Aurélien BELOT
Faculty of Epidemiology and Population Health, Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine - London, United Kingdom

A multilevel excess hazard model to estimate net survival on hierarchical data allowing for non-linear and non-proportional effects of covariates.

Un modèle multi-niveaux du taux de mortalité en excès pour estimer la survie nette sur des données hiérarchiques, avec prise en comptes des effets non linéaires et non proportionnel des covariables.

décembre 2015

A multilevel excess hazard model to estimate net survival on hierarchical data allowing for non-linear and non-proportional effects of covariates

Hadrien Charvat[1], Laurent Remontet[2], Nadine Bossard[2], Laurent Roche[2], Olivier Dejardin[3], Bernard Rachet[4], Guy Launoy[3], **Aurélien Belot[4]**

And the CENSUR Working Survival Group

[1] Epidemiology and Prevention Group, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan
[2] Hospices Civils de Lyon, Service de Biostatistique, F-69003, Lyon, France
[3] U1086 INSERM, Cancers & Preventions, Avenue du Général Harris, 14076 Caen, France
[4] Cancer Research UK Cancer Survival Group, Faculty of Epidemiology and Population Health, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Webinar QUANTIM, 11/12/2015

Context

- Interest in the relationship between socio-economic status and cancer survival: important public health issue
- Mostly based on population-based cancer registry data

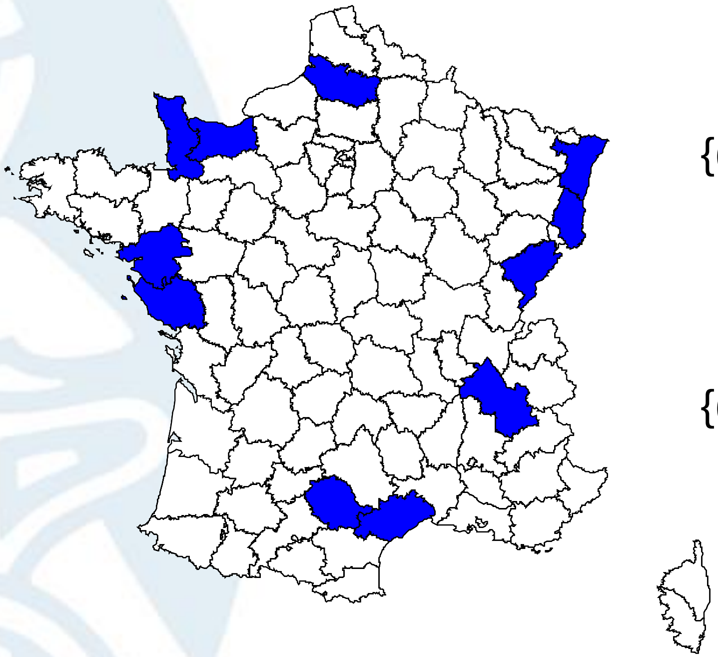
➔ socio-economic level of the patients is described by an ecological measure

➔ No cause of death information

- Hierarchical structure of the data: assumption of independence of the survival times is violated

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Context



$\{(T_{67,1},\delta_{67,1}), (T_{67,2},\delta_{67,2}), \ldots, (T_{67,N},\delta_{67,N})\}$

$\{(T_{38,1},\delta_{38,1}), (T_{38,2},\delta_{38,2}), \ldots, (T_{38,N},\delta_{38,N})\}$

These survival times in one *département* may be correlated (shared factors as environmental, health resources,...)

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Context

- Relationship between socio-economic status and cancer survival: important public health issue
- Mostly based on population-based cancer registry data

➔ socio-economic level of the patients is described by an ecological measure

- Hierarchical structure of the data: assumption of independence of the survival times is violated

Mixed effect models (multilevel models) provide a satisfying and convenient theoretical framework to handle such hierarchical structure by introducing a random effect at the cluster level

Objective

Mixed effect models, or shared frailty models, have been well developed in the context of **overall** survival.

