Modelling geoadditive survival data

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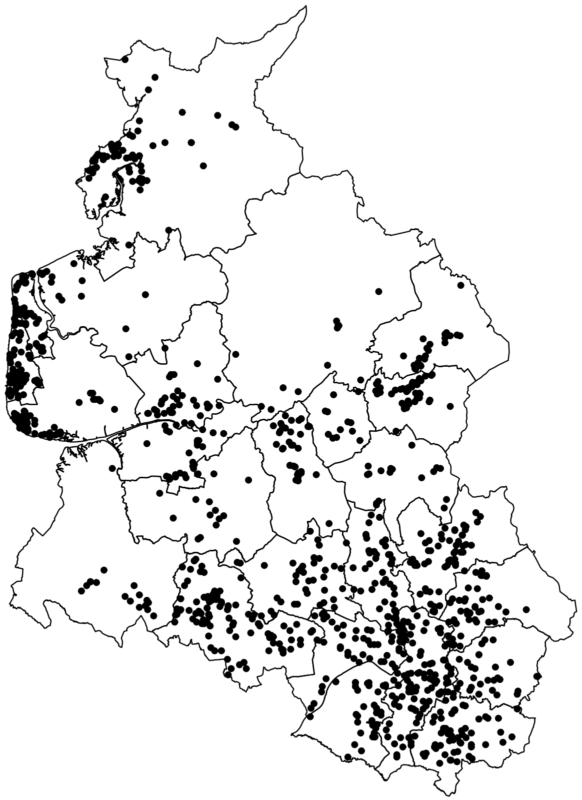
Leukemia survival data

- 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:
  - Estimate the baseline simultaneously with 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.

Structured hazard regression

- Replace usual parametric predictor with a flexible semiparametric predictor

$$\lambda(t;\cdot) = \lambda_0(t)\exp[f_1(age) + f_2(wbc) + f_3(tpi) + f_{spat}(s_i) + \gamma_1 sex]$$

and absorb the baseline

$$\lambda(t;\cdot) = \exp[f_0(t) + f_1(age) + f_2(wbc) + f_3(tpi) + f_{spat}(s_i) + \gamma_1 sex]$$

where

  - $f_0(t) = \log(\lambda_0(t))$ 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.

- $f_0(t), f_1(age), f_2(wbc), f_3(tpi)$: P-splines
  - Approximate f_j by a B-spline of a certain degree (basis function approach).
  - Penalize differences between parameters of adjacent basis functions to ensure smoothness.
  - Alternatives: Random walks, more general autoregressive priors.

- $f_{spat}(s)$: District-level analysis
  - Markov random field approach.
  - Generalization of a first order random walk to two dimensions.
  - Consider two districts as neighbors if they share a common boundary.
  - Assume that the expected value of $f_{spat}(s)$ is the average of the function evaluations of adjacent sites.

- $f_{spat}(s)$: Individual-level analysis
  - Stationary Gaussian random field (kriging).
  - Spatial effect follows a zero mean stationary Gaussian stochastic process.
  - Correlation of two arbitrary sites is defined by an intrinsic correlation function.
  - Low-rank approximations to Gaussian random fields.
- Extensions
  - Cluster-specific frailties.
  - Surface smoothers based on two-dimensional P-splines.
  - Varying coefficient terms with continuous or spatial effect modifiers.
  - Time-varying effects based on varying coefficient terms with survival time as effect modifier.
- Structured hazard regression handles all model terms in a unified way.

- Express f_j as the product of a design matrix Z_j and regression coefficients β_j.

- Rewrite the model in matrix notation as

$$\log(\lambda(t;\cdot)) = Z_0(t)\beta_0 + Z_1\beta_1 + Z_2\beta_2 + Z_3\beta_3 + Z_{spat}\beta_{spat} + U\gamma.$$

- Bayesian approach: Assign an appropriate prior to β_j.

- Frequentist approach: Assume (correlated) random effects distribution for β_j.

- All priors can be cast into the general form

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

  where K_j is a penalty matrix and τ_j^2 is a smoothing parameter.

- Type of the covariate and prior beliefs about the smoothness of f_j determine special Z_j and K_j.

Mixed model based inference

- Each parameter vector β_j can be partitioned into an unpenalized part (with flat prior) and a penalized part (with i.i.d. Gaussian prior), i.e.

$$\beta_j = Z_j^{unp} \beta_j^{unp} + Z_j^{pen} \beta_j^{pen}$$

- This yields a variance components model

$$\eta = X^{unp} \beta^{unp} + X^{pen} \beta^{pen}$$

with

$$p(\beta^{unp}) \propto const \qquad\qquad \beta^{pen} \sim N(0, \Lambda)$$

and

$$\Lambda = \mathrm{blockdiag}(\tau_0^2 I, \dots, \tau_{spat}^2 I).$$

- Regression coefficients are estimated via a Newton-Raphson-algorithm.

