# Semiparametric Event History Models for Analyzing Human Sleep Data

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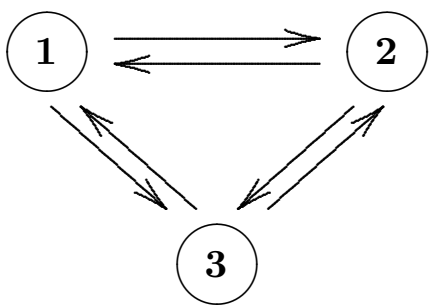
# Multi-State Models

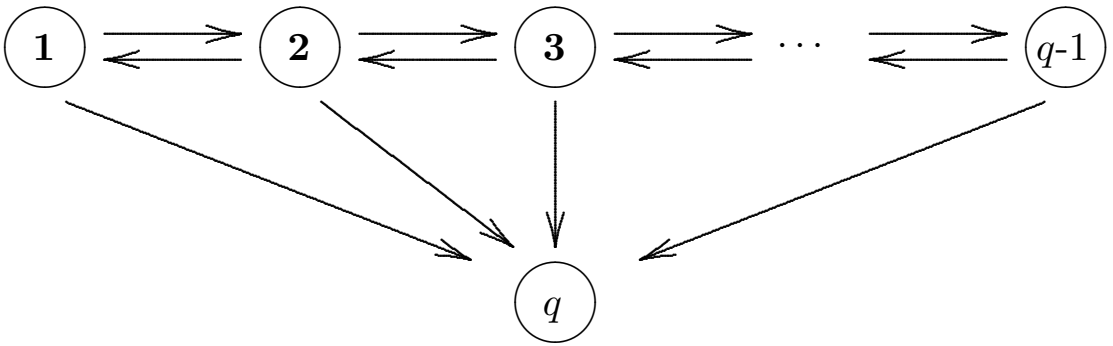
- Multi-state models form a general class for the description of the evolution of discrete phenomena in continuous time (i.e. event history analysis).
- We observe paths of a process

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

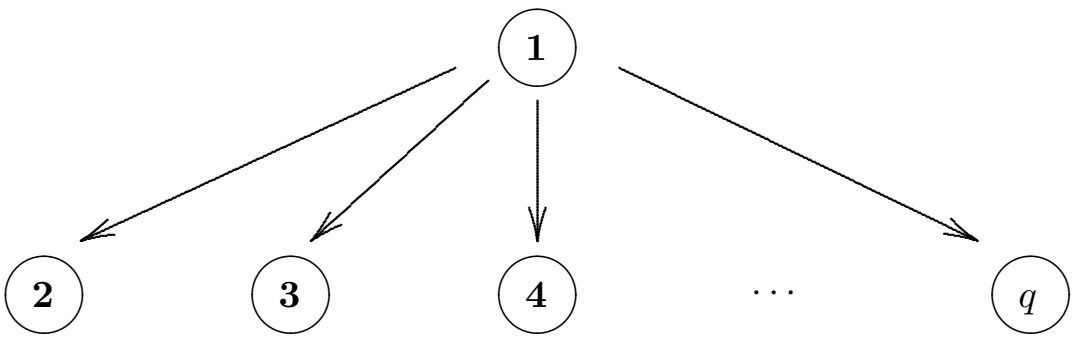
- Yields a similar data structure as for Markov processes.
- Examples:
  - Recurrent events:



– Disease progression:




– Competing risks:




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

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

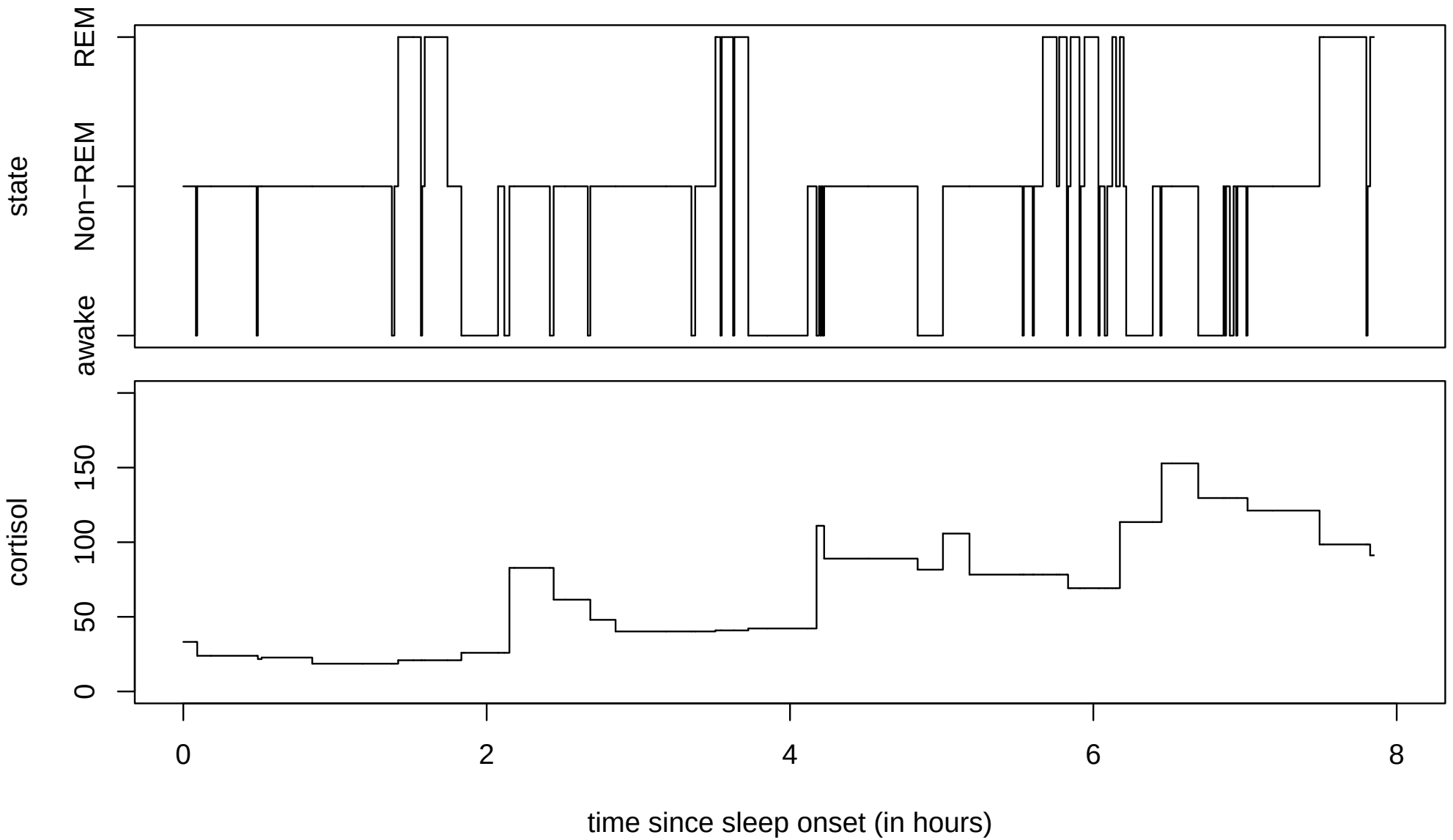
# Human Sleep Data

- 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
awake
Non−REM
REM
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 familiarizes the participants of the study with the experimental environment.

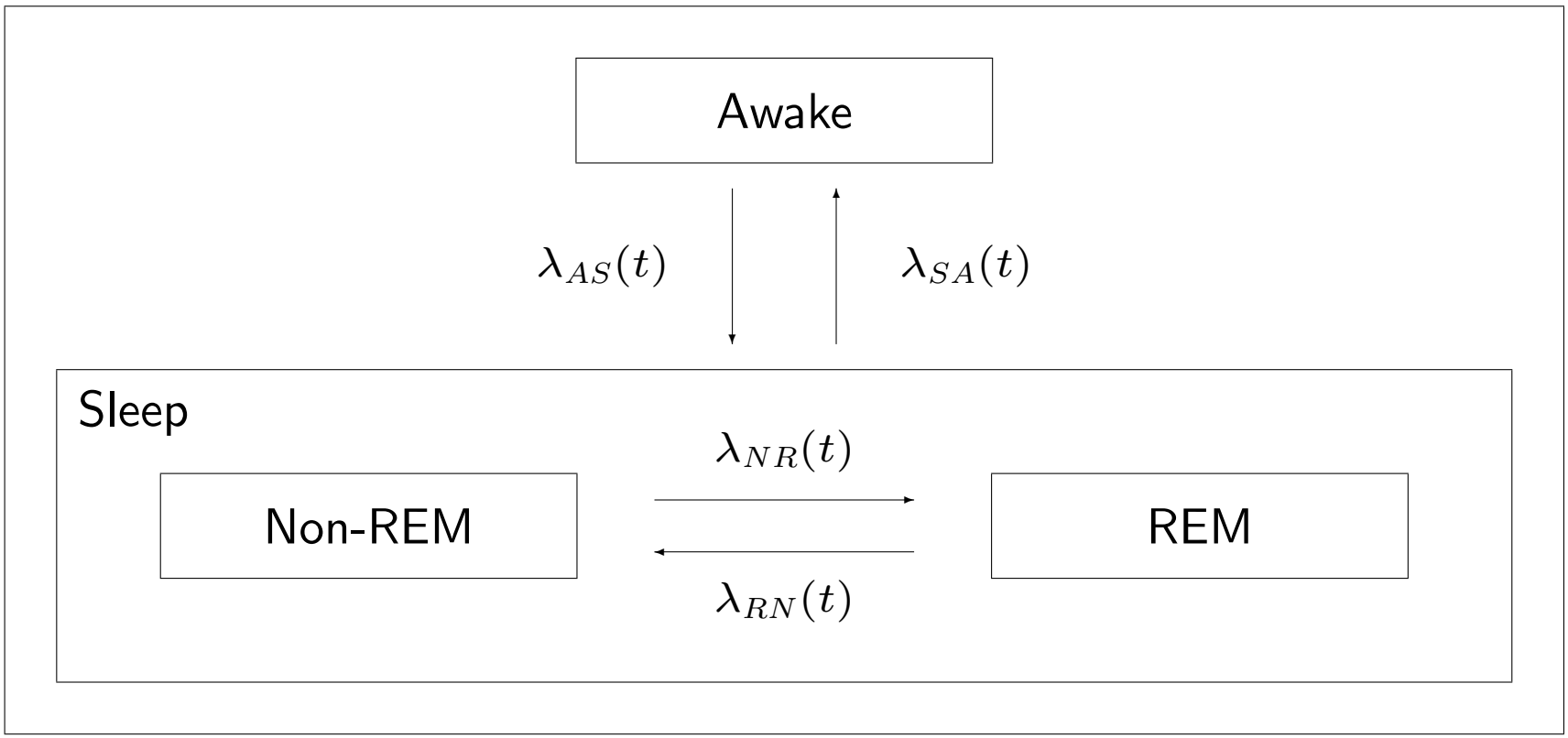
  $\Rightarrow$ Sleep processes of 70 participants.