But lack of tools/development in the context of net survival/excess hazard

➔ Objective

- To propose an approach allowing to fit an **excess** hazard model with a random effect, with non linear and time-dependent effect
- To evaluate the performances of the proposed approach in a simulation study

Outline

- The “classical” hazard model with a random effect (shared frailty)
- The excess hazard setting
- Combining the two: the proposed excess hazard model with a random effect
  - Definition and optimisation method
  - Performances: simulation study
- Application
- Conclusion and discussion

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

The classical hazard model with a random effect, "shared frailty"

- In survival analysis, random effect is usually called "frailty" (historical reasons - Vaupel, 1979)
- The frailty, u, can be viewed as a random variable that acts multiplicatively on the baseline hazard (Duchateau 2008, Wienke 2011)
- Multivariate shared frailty

$$\lambda(t, x_{ij}, u_i) = \lambda_0(t) u_i \exp(\beta x_{ij}) = \lambda_0(t) \exp(\beta x_{ij} + w_i)$$

Assumption : each geographical unit i has a frailty value u_i [=$log(w_i)$] which is shared by individuals j observed in this unit

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

The classical hazard model with a random effect

- To fit a shared frailty hazard model, the analyst has to choose :
  - The distribution of the frailty
  - The distribution of the baseline hazard

- A common choice is
  - The parametric setting with a Weibull baseline hazard and
  - A gamma distribution for the frailty

Why ?

The classical hazard model with a random effect

Summary in 3 steps

- Conditional likelihood for the i^{th} cluster

$$L_i^C(\beta|u_i) = \prod_{j=1}^{N_i} \left(\lambda_0(t_{ij})u_i \exp(\beta x_{ij})\right)^{\delta_{ij}} \exp(-\Lambda_0(t_{ij})u_i \exp(\beta x_{ij}))$$

- Marginal likelihood for the i^{th} cluster

$$L_i^M(\beta) = \int L_i^C(\beta|u) f_U(u)du$$

⟵ With a parametric model and a frailty gamma, this integral can be expressed analytically when the frailty is integrated out

- Full marginal likelihood

$$L(\beta) = \prod_{i=1}^{I} L_i^M(\beta)$$

➔ Optimization with Newton-Raphson routine

The excess hazard setting

Idea: to estimate the disease-specific hazard using the overall (i.e. observed) hazard and the other-cause hazard

This latter approximated by population hazard (i.e. all cause).

The overall mortality hazard, λ, is split into an excess mortality hazard, λ_+, and a population (or expected) hazard, λ_P

$$\lambda(t, a, \mathbf{x}, \mathbf{z}) = \lambda_+(t, \mathbf{x}) + \lambda_P(a + t, \mathbf{z})$$

where t is the time since diagnosis, a the age at diagnosis, $\mathbf{x}_\mathrm{i}$ a vector of covariates, and $\mathbf{z}$ a vector of population characteristics

λ_+ is the quantity to be estimated

The excess hazard model with a random effect

Back to the Summary in 3 steps (with w_i instead of u_i)

- Conditional likelihood for the i^{th} cluster

$$L_i^C(\beta|w_i) = \prod_{j=1}^{N_i} \left(\lambda_0(t_{ij})\exp(\beta x_{ij} + w_i) + \lambda_P(a_{ij} + t_{ij}, z_{ij})\right)^{\delta_{ij}} \exp(-\Lambda_0(t_{ij})\exp(\beta x_{ij} + w_i))$$

