Bayesian Structured Hazard Regression

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Outline

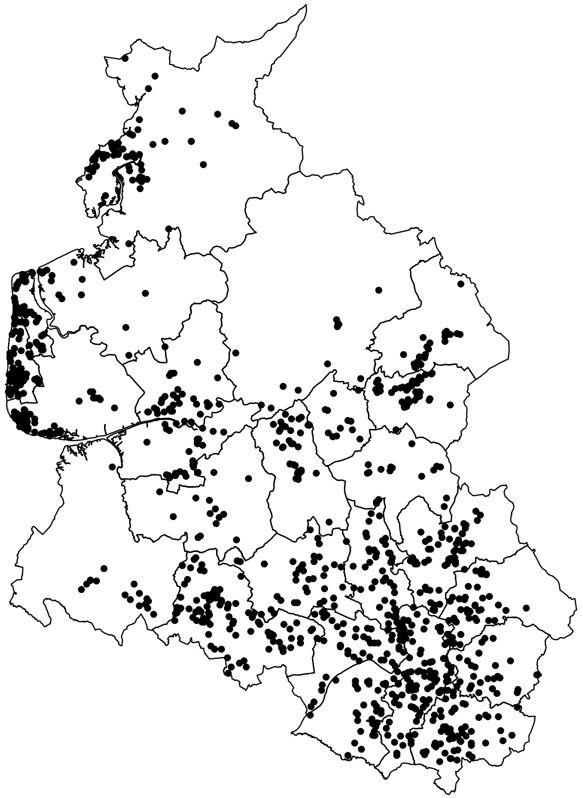
- Leukemia survival data.
- Structured hazard regression for survival times.
- Bayesian inference in structured hazard regression.
  - Full Bayesian inference based on MCMC.
  - Empirical Bayes inference using mixed model methodology.
- Multi-state models for the analysis of human sleep.

Leukemia Survival Data

- Survival time of adults after diagnosis of acute myeloid leukemia.
- 1,043 cases diagnosed between 1982 and 1998 in Northwest England.
- 16 % (right) censored.
- Continuous and categorical covariates:

age	age at diagnosis,
wbc	white blood cell count at diagnosis,
sex	sex of the patient,
tpi	Townsend deprivation index.

- Spatial information in different resolution.



- Classical Cox proportional hazards model:

$$\lambda(t; x) = \lambda_0(t) \exp(x'\gamma).$$

- Baseline hazard $\lambda_0(t)$ is a nuisance parameter and remains unspecified.
- Estimate γ based on the partial likelihood.
- Questions / Limitations:
  - Simultaneous estimation of baseline hazard rate and covariate effects.
  - Flexible modelling of covariate effects (e.g. nonlinear effects, interactions).
  - Spatially correlated survival times.
  - Non-proportional hazards models / time-varying effects.

$\Rightarrow$ Structured hazard regression models.

- Replace usual parametric predictor with a flexible semiparametric predictor

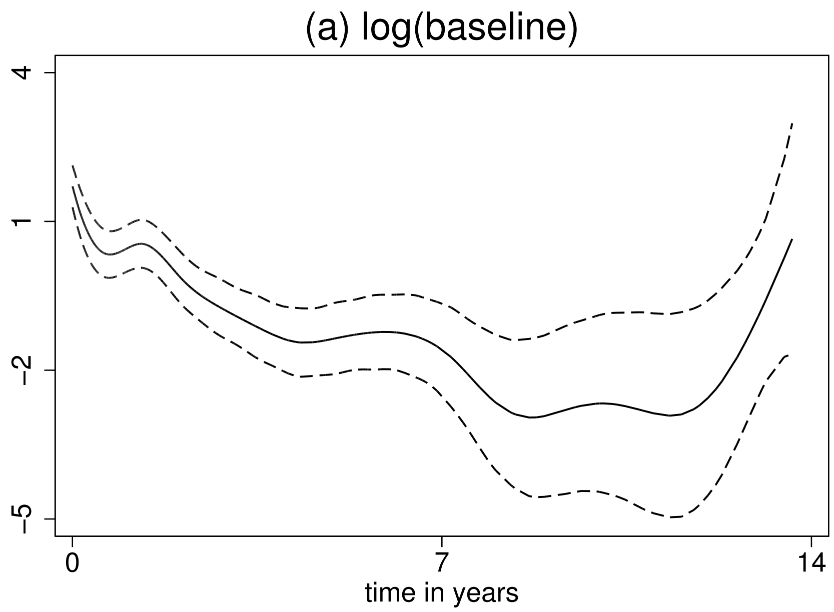
$$\lambda(t; \cdot) = \lambda_0(t) \exp[f_1(age) + f_2(wbc) + f_3(tpi) + f_{spat}(s_i) + \beta_1 sex]$$

  and absorb the baseline

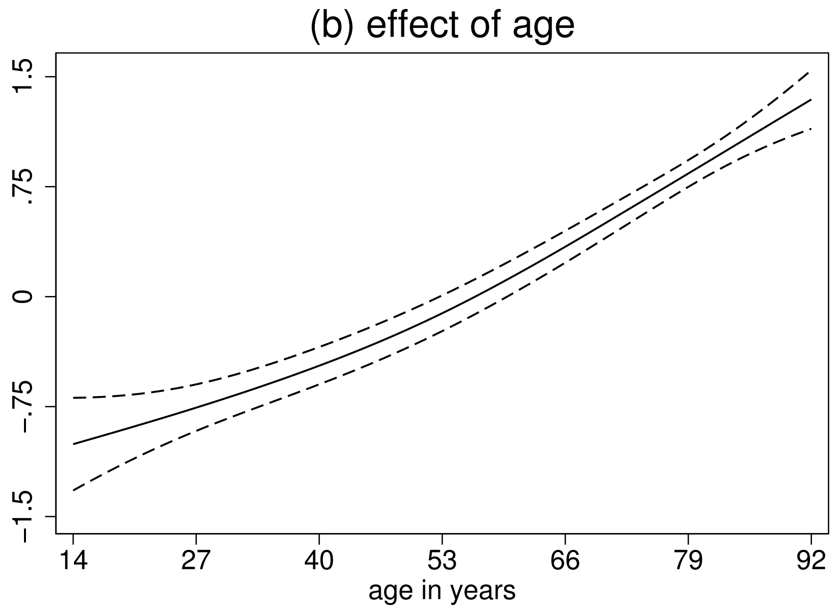
$$\lambda(t; \cdot) = \exp[g_0(t) + f_1(age) + f_2(wbc) + f_3(tpi) + f_{spat}(s_i) + \beta_1 sex]$$