- 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

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

- Penalized splines for baseline 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.
  - Penalize $k$-th order differences between parameters of adjacent basis functions to ensure smoothness:

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

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

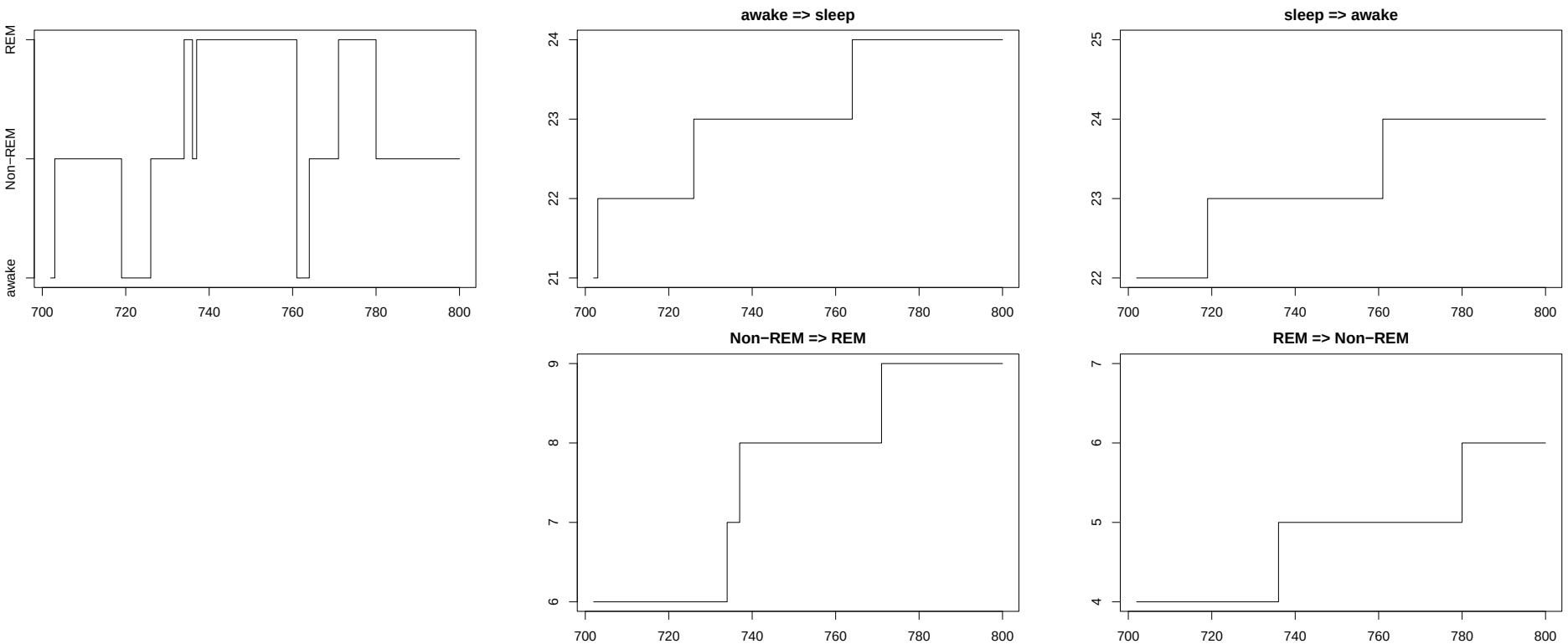
$$\xi_j = 2\xi_{j-1} - \xi_{j-2} + u_j, \quad u_j \sim N(0, \tau^2) \qquad \text{(RW2)}.$$

  - 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 $N_h(t)$, $h = 1, \ldots, k$ counting these transitions.



- From the counting process representation we can derive the likelihood contributions.
- The counting process representation also provides a possibility for model validation based on martingale residuals.
- Every counting process is a submartingale and can therefore be (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

  $\Rightarrow$ 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, 2007):
  - 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

