A nonparametric multi-state model for the analysis of human sleep

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Human Sleep

- Human sleep can be considered a time-continuous stochastic process with discrete state space.

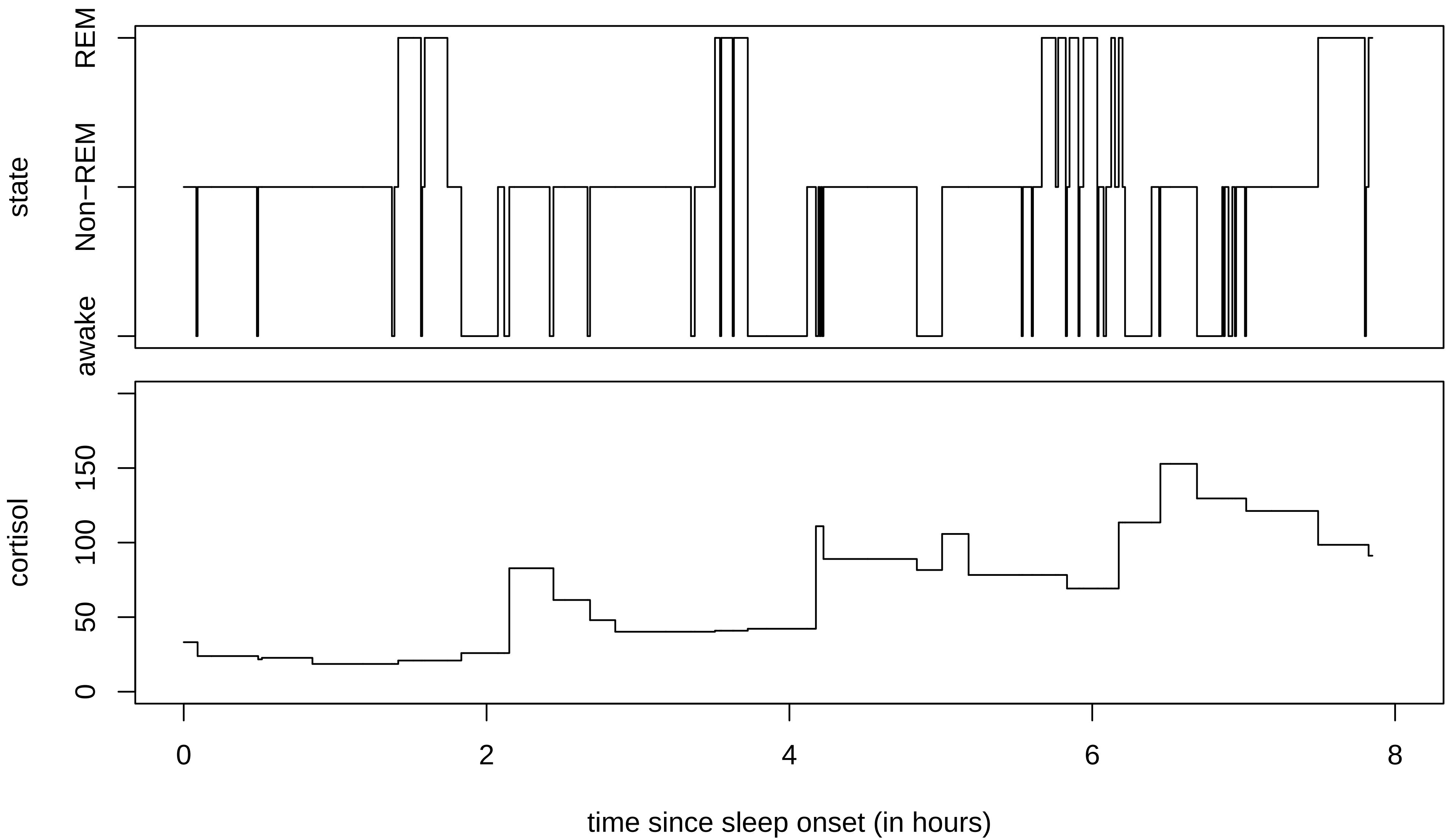
- Possible states:

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.)