  where

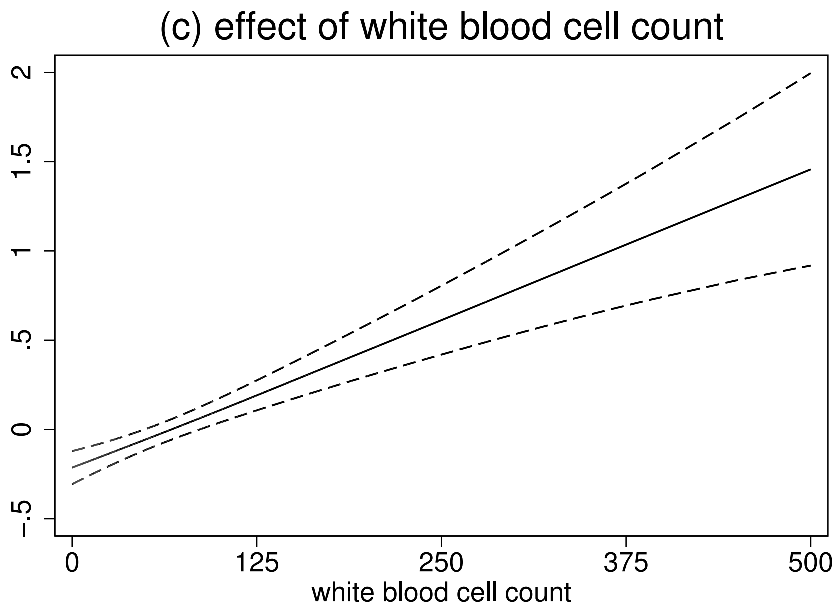
  - $g_0(t) = \log(\lambda_0(t))$ is the log-baseline hazard,
  - f_1, f_2, f_3 are nonparametric functions of age, white blood cell count and deprivation, and
  - f_{spat} is a spatial function.



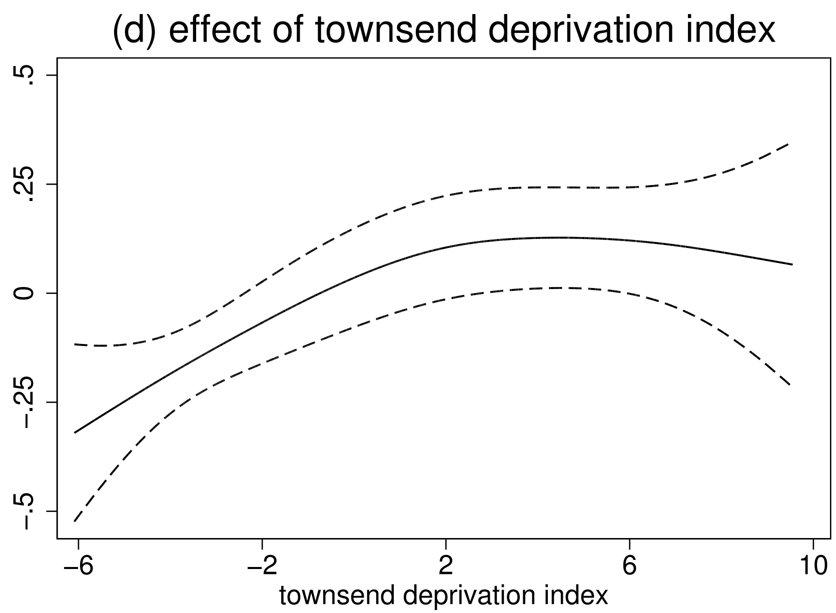
Log-baseline hazard.



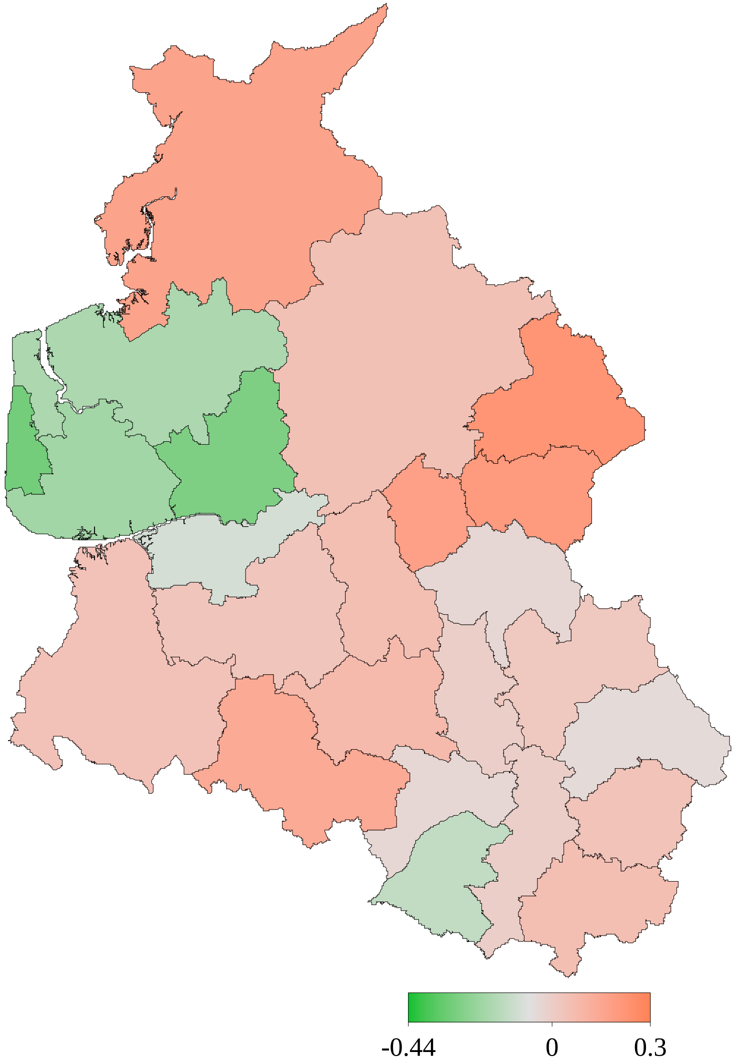
Effect of age at diagnosis.