- Marginal likelihood for the i^{th} cluster

$$L_i^M(\beta) = \int L_i^C(\beta|w) f_W(w) dw$$

← BUT

Now, this integral can no more be expressed analytically

➔ Need of specific techniques. Here we will use numerical integration

Numerical integration technique

General principle of the Gauss-Hermite quadrature

$$\int L_d(\beta|u) f_U(u) du \approx \sum_{q=1}^{Q} w_q L_d(z_q)$$

where

$f_U(u)$ is the normal density

Q number of quadrature points

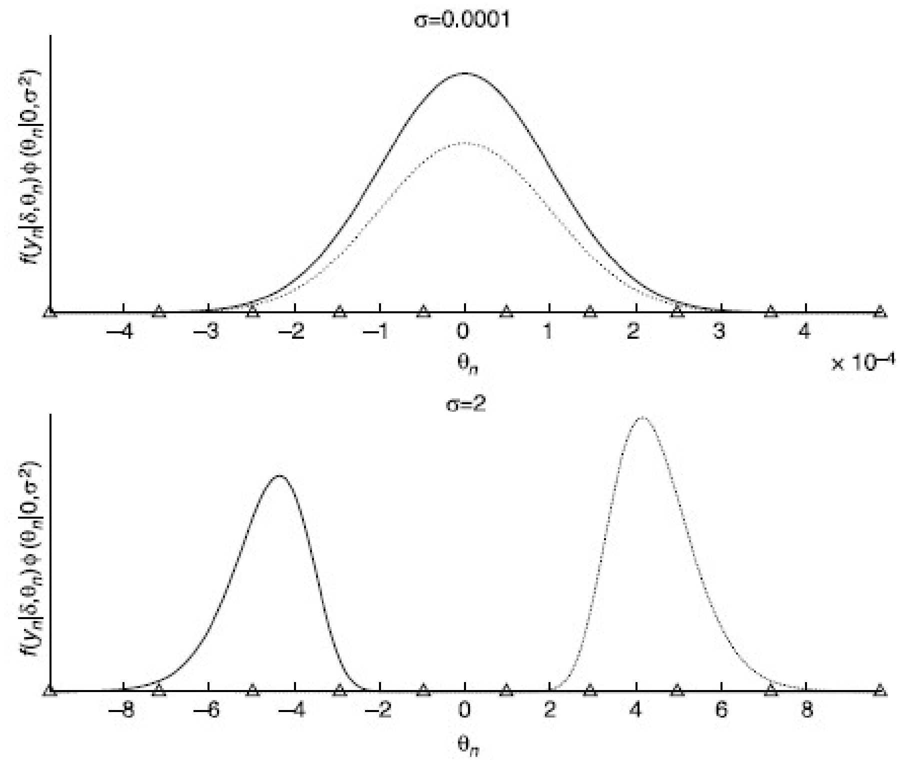
w_q and z_q are the weigth and the quadrature points

of the Q^{th} order Hermite polynomial

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Numerical integration technique

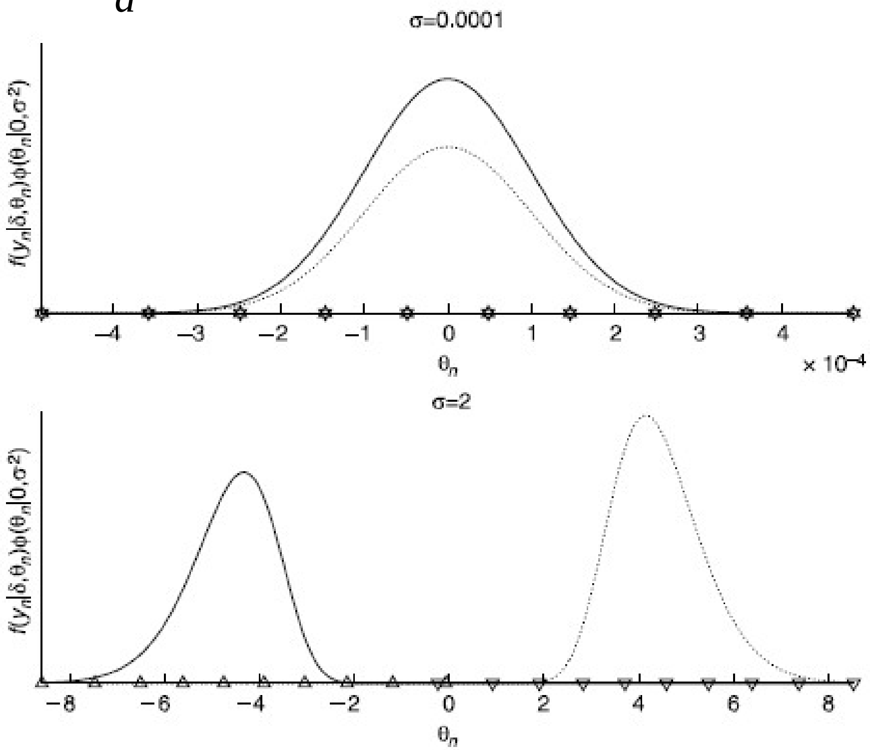
Limit of the Gauss-Hermite quadrature: the nodes z_q and weights w_q do not depend on the conditional likelihood function L_d



Tuerlinckx F et al., British Journal of Mathematical and Statistical Psychology, 2006

Numerical integration technique

General principle of the Adaptive Gauss-Hermite quadrature: to adapt the nodes and weights according to the conditional likelihood function L_d



Tuerlinckx F et al., British Journal of Mathematical and Statistical Psychology, 2006

Mixed effect excess hazard model

Definition

$$\lambda_+(t, \mathbf{x}_{ij}, w_i) = \lambda_0(t)\exp(\beta x_{1,ij} + f(t) * x_{2,ij} + g(x_{2,ij}) + w_i)$$

where

λ_0 is the baseline excess hazard (modelled with a cubic regression spline)

$\mathbf{x}_{\mathbf{ij}}$ is a vector of covariates measured at the individual level for patient j in cluster i

The functions f and g are cubic regression splines that allow non-proportional effect and non-linear effect, respectively.

