500
t = 700
sleep => awake
t = 100
t = 300
t = 500
t = 700
Non−REM => REM
t = 200
t = 400
t = 600
t = 800
REM => Non−REM
t = 200
t = 400
t = 600
t = 800



awake => sleep
t = 100
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sleep => awake
Non−REM => REM
t = 200
t = 400
t = 600
t = 800
REM => Non−REM
Markov
Mixed Model
MCMC

Things to remember. . .

- Computationally feasible semiparametric approach for the analysis of multi-state models.

- Fully Bayesian and empirical Bayes inference.

- Model validation based on martingale residuals.

- Directly extendable to more complicated models including
  - Nonparametric effects of continuous covariates.
  - Spatial effects.
  - Interaction surfaces and varying coefficients.

- Future work:
  - Application to larger data sets and different types of multi-state models.
  - Consider coarsened observations, i.e. interval censored multi-state data.

References

- Brezger, Kneib & Lang (2005): BayesX: Analyzing Bayesian structured additive regression models. *Journal of Statistical Software*, **14** (11).

- Hennerfeind, Brezger, and Fahrmeir (2006): Geoadditive survival models. *Journal of the American Statistical Association*, **101**, 1065-1075.

- Kneib & Fahrmeir (2006): A mixed model approach for geoadditive hazard regression. *Scandinavian Journal of Statistics*, to appear.

- A place called home:

`http://www.stat.uni-muenchen.de/~kneib`