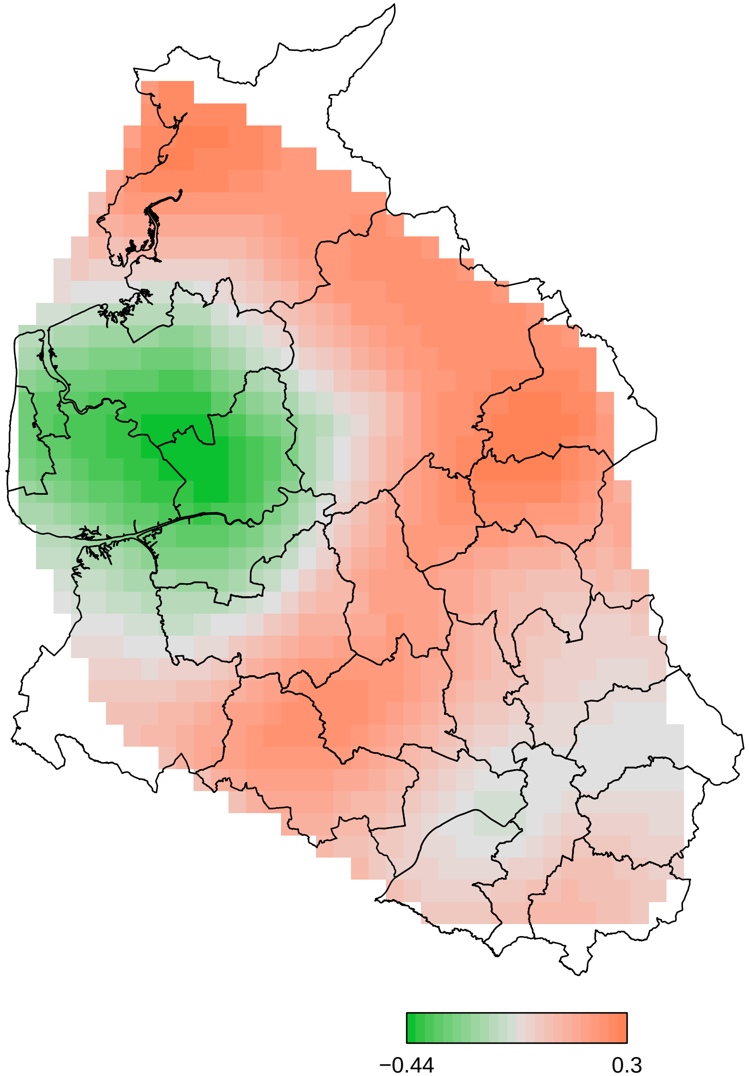
Effect of white blood cell count.



Effect of deprivation.



District-level analysis



Individual-level analysis

Structured Hazard Regression

- A general structured hazard regression model consists of an arbitrary combination of the following model terms:
  - Log baseline hazard $g_0(t) = \log(\lambda_0(t))$.
  - Time-varying effects $g_l(t)u_l$ of covariates u_l.
  - Nonparametric effects $f_j(x_j)$ of continuous covariates x_j.
  - Spatial effects $f_{spat}(s)$ of a spatial location variable s.
  - Interaction surfaces $f_{j,k}(x_j, x_k)$ of two continuous covariates.
  - Varying coefficient interactions $u_j f_k(x_k)$ or $u_j f_{spat}(s)$.
  - Frailty terms b_g (random intercept) or $x_j b_g$ (random slopes).

- Penalised splines for the baseline effect, time-varying effects, and nonparametric effects:

  – Approximate $f(x)$ (or $g(t)$) by a weighted sum of B-spline basis functions

$$f(x) = \sum \xi_j B_j(x).$$

  – Employ a large number of basis functions to enable flexibility.

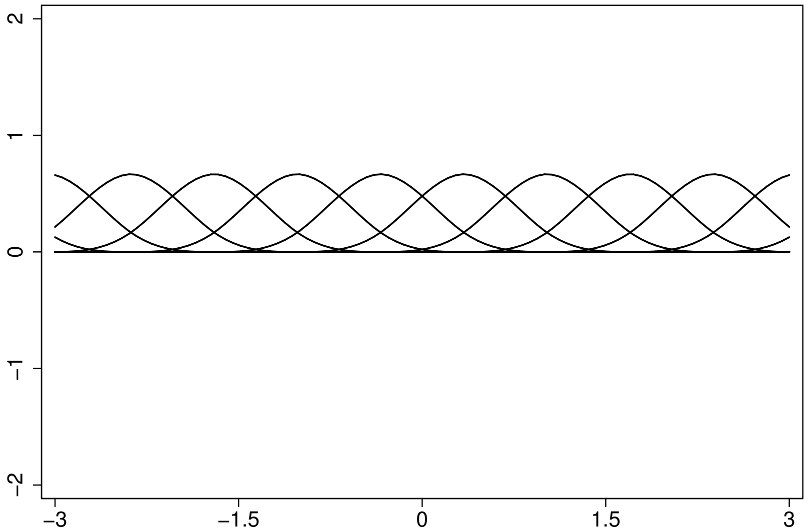
  – Penalise differences between parameters of adjacent basis functions to ensure smoothness:

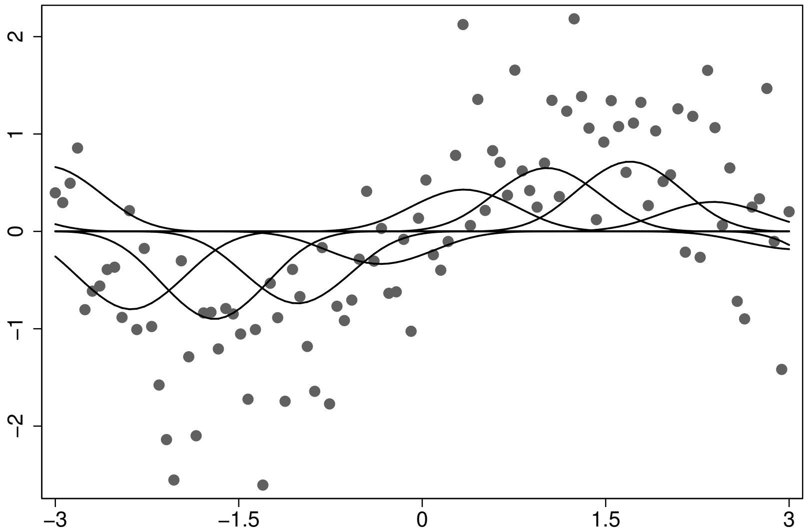
$$Pen(\xi|\tau^2) = \frac{1}{2\tau^2} \sum (\Delta_k \xi_j)^2.$$