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

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

# Software

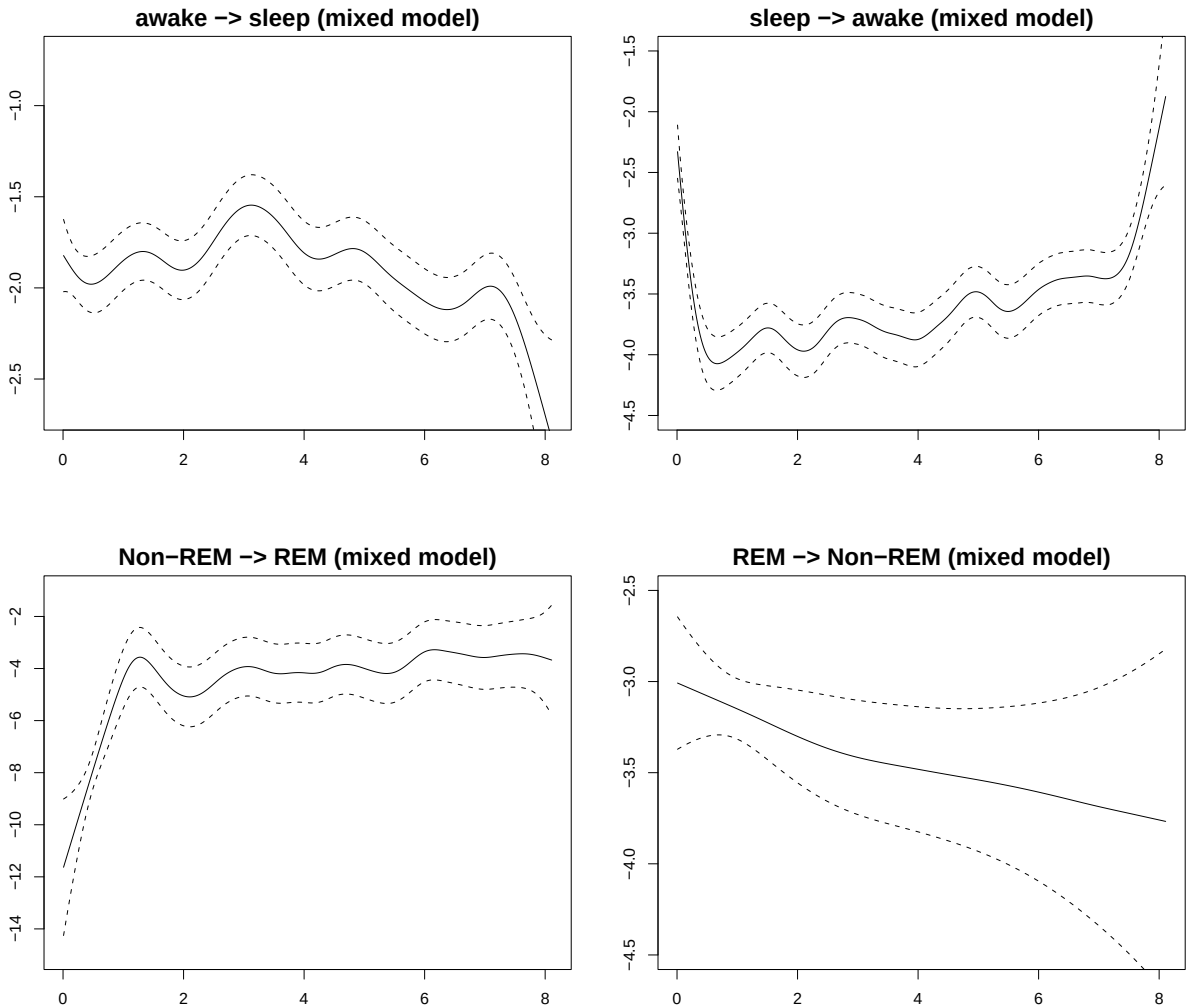
- Implemented in BayesX.
- Free software package for Bayesian inference in geoadditive and related models.


- Available from

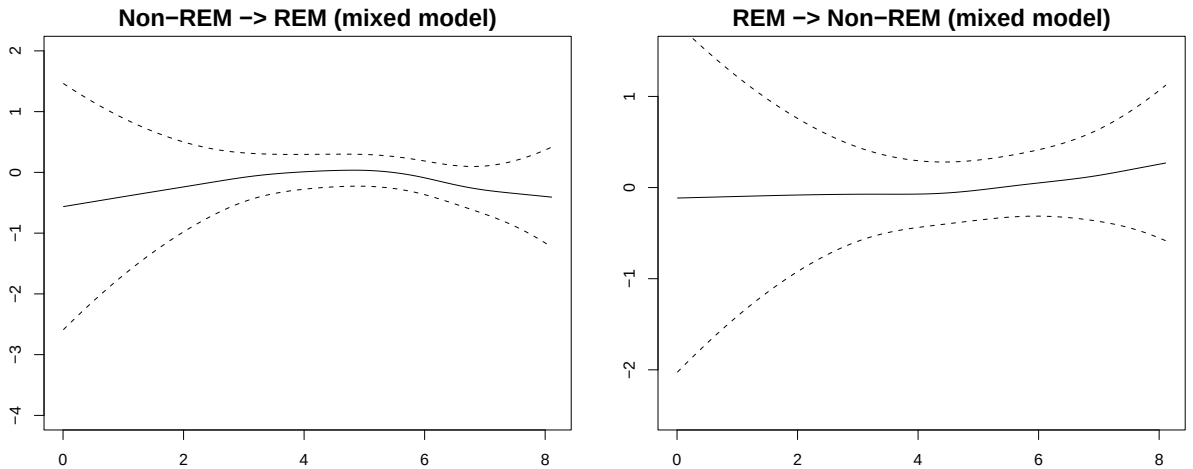
`http://www.stat.uni-muenchen.de/~bayesx`

# Human Sleep Data II

- Baseline effects:

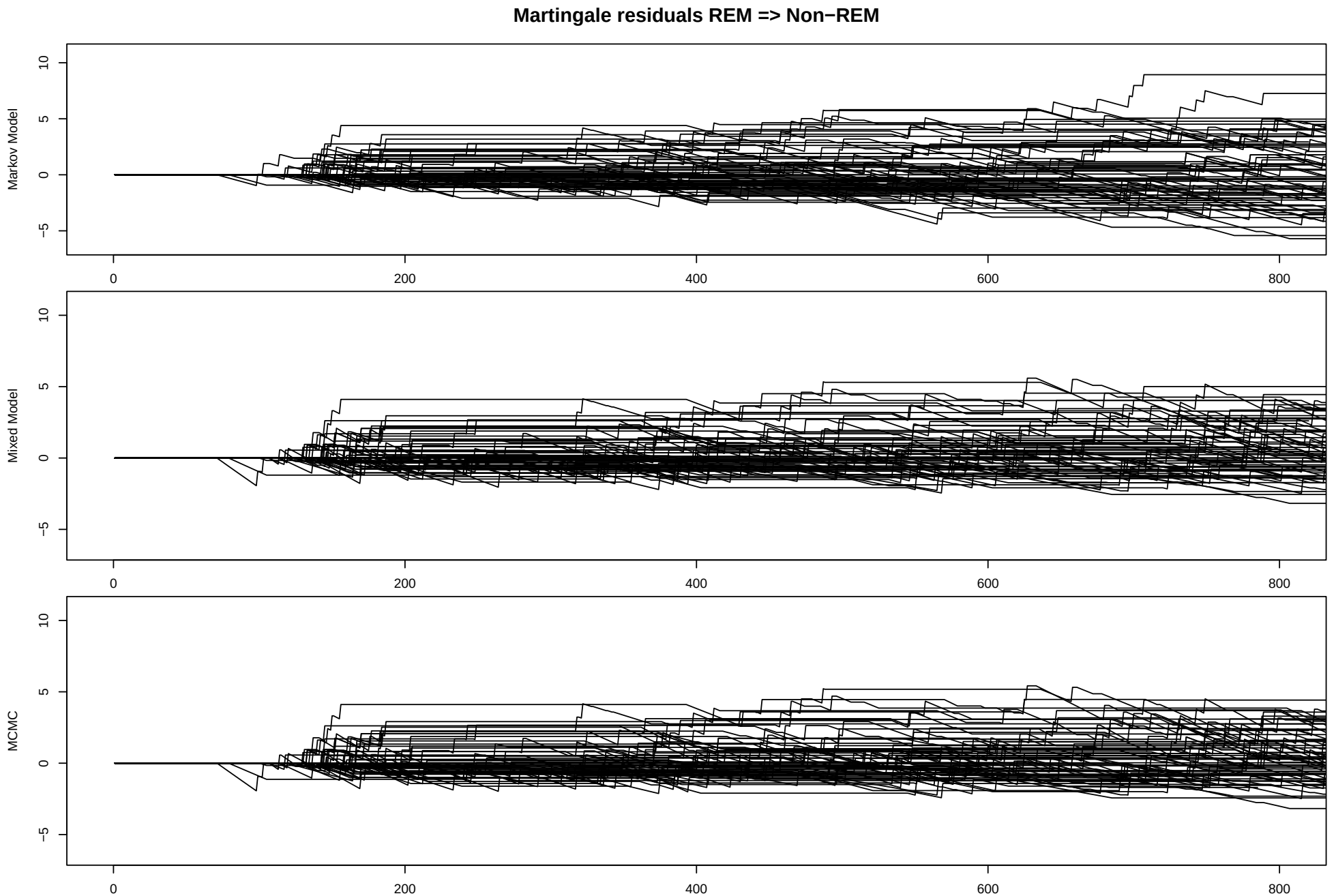


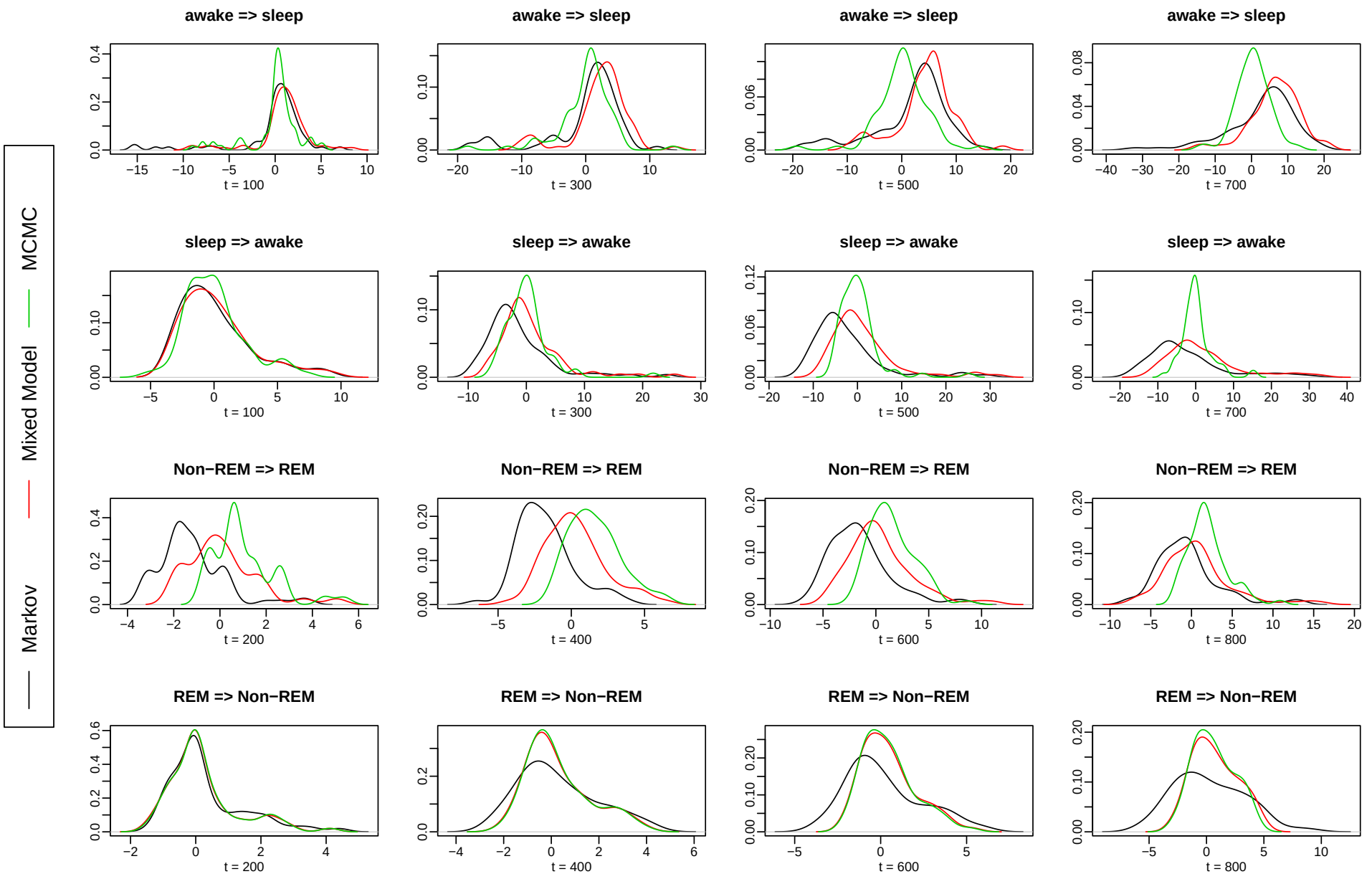
- Time-varying effects for a high level of cortisol:




- 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


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

# Summary and Outlook

- Computationally feasible semiparametric multi-state models for the analysis of event-history data.
- 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 (2007): A mixed model approach for geoadditive hazard regression. *Scandinavian Journal of Statistics*, **34**, 207-228.

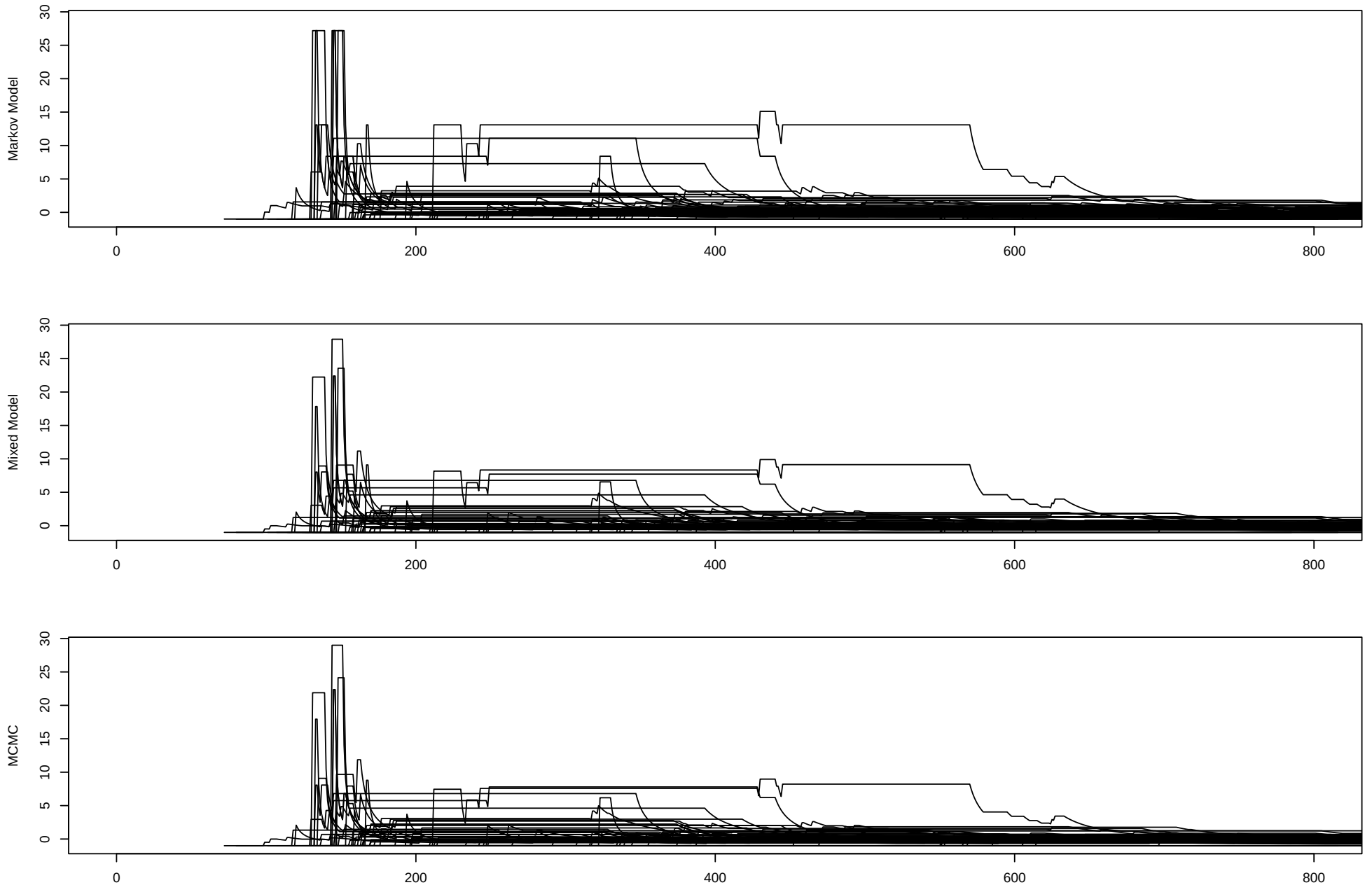
- Kneib & Hennerfeind (2007): Bayesian semiparametric multi-state models. *Statistical Modelling*, to appear.