The parameter w_i is the random effect of cluster i, which is shared by all individuals from this cluster. It is assumed to follow a normal distribution with mean 0 and variance σ^2.

Allows more than one time-dependent and non-linear effects

Mixed effect excess hazard model

Optimisation

The Full log-likelihood function is defined using adaptive Gaussian quadrature, and the cumulative excess hazard was computed using Gauss-Legendre quadrature method

Maximisation of the full log-likelihood using optimisation routine (function `nlm` in R)

R-Package `mexhaz`, including some C routines

Simulation study – scenarios overview

In **scenarios A and B**, the impact of the **Design** and the values of the variance of the random effect were studied (number of clusters & number of patients by cluster)

- scenario A: **Balanced-Design**: number of patients by cluster is fixed
- scenario B: **UnBalanced-Design** number of patients by cluster is variable

In the **scenario C**, we additionally studied the ability of our approach to model **non proportional effect** (**NPH**) of covariates
(unbalanced design)

In the **scenario D**, we additionally check the **robustness** of our approach in case of miss-specified distribution of the random effect
(unbalanced design)

Simulation study
Design of the simulated data

- Age : 25% of [30, 65], 35% of [65, 75], 40% of [75, 85]
following an uniform distribution in each age-class
- Sex : Binomial distribution with P(sex=man)=0.5
- Deprivation Index (DI) : Normal(0,sd=1.5)
- Cluster: the number *NClus* of clusters (D = 10, 20, 50, 100)

Balanced-Design: the number of patients by cluster is exactly equal to 10, 20, 50 or 100.

UnBalanced-Design: the number of patients by cluster is variable and equal, on average, to 10, 20, 50 or 100.

One additional simulated condition with 800 clusters with 10 patients on average

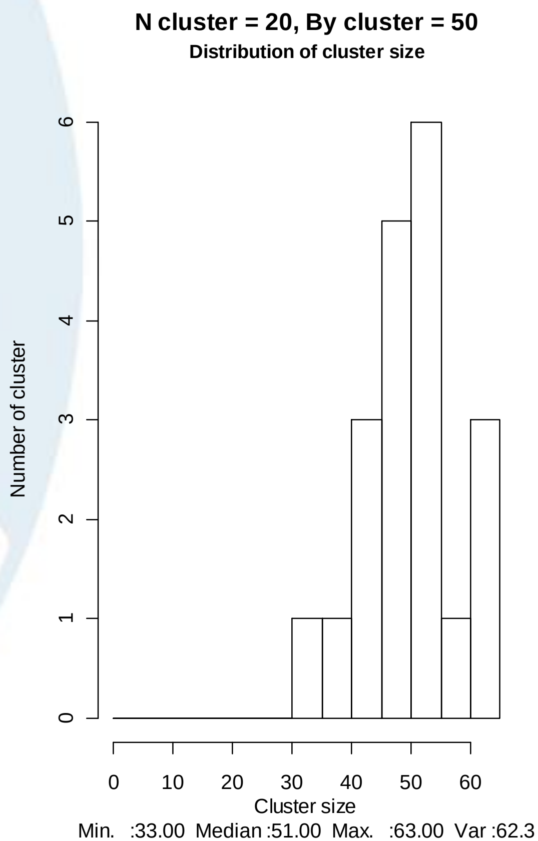
Simulation study
Design of the simulated data