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

$$\xi_j = \xi_{j-1} + u_j, \quad u_j \sim N(0, \tau^2) \qquad \text{(RW1)}.$$

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


2
1
0
−1
−2
−3
−1.5
0
1.5
3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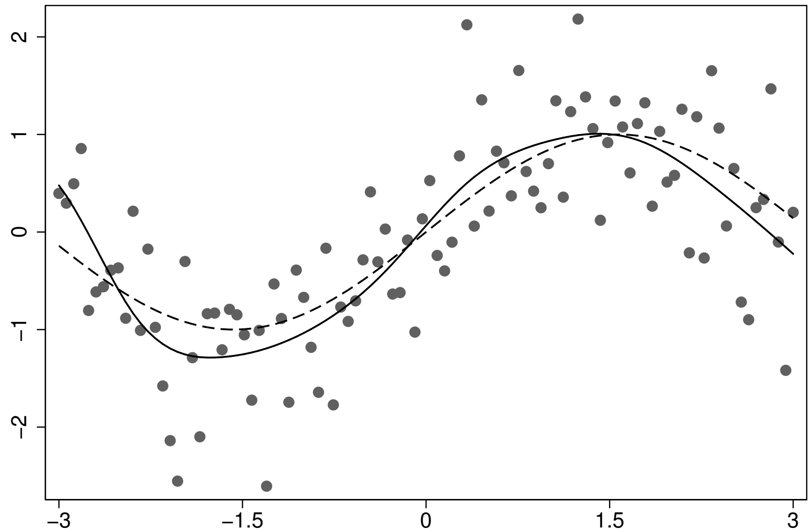
2
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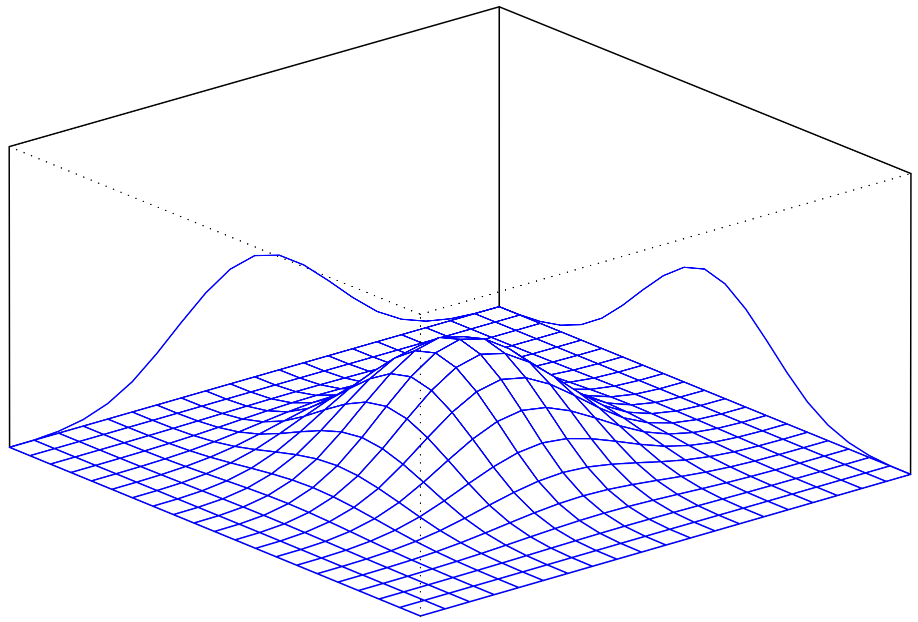
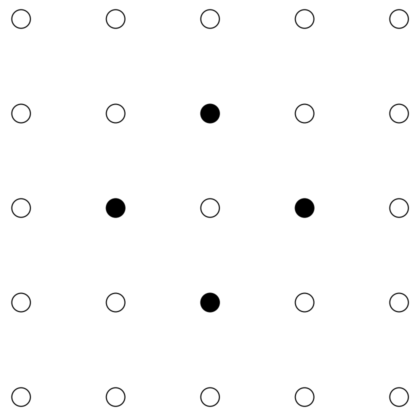
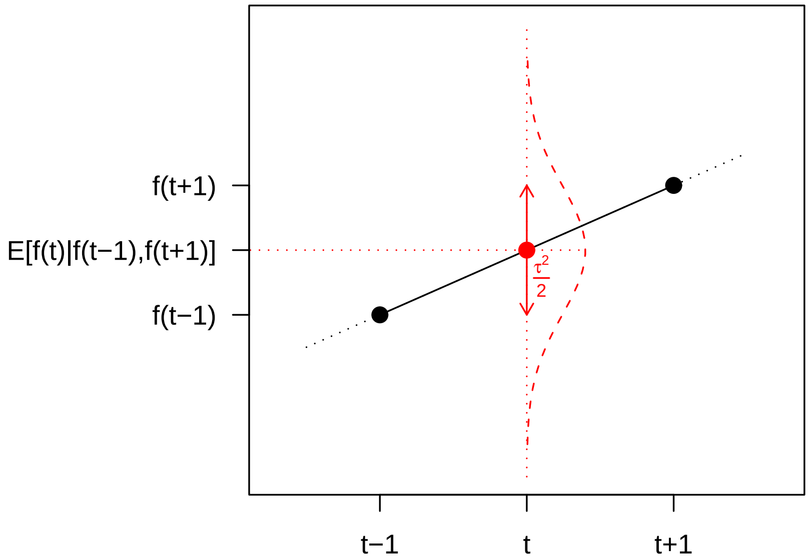
- Bivariate Tensor product P-splines for interaction surfaces:
  - Define bivariate basis functions (Tensor products of univariate basis functions).
  - Extend random walks on the line to random walks on a regular grid.