- A place called home:

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

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

| | |
|---|---|
| $k$ | 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. |


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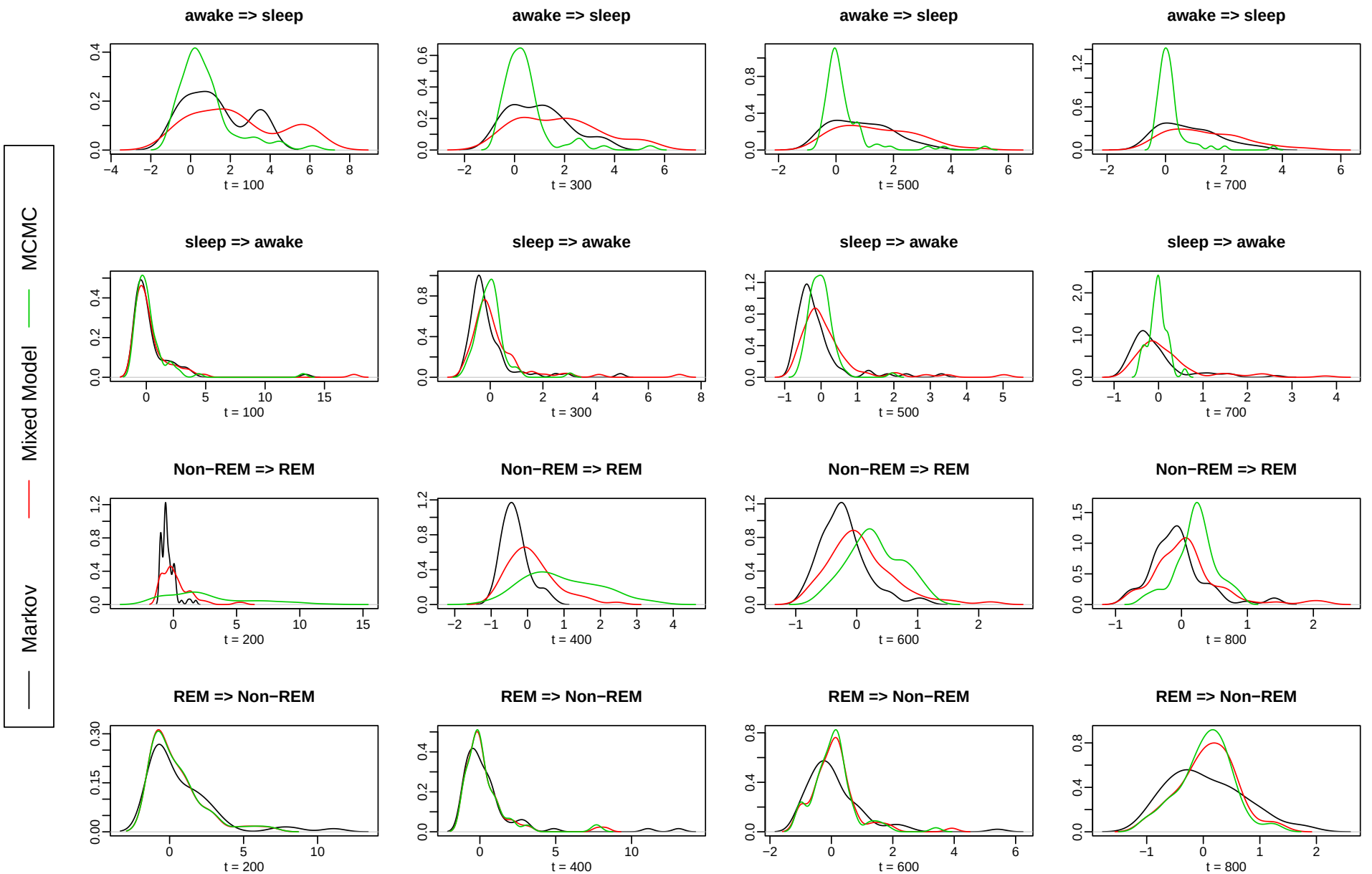
5
10
15
20
25
30
0
200
400
600
800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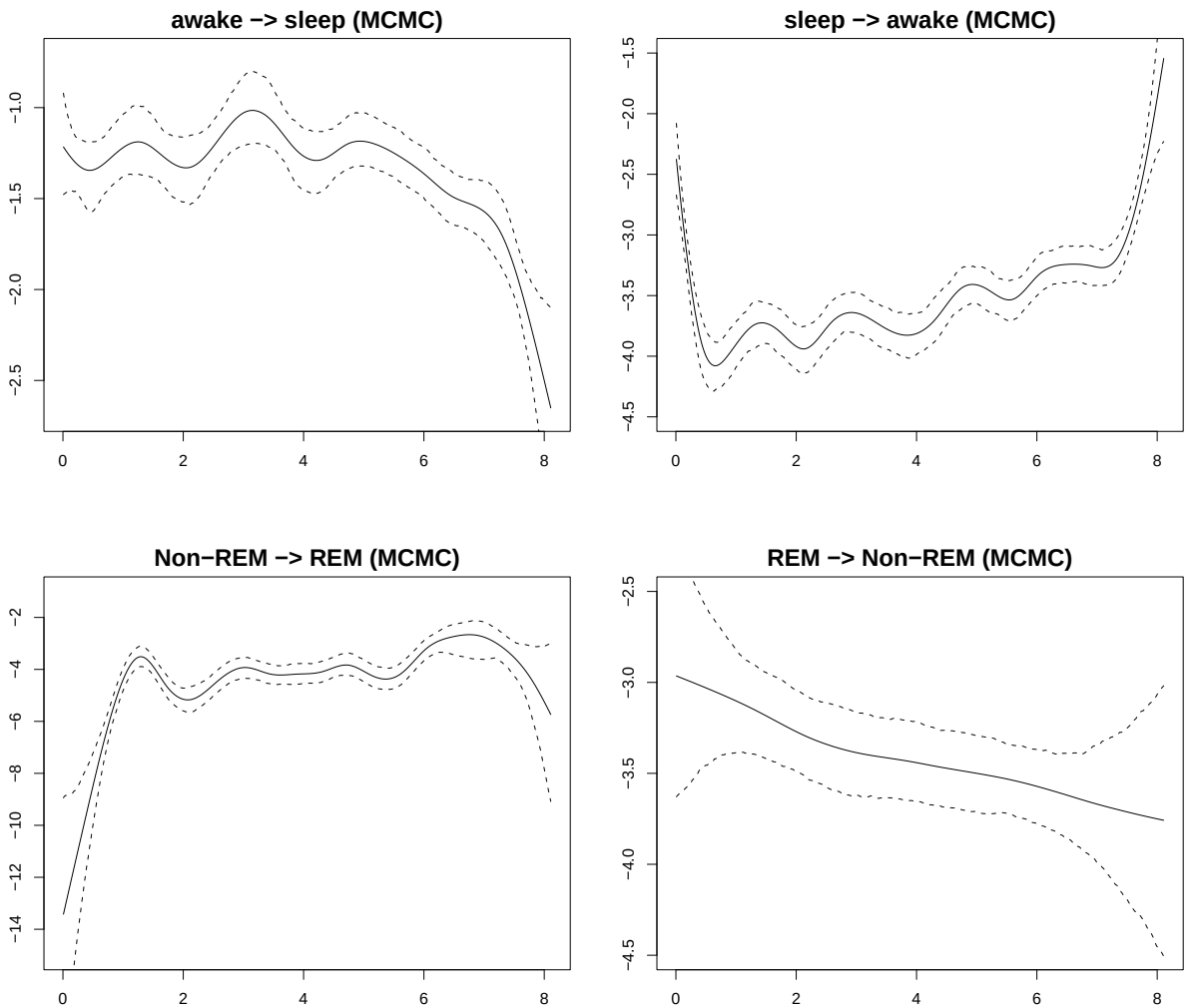