- 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.

- Available data:
  - 39 healthy "patients".
  - 21 male, 18 female.
  - Part of a larger study that investigates the impact of sleep withdrawal.

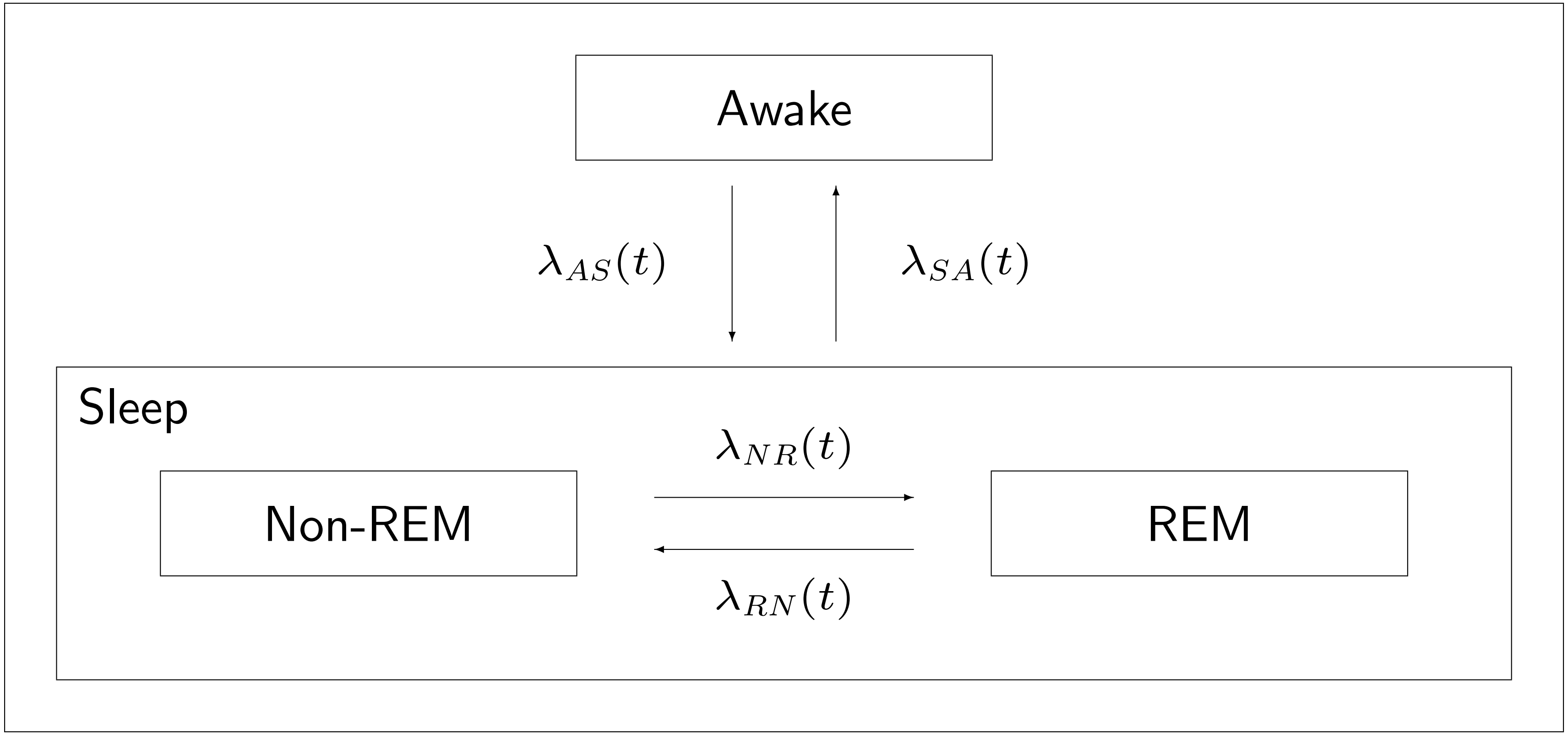

state
REM
Non−REM
awake
cortisol
0
50
100
150
0
2
4
6
8
time since sleep onset (in hours)

Multi-State Models

- Data structure similar to that of discrete Markov processes.
- Compact description of such a process in terms of transition intensities between the states.
- Simple parametric approaches are not appropriate in our application due to
  - Changing dynamics of human sleep over night.
  - Individual sleeping habits to be described by covariates.
  - A small number of available covariates (unobserved heterogeneity).