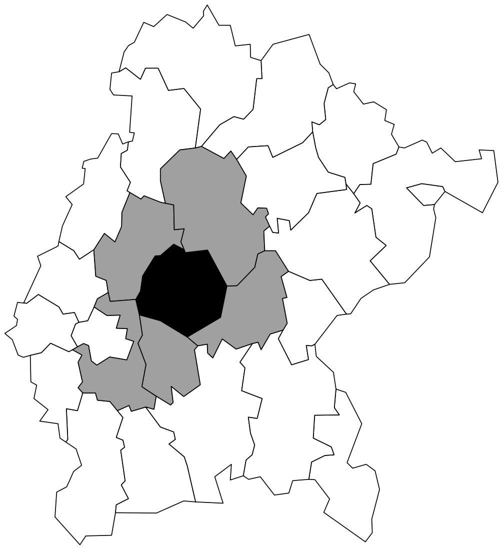




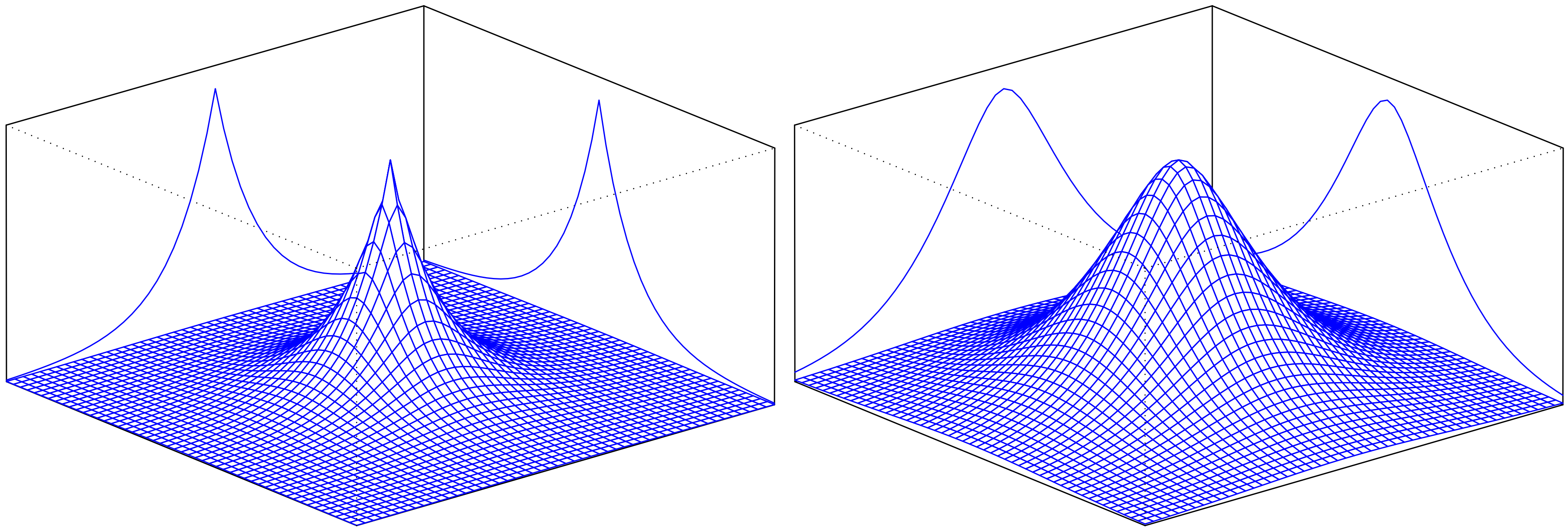
- Spatial effects for regional data $s \in \{1, \dots, S\}$: Markov random fields.
  - Bivariate extension of a first order random walk on the real line.
  - Define appropriate neighbourhoods for the regions.
  - Assume that the expected value of $f_{spat}(s) = \xi_s$ is the average of the function evaluations of adjacent sites:

$$\xi_s | \xi_{s'}, s' \neq s, \tau^2 \sim N\left(\frac{1}{N_s} \sum_{s' \in \partial_s} \xi_{s'}, \frac{\tau^2}{N_s}\right).$$





- Spatial effects for point-referenced data: Stationary Gaussian random fields.
  - Well-known as Kriging in the geostatistics literature.
  - Spatial effect follows a zero mean stationary Gaussian stochastic process.
  - Correlation of two arbitrary sites is defined by an intrinsic correlation function.
  - Can be interpreted as a basis function approach with radial basis functions.



- Cluster-specific frailty terms:
  - Account for unobserved heterogeneity.
  - Easiest case: i.i.d Gaussian frailty.
- All covariates in the discussed model terms are allowed to be piecewise constant time-varying.

Bayesian Inference

- Generic representation of structured hazard regression models:

$$\lambda(t) = \exp\left[x(t)'\gamma + f_1(z_1(t)) + \ldots + f_p(z_p(t))\right]$$

- For example:

$f(z(t)) = g(t)$	$z(t) = t$	log-baseline effect,
$f(z(t)) = u(t)g(t)$	$z(t) = (u,t)$	time-varying effect of $u(t)$,
$f(z(t)) = f(x(t))$	$z(t) = x(t)$	smooth function of a continuous covariate $x(t)$,
$f(z(t)) = f_{spat}(s)$	$z(t) = s$	spatial effect,
$f(z(t)) = f(x_1(t), x_2(t))$	$z(t) = (x_1(t), x_2(t))$	interaction surface,
$f(z(t)) = b_g$	$z(t) = g$	i.i.d. frailty b_g, g is a grouping index.

- The generic representation facilitates description of inferential details.

- All vectors of function evaluations f_j can be expressed as

$$f_j = Z_j \xi_j$$

with design matrix Z_j, constructed from $z_j(t)$, and regression coefficients ξ_j.

- Generic form of the prior for ξ_j:

$$p(\xi_j|\tau_j^2) \propto (\tau_j^2)^{-\frac{k_j}{2}} \exp\left(-\frac{1}{2\tau_j^2}\xi_j' K_j \xi_j\right)$$

- $K_j \geq 0$ acts as a penalty matrix, $\mathrm{rank}(K_j) = k_j \leq d_j = \dim(\xi_j)$.

- $\tau_j^2 \geq 0$ can be interpreted as a variance or (inverse) smoothness parameter.

- Relation to penalized likelihood: Penalty terms

$$P_{\lambda_j}(\xi_j) = \log[p(\xi_j|\tau_j^2)] = -\frac{1}{2}\lambda_j \xi_j' K_j \xi_j, \qquad \lambda_j = \frac{1}{\tau_j^2}.$$

- Likelihood for right censored survival times under the assumption of noninformative censoring:

$$\prod_{i=1}^{n} \lambda_i(T_i)^{\delta_i} \exp\left(-\int_0^{T_i} \lambda_i(t)dt\right),$$

where δ_i is the censoring indicator.

- In general, numerical integration has to be used to evaluate the cumulative hazard rate (e.g. the trapezoidal rule).