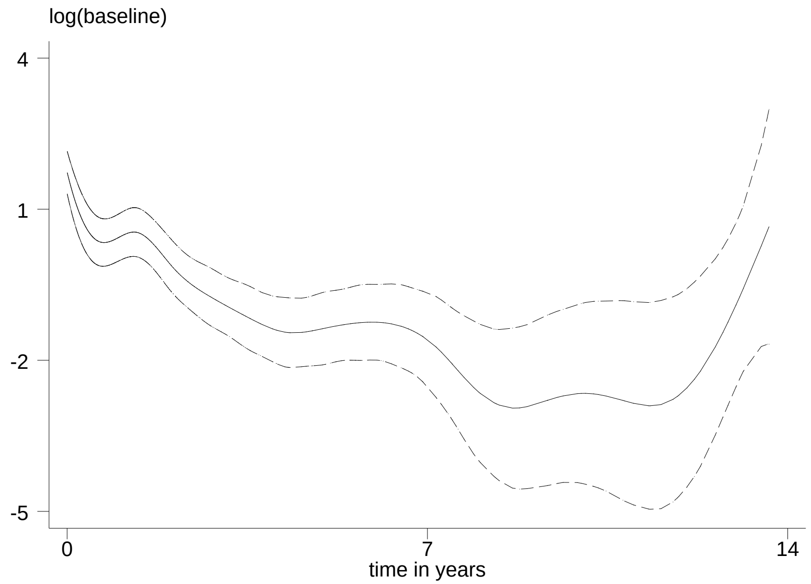
- Numerical integration has to be used to evaluate the log-likelihood and its derivatives.

- The variance components representation with proper priors allows for restricted maximum likelihood / marginal likelihood estimation of the variance components:

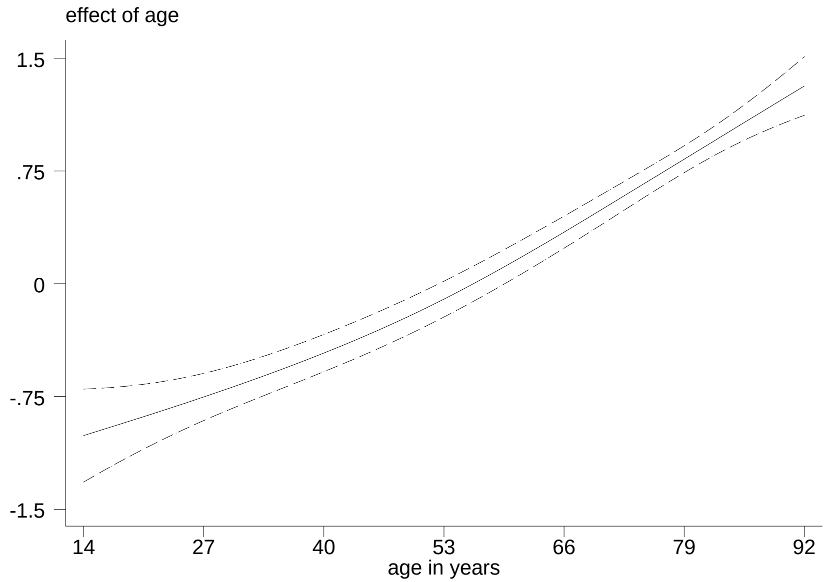
$$L(\Lambda) = \int L(\beta^{unp}, \beta^{pen}, \Lambda) p(\beta^{pen}) d\beta^{pen} d\beta^{unp} \rightarrow \max_{\Lambda}.$$

- The marginal likelihood can not be derived analytically.
- Some approximations lead to a simple Fisher-scoring-algorithm.
- Proved to work well in simulations and applications.
- We obtain empirical Bayes / posterior mode estimates.