$\Rightarrow$ Model transition intensities nonparametrically.

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



- Specification of the transition intensities:

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

where

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

- 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:

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

- I.i.d. Gaussian priors for the frailty terms (with transition-specific variances):

$$b_i^{(j)} \sim N(0, \tau_j^2).$$

Bayesian Inference

- The likelihood contribution for individual i can be constructed based on a counting process formulation of the model:

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

k	number of possible transitions.
$N_{hi}(t)$	counting process for type h event.
$Y_{hi}(t)$	at risk indicator for type h event.
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.

- In principle, similar structure as in survival models with nonparametric hazard rate

  $\Rightarrow$ 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, 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

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

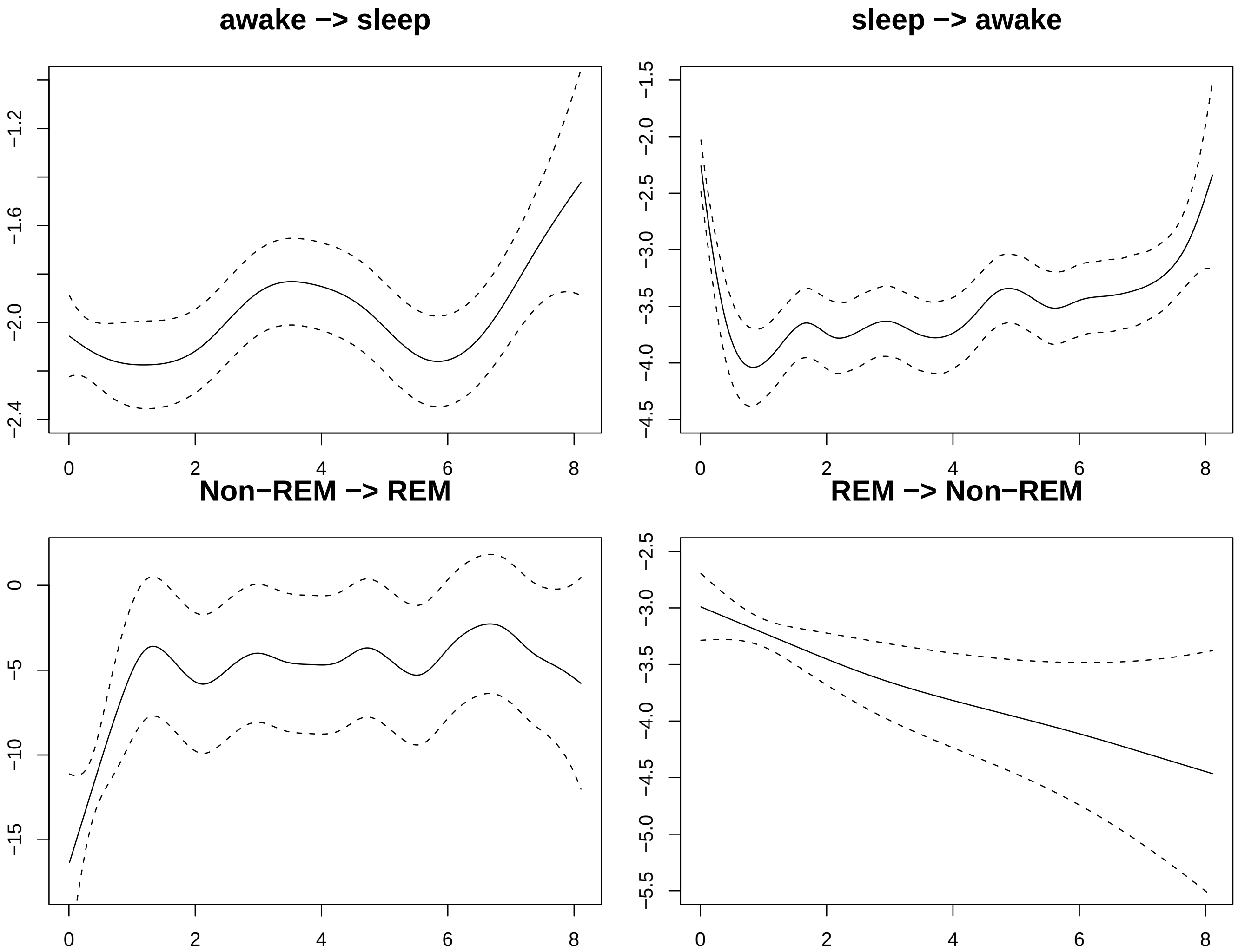
    where

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

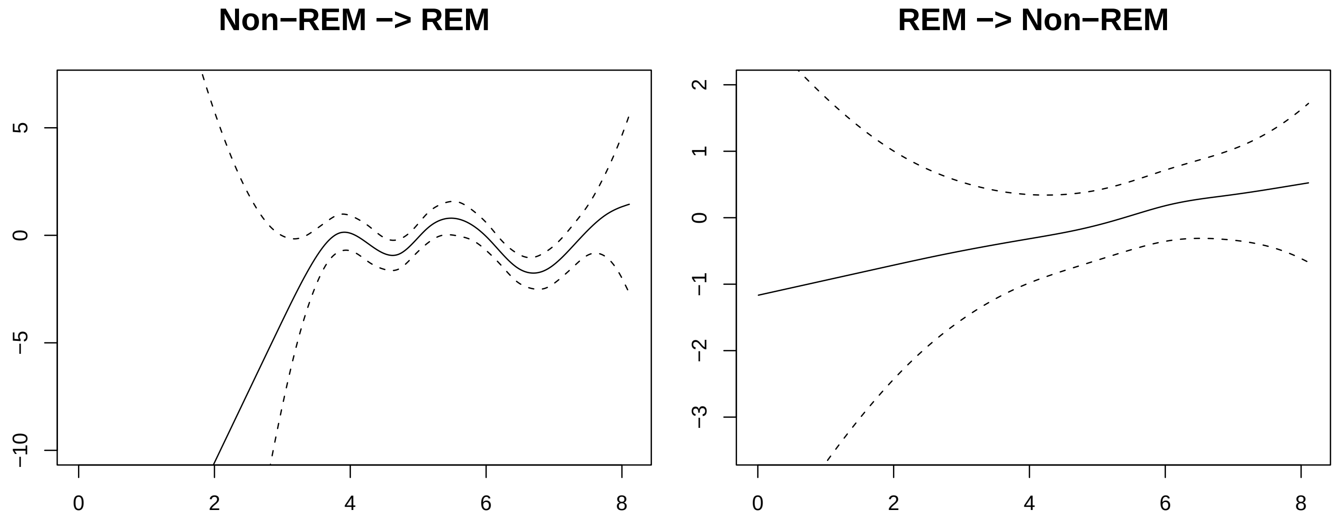
    $\Rightarrow$ β is a fixed effect and b is an i.i.d. random effect.
  - Penalised likelihood estimation of the regression coefficients in the mixed model (posterior modes).
  - Marginal likelihood estimation of the variance and smoothing parameters.

Results

- Baseline effects:



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



- Gender differences for all the transitions (mostly increased for males).

- Only the fully Bayesian approach identifies individual-specific variation.

Software

- Multi-state models will be part of the next release of BayesX.
- Public domain software package for Bayesian inference in geoadditive and related models.

- Available from

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

Discussion

- Computationally feasible nonparametric approach for the analysis of multi-state models.
- Fully Bayesian and empirical Bayes inference.
- 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*, to appear.

- 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`