Fully Bayesian inference based on MCMC

- Assign inverse gamma prior to τ_j^2:

$$p(\tau_j^2) \propto \frac{1}{(\tau_j^2)^{a_j+1}} \exp\left(-\frac{b_j}{\tau_j^2}\right).$$

Proper for	$a_j > 0,\ b_j > 0$	Common choice: $a_j = b_j = \varepsilon$ small.
Improper for	$b_j = 0,\ a_j = -1$	Flat prior for variance τ_j^2,
	$b_j = 0,\ a_j = -\frac{1}{2}$	Flat prior for standard deviation τ_j.

- Conditions for proper posteriors in structured hazard regression: Enough uncensored observations and either
  - proper priors for the variances or
  - $a_j < b_j = 0$ and rank deficiency in the prior for ξ_j not too large.

- MCMC sampling scheme:
  - Metropolis-Hastings update for $\xi_j|\cdot$:

    Propose new state from a multivariate Gaussian distribution with precision matrix and mean

    $$P_j = Z_j' W Z_j + \frac{1}{\tau_j^2} K_j \qquad \text{and} \qquad m_j = P_j^{-1} Z_j' W (\tilde{y} - \eta_{-j}).$$

    IWLS-Proposal with appropriately defined working weights W and working observations $\tilde{y}$.
  - Gibbs sampler for $\tau_j^2|\cdot$:

    Sample from an inverse Gamma distribution with parameters

    $$a_j' = a_j + \frac{1}{2}\text{rank}(K_j) \qquad \text{and} \qquad b_j' = b_j + \frac{1}{2}\xi_j' K_j \xi_j.$$

- Efficient algorithms make use of the sparse matrix structure of P_j and K_j.

Empirical Bayes inference based on mixed model methodology

- Consider the variances τ_j^2 as unknown constants to be estimated.
- Idea: Consider ξ_j a correlated random effect with multivariate Gaussian distribution and use mixed model methodology.
- Problem: In most cases partially improper random effects distribution.
- Mixed model representation: Decompose

$$\xi_j = X_j \beta_j + Z_j b_j,$$

where

$$p(\beta_j) \propto const \qquad \text{and} \qquad b_j \sim N(0, \tau_j^2 I_{k_j}).$$

$\Rightarrow$ β_j is a fixed effect and b_j is an i.i.d. random effect.

- This yields the variance components model

$$\lambda(t;\cdot) = \exp\left[x'\beta + z'b\right],$$

where in turn

$$p(\beta) \propto const \qquad \text{and} \qquad b \sim N(0, Q).$$

- Obtain empirical Bayes estimates / penalized likelihood estimates via iterating
  - Penalized maximum likelihood for the regression coefficients β and b.
  - Restricted Maximum / Marginal likelihood for the variance parameters in Q:

$$L(Q) = \int L(\beta, b, Q) p(b) d\beta db \rightarrow \max_{Q}.$$

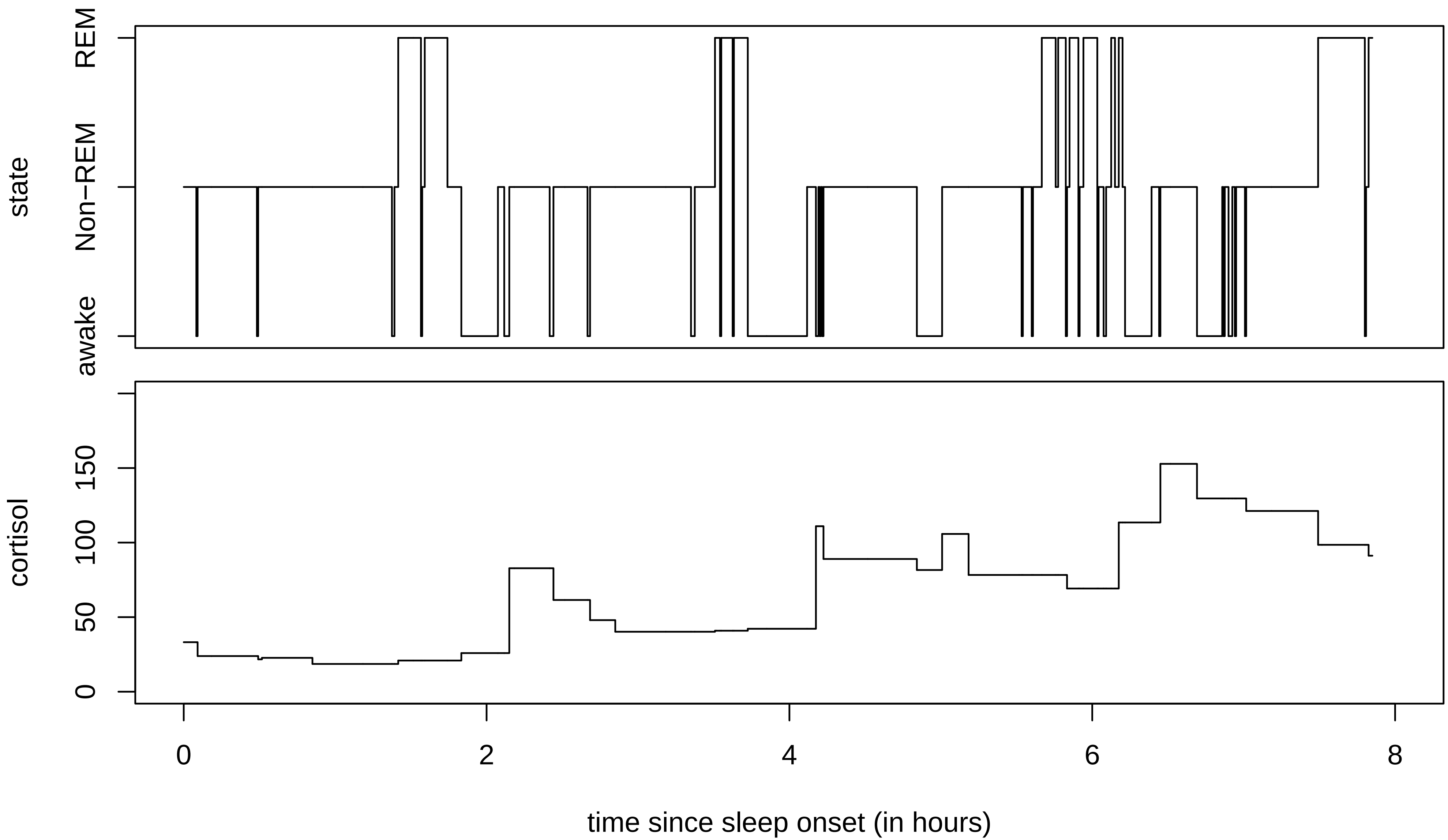
- Involves Laplace approximation to the marginal likelihood (similar as in the previous talk by Håvard Rue).