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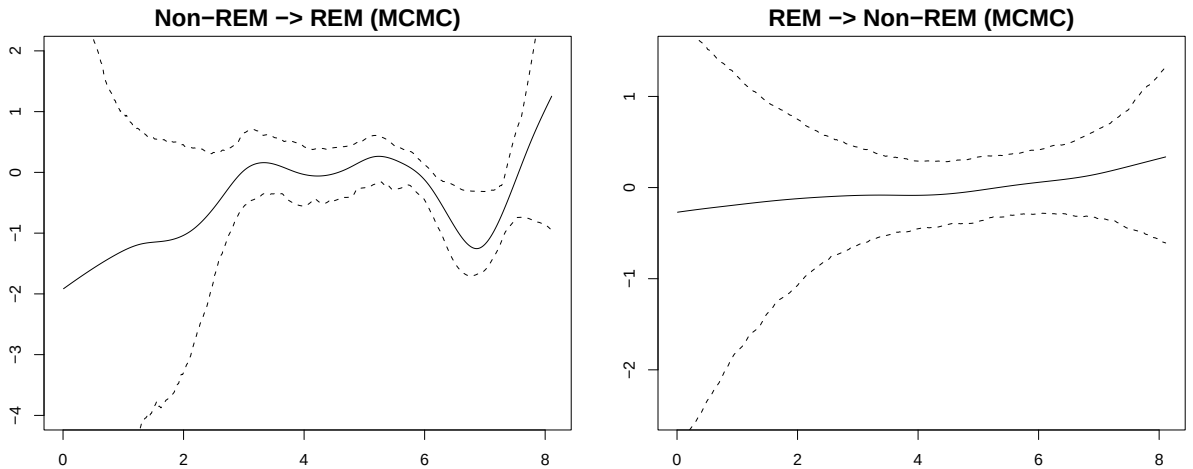

- Extensions for signal regression:
  - Sleep stages are obtained from the aggregated EEG signals.
  - Penalised splines can also be used in the analysis of the raw data.
  - Example: Analyse differences in signal intensities between healthy and depressed study participants.
  - Logit signal regression:
    $$P(Y = 1) = h(Z\gamma)$$
    where $Z$ is the matrix of signal intensities and $\gamma$ the corresponding regression coefficient.
  - Assume that the effect of the signals varies smoothly over time

    $\Rightarrow$ Model $\gamma = \gamma(t)$ as a P-spline.
  - First promising results have been achieved with this approach.