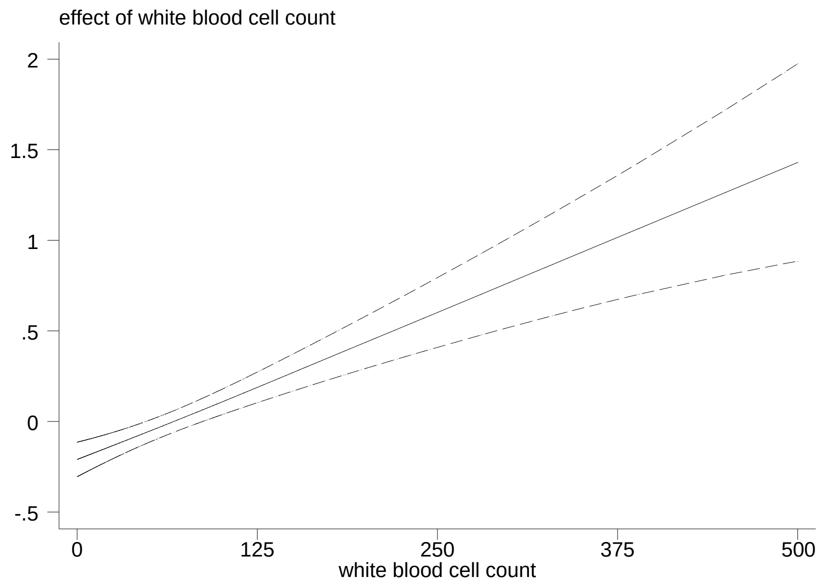
Results



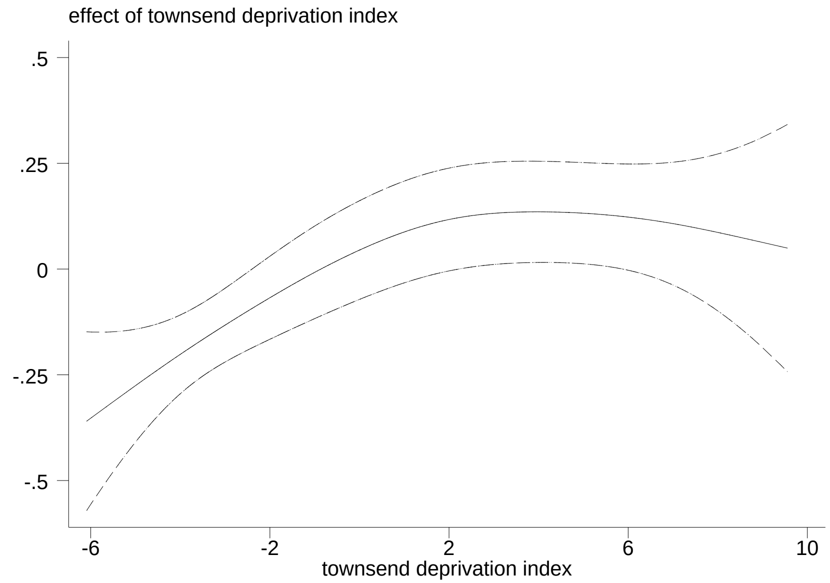
Log-baseline hazard.



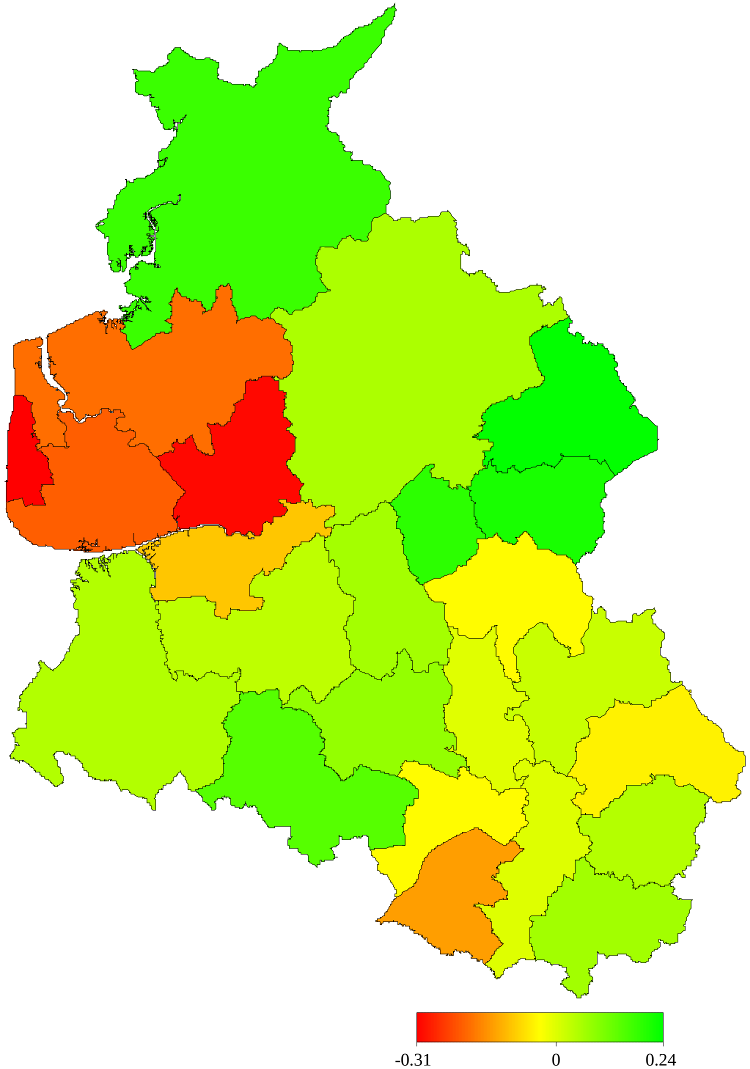
Effect of age at diagnosis.