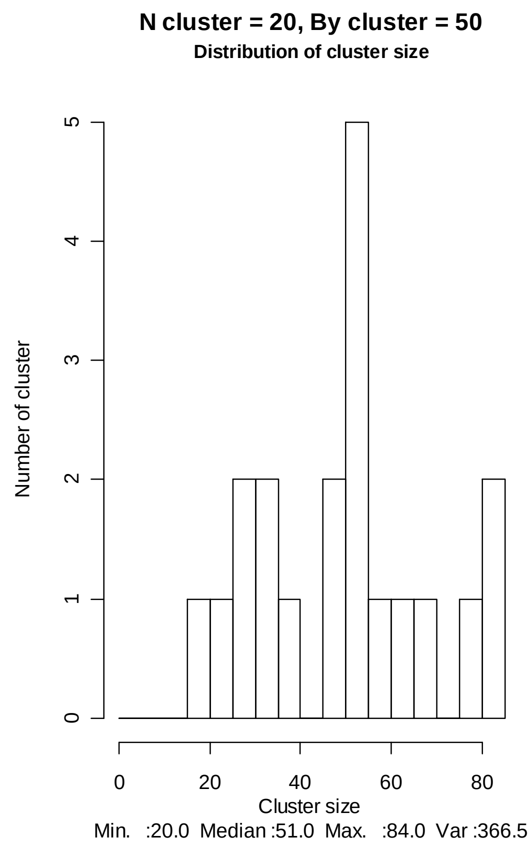
Illustration of the UnBalanced-Design

Low

heterogeneity

unbal=0.25





High

heterogeneity

unbal=0.5

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Simulation study
Data generation

$$\lambda_+(t, \mathbf{x}_{ij}, DI_i, w_i) = \lambda_0(t, \xi)\exp(\beta_{age} age_{ij} + \beta_{sex} sex_{ij} + \beta_{DI} DI_i + w_i)$$

- Baseline hazard: Weibull distribution with parameters scale λ = 0.25 and shape ρ = 0.7
- Age effect: Hazard ratio equal to exp(0.05) for 1 year increase
- Sex effect: Hazard ratio equal to exp(1) (Men *vs.* women)
- Di effect: Hazard ratio equal to exp(0.02) for 1 unit increase
- Random effect w_i: Normal law with mean 0 and standard deviation = 0.25, 0.5 or 1

➔ Time to death due to cancer T_1

- Time to death due to other causes T_2 : yearly piecewise exponential law using population lifetable

➔ Final time = min(T_1;T_2).

1000 samples were simulated for each scenario

Simulation study
Modifications of the data generation

For the scenarios "**NPH**"

- Times to cancer-death in men = Weibull (shape=0.7, scale=0.25)
- Times to cancer-death in women = Weibull (shape=0.8, scale=0.18).

➔ the Hazard Ratio between Men vs. Women is time-dependent

$$\lambda_{+}(t, \mathbf{x}_{ij}, w_i) = \lambda_0(t)\exp(\beta_{age} age + \beta_{sex}(t) sex + \beta_{DI} DI_i + w_i)$$

For the scenarios "**Robustness**"

The random effect w was drawn from a normal distribution with standard deviation σ equal to 0.5 but

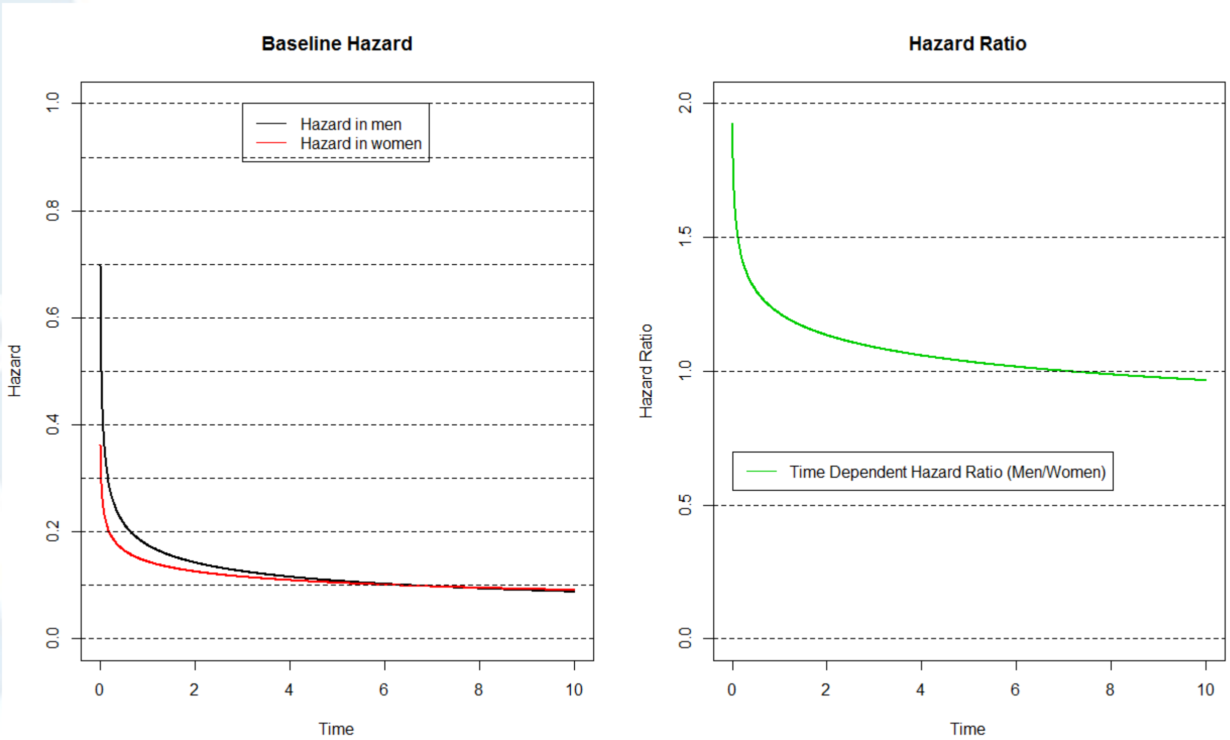
- with mean -1 for the first half of the clusters, and
- with mean 1 for the other half.