- Corresponds to REML estimation of variances in Gaussian mixed models.

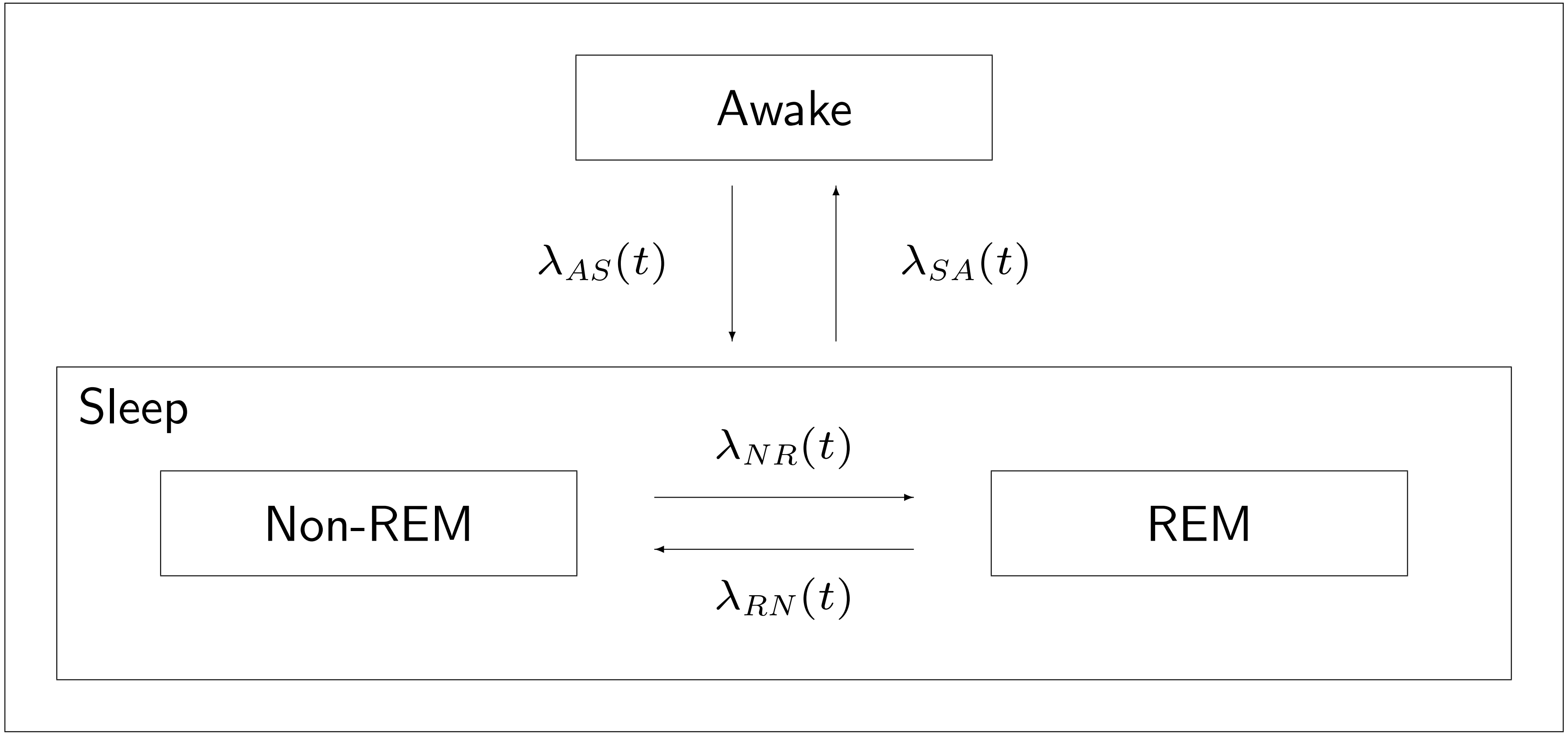
Human Sleep Data

- Consider individual human sleep data as independent realisations of time-continuous stochastic processes with discrete state space {awake, REM, non-REM}.
- Compact description of such a process in terms of transition intensities between these states.
- Simple approaches: Markov or Semi-Markov processes.
- Limitations / Questions:
  - Changing dynamics of human sleep over night.
  - Individual sleeping habits to be described by covariates.
  - Only a small number of covariates is available (unobserved heterogeneity).

$\Rightarrow$ Model the transition intensities in analogy to survival models.


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

- Simplified structure for the transitions:



- Model for the transitions:

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

where

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

- Use penalized splines for the baseline and time-varying effects.
- I.i.d. Gaussian priors for the frailty terms (with transition-specific variances).
- The likelihood contribution for individual i can be constructed based on a counting process formulation of the model:

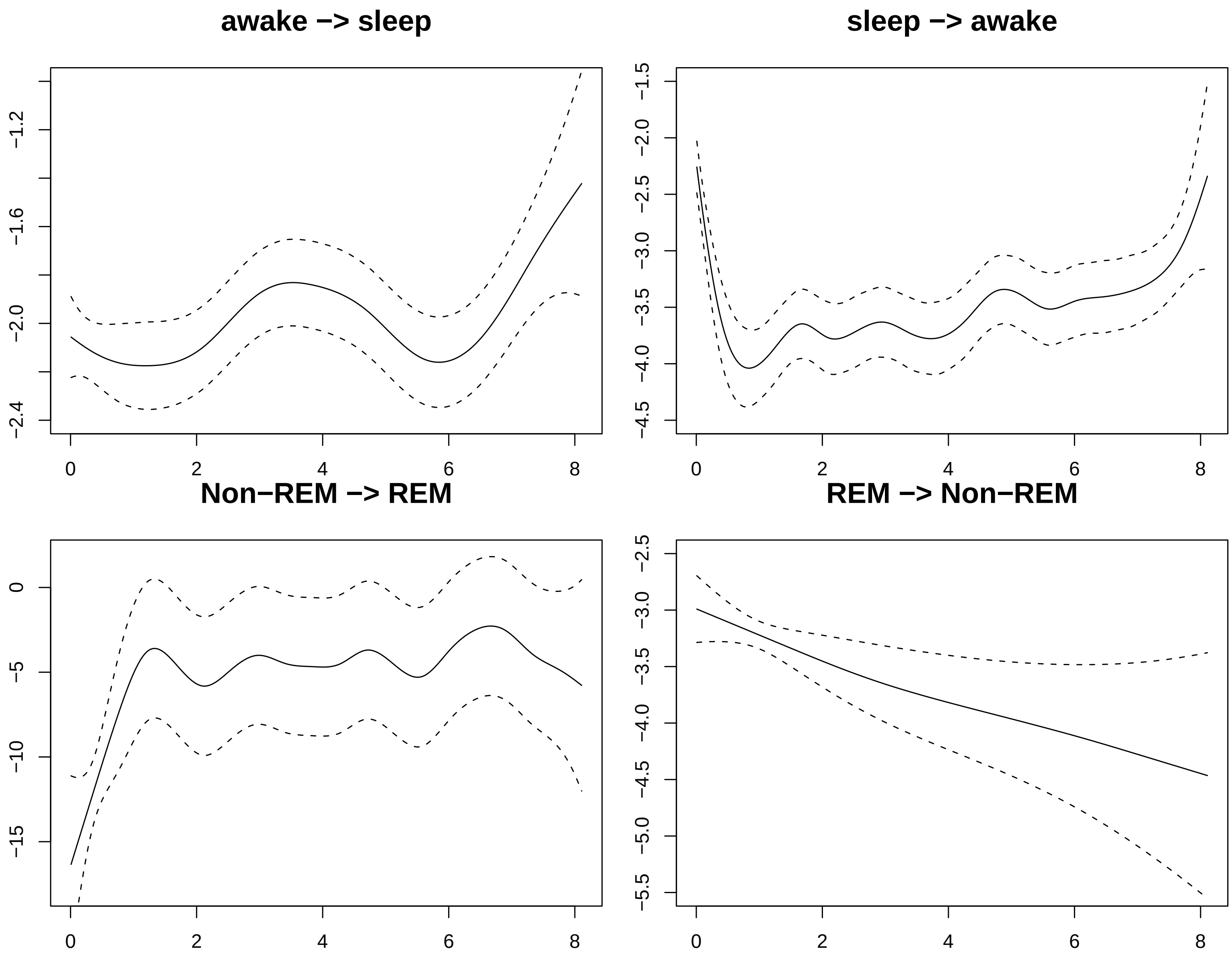
$$\begin{aligned} l_i &= \sum_{h=1}^{k} \left[\int_0^{T_i} \log(\lambda_{hi}(t)) dN_{hi}(t) - \int_0^{T_i} \lambda_{hi}(t) Y_{hi}(t) dt \right] \\ &= \sum_{j=1}^{n_i} \sum_{h=1}^{k} \left[\delta_{hi}(t_{ij}) \log(\lambda_{hi}(t_{ij})) - Y_{hi}(t_{ij}) \int_{t_{i,j-1}}^{t_{ij}} \lambda_{hi}(t) dt \right].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

$N_{hi}(t)$	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 individal i.
$\delta_{hi}(t_{ij})$	transition indicator for type h transition.

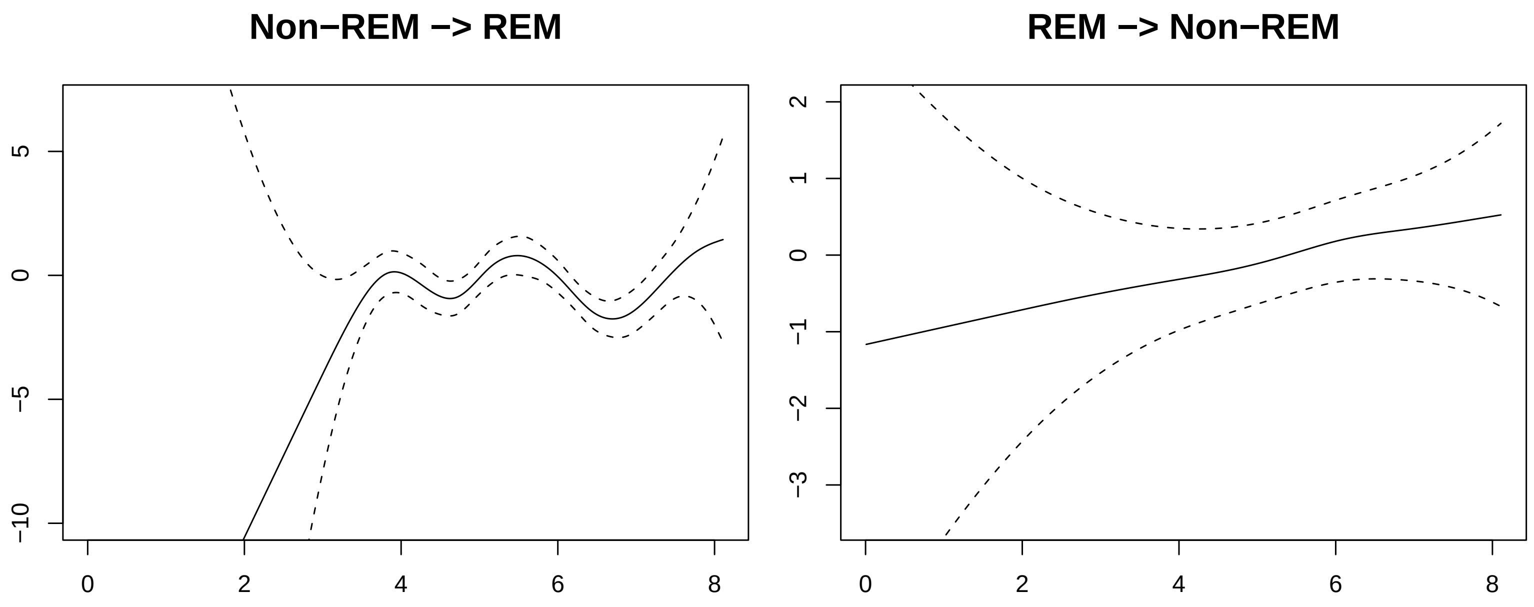
⇒ Concepts from survival analysis can be adapted.

- In particular:
  - Fully Bayesian inference based on MCMC and
  - Mixed model based empirical Bayes inference.

- Baseline effects:



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



Software

- Estimation was carried out using BayesX.
- Public domain software package for Bayesian inference in geoadditive and related models.

- Available from

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

Conclusions

- Unified framework for general regression models describing the hazard rate of survival models.
- Bayesian inference based on MCMC or mixed model methodology.
- Extendable to models for transition intensities in multi state models.
- Future work:
  - More general censoring mechanisms.
  - Conditions for propriety of posteriors.
  - Joint modelling of covariates and duration times.

References

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