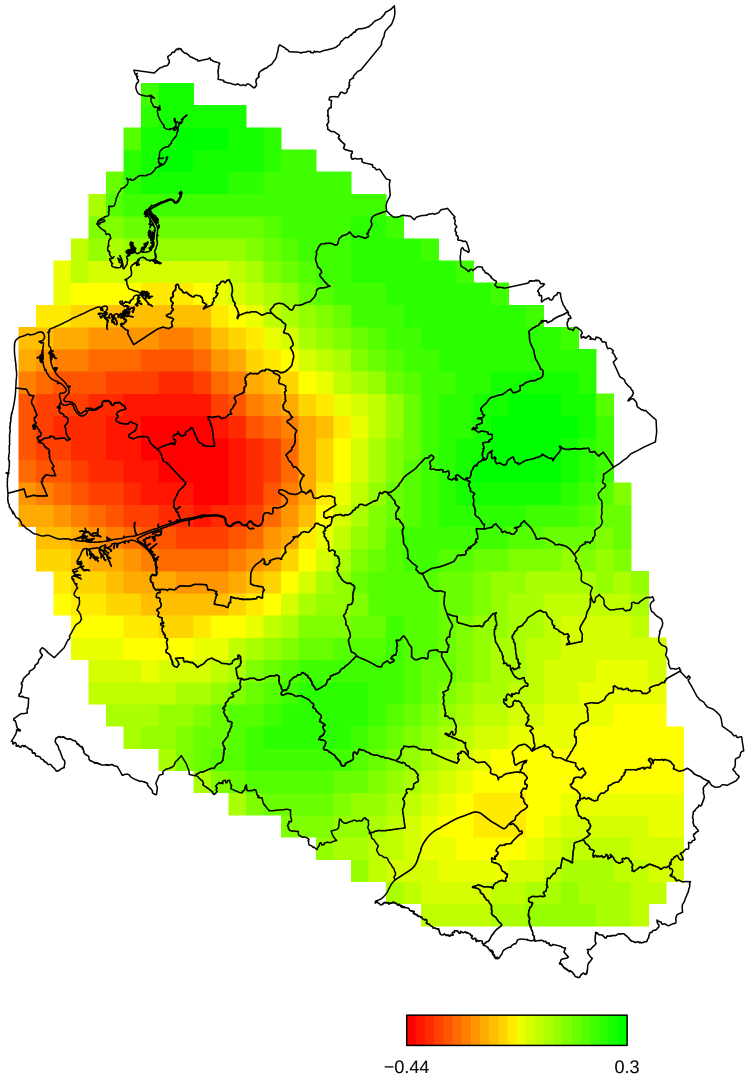
Effect of white blood cell count.



Effect of deprivation.



District-level analysis



Individual-level analysis

Software

- Estimation was carried out using BayesX, a public domain software package for Bayesian inference.

- Available from

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

- Features (within a mixed model setting):
  - Responses: Gaussian, Gamma, Poisson, Binomial, ordered and unordered multinomial, Cox models.
  - Nonparametric estimation of the log-baseline and time-varying effects based on P-splines.
  - Continuous covariates and time scales: Random Walks, P-splines, autoregressive priors for seasonal components.
  - Spatial Covariates: Markov random fields, stationary Gaussian random fields, two-dimensional P-Splines.
  - Interactions: Two-dimensional P-splines, varying coefficient models with continuous and spatial effect modifiers.
  - Random intercepts and random slopes (frailties).

Discussion

- Comparison with fully Bayesian approach based on MCMC (Hennerfeind et al., 2003):

  Cons:

  - Credible intervals rely on asymptotic normality.
  - Only plug-in estimates for functionals.
  - Approximations for marginal likelihood estimation.

  Pros:

  - No questions concerning mixing and convergence.
  - No sensitivity with respect to prior assumptions on variance parameters.
  - Somewhat better point estimates (in simulations).
  - Numerical integration is required less often.

- Future work:
  - More general censoring / truncation schemes.
  - Event history / competing risks models

References

- Kneib, T. and Fahrmeir, L. (2004): A mixed model approach for structured hazard regression. SFB 386 Discussion Paper 400, University of Munich.

- Fahrmeir, L., Kneib, T. and Lang, S. (2004): Penalized structured additive regression for space-time data: A Bayesian perspective. *Statistica Sinica*, 14, 715-745.

- Available from

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