(standard deviation of the resulting distribution is equal to $\sqrt{1.25} \approx 1.12$)

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Simulation study
Modifications of the data generation

- For the scenarios “**NPH**” :



Models used for the analysis of the simulated data

- In the scenarios "**Design**" and "**Robustness**",

$$\lambda_{+}(t, \mathbf{x}_{ij}, DI_i, w_i) = \lambda_0(t)\exp(\beta_{age} age_{ij} + \beta_{sex} sex_{ij} + \beta_{DI} DI_i + w_i)$$

With baseline hazard modelled either as Weibull or Cubic B-splines (1 knot at 1 year)

- In the scenarios "**NPH**", cubic B-splines (1 knot at 1 year) used to model the baseline hazard and the time-dependent effect of sex

$$\lambda_{+}(t, \mathbf{x}_{ij}, DI_i, w_i) = \lambda_0(t)\exp(\beta_{age} age_{ij} + \beta_{sex}(t) sex_{ij} + \beta_{DI} DI_i + w_i)$$

Simulation study Indicators provided

The bias

- difference between the average of the 1000 estimated values and the simulated (true) value

The percentage bias

- 100*(the bias divided by the true value)

The empirical coverage probability (CP)

- proportion of estimated 95% confidence intervals that included the true value of the parameter

The root mean square error (RMSE)

- the square root of the average of the squared differences between the 1000 estimated values and the true value

Simulation results - summary

- Scenarios **Design, balanced and unbalanced**
  - Fixed effects estimates of individual-level covariates unbiased and CP~95% whatever number and size of clusters, the level of heterogeneity (standard deviation of the simulated random effect), level of unbalance
  - Same performances with B-spline instead of Weibull for the baseline hazard
  - When the number of clusters is small (10 or 20), bias and lower CP than 95% for cluster level covariate β_{DI} and for σ std.dev of the random effect
  - Decreasing trends in RMSEs for β_{DI} and σ when the number of clusters increased
  - Time-dependent effects correctly modelled

- Scenarios **NPH**
  - idem as scenarios Scenarios Design Time-dependent effects correctly modelled

- Scenarios **robustness**
  - Fixed effects estimates of individual-level covariates unbiased and CP~95%
  - Bias and bad CP for cluster level covariate β_{DI}
  - Bad CP for the std.dev σ of the random effect

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Simulation results

scenario A Design balanced

Simulation condition	Parameters (True value)	Weibull mixed Bias	Weibull mixed Percentage Bias	Weibull mixed CP[a]	Weibull mixed RMSE[b]	Spline mixed Bias	Spline mixed Percentage Bias	Spline mixed CP[a]	Spline mixed RMSE[b]
Number of clusters: 10, Cluster size: 100	λ (0.25)	0.0019	0.8	90.2	0.045	NA	NA	NA	NA
	ρ (0.7)	-0.0014	-0.2	93.8	0.023	NA	NA	NA	NA
	β_{age} (0.05)	-0.0002	-0.5	93.8	0.004	-0.0002	-0.5	94.5	0.004
	β_{sex} (1)	0.0053	0.5	93.9	0.085	0.006	0.6	94.3	0.085
	β_{DI} (0.02)	0.0095	47.6	88.1	0.157	0.0095	47.4	87.9	0.158
	σ (0.5)	-0.0673	-13.5	78	0.146	-0.0668	-13.4	77.6	0.146
Number of clusters: 20, Cluster size: 50	λ (0.25)	-0.0005	-0.2	92.9	0.033	NA	NA	NA	NA
	ρ (0.7)	-0.0004	-0.1	94.8	0.022	NA	NA	NA	NA
	β_{age} (0.05)	0	0	94.7	0.004	0	-0.1	95.4	0.004
	β_{sex} (1)	0.0073	0.7	95.7	0.082	0.0073	0.7	96.2	0.083
	β_{DI} (0.02)	-0.0033	-16.4	92.5	0.08	-0.0033	-16.6	92.4	0.08
	σ (0.5)	-0.0311	-6.2	87.7	0.096	-0.0307	-6.1	88.2	0.096
Number of clusters: 50, Cluster size: 20	λ (0.25)	-0.0021	-0.8	93.2	0.026	NA	NA	NA	NA
	ρ (0.7)	-0.0011	-0.2	95.5	0.023	NA	NA	NA	NA
	β_{age} (0.05)	-0.0002	-0.3	95.6	0.004	-0.0002	-0.4	94.4	0.004
	β_{sex} (1)	0.012	1.2	95.1	0.085	0.0122	1.2	95.6	0.086
	β_{DI} (0.02)	0.0007	3.6	94.7	0.069	0.0007	3.6	94.7	0.069
	σ (0.5)	-0.013	-2.6	92.6	0.073	-0.0124	-2.5	92.3	0.074
Number of clusters: 100, Cluster size: 10	λ (0.25)	-0.0018	-0.7	94.7	0.022	NA	NA	NA	NA
	ρ (0.7)	-0.0005	-0.1	96.1	0.023	NA	NA	NA	NA
	β_{age} (0.05)	0.0001	0.2	94.8	0.004	0.0001	0.2	94.8	0.004
	β_{sex} (1)	0.008	0.8	95.1	0.086	0.0089	0.9	95.4	0.087
	β_{DI} (0.02)	-0.0033	-16.5	94.3	0.045	-0.0033	-16.5	94.7	0.045
	σ (0.5)	-0.0038	-0.8	95.3	0.064	-0.0027	-0.5	94.9	0.065

Simulation results

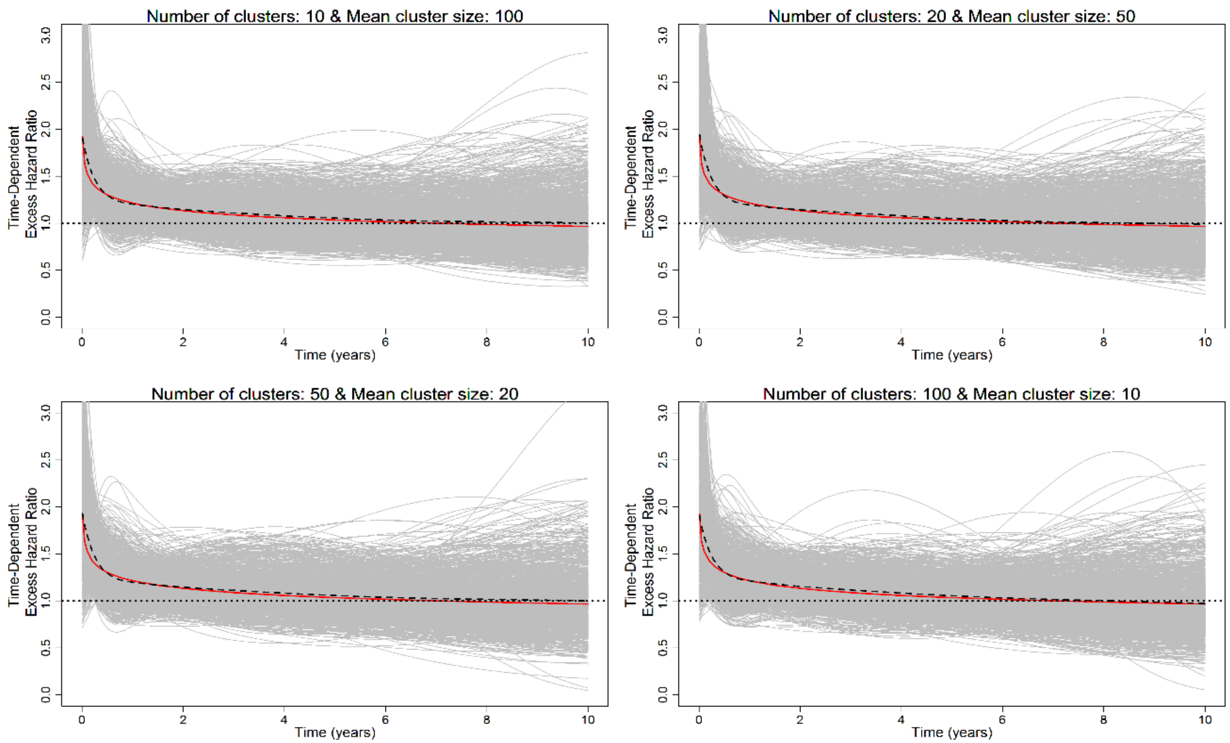
scenario B Design unbalanced

Simulation condition	Parameters (True value)	Medium Unbalance Design				High Unbalance Design			
		Bias	Percentage Bias	CP[a]	RMSE[b]	Bias	Percentage Bias	CP[a]	RMSE[b]
Number of clusters: 10	β_{age} (0.05)	-0.0003	-0.5	95.7	0.004	-0.0003	-0.6	95.8	0.004
	β_{sex} (1)	0.007	0.7	94.6	0.085	0.0073	0.7	94.4	0.085
Mean cluster size: 100	β_{DI} (0.02)	-0.006	-29.8	87.8	0.123	-0.0061	-30.6	85.9	0.125
	σ (0.5)	-0.0694	-13.9	79.1	0.148	-0.0802	-16	76.9	0.164
Number of clusters: 20	β_{age} (0.05)	-0.0002	-0.5	95.8	0.004	-0.0003	-0.7	95.9	0.004
	β_{sex} (1)	0.0049	0.5	95.7	0.084	0.007	0.7	95	0.085
Mean cluster size: 50	β_{DI} (0.02)	0.0048	23.8	92.6	0.07	0.0073	36.5	92.9	0.097
	σ (0.5)	-0.0322	-6.4	87.7	0.099	-0.0358	-7.2	87.5	0.106
Number of clusters: 50	β_{age} (0.05)	-0.0002	-0.4	95.2	0.004	-0.0002	-0.4	95.1	0.004
	β_{sex} (1)	0.0107	1.1	94.6	0.089	0.0082	0.8	93.8	0.09
Mean cluster size: 20	β_{DI} (0.02)	0.0009	4.3	94.8	0.056	0.0003	1.3	94.1	0.058
	σ (0.5)	-0.0127	-2.5	93.2	0.074	-0.0167	-3.3	90.8	0.081
Number of clusters: 100	β_{age} (0.05)	-0.0003	-0.6	95.6	0.004	-0.0003	-0.6	94.9	0.004
	β_{sex} (1)	0.0098	1	94.7	0.091	0.0106	1.1	95.5	0.09
Mean cluster size: 10	β_{DI} (0.02)	-0.0014	-6.8	94.8	0.043	-0.0003	-1.7	95.6	0.045
	σ (0.5)	-0.0065	-1.3	93.5	0.07	-0.0071	-1.4	92.7	0.071
Number of clusters: 800	β_{age} (0.05)	-0.0003	-0.6	95	0.001	-0.0003	-0.7	92.5	0.001
	β_{sex} (1)	0.0077	0.8	93	0.033	0.0078	0.8	92.7	0.033
Mean cluster size: 10	β_{DI} (0.02)	0.0003	1.7	96.5	0.015	0	-0.1	95.3	0.016
	σ (0.5)	0.0028	0.6	95	0.023	0.0024	0.5	95.3	0.023

Simulation results

scenario C NPH

Good performances of the approach in term of bias, CR and RMSE



Simulation results

scenario D robustness

Good performances for the individual level covariates
Biased for the cluster level covariate

Simulation condition	Parameters (True value)	Spline mixed			
		Bias	Percentage Bias	CP[a]	RMSE[b]
Number of clusters: 10	β_{age} (0.05)	-0.0004	-0.8	94.6	0.004
	β_{sex} (1)	0.0109	1.1	96	0.088
Mean cluster size: 100	β_{DI} (0.02)	0.3173	1586.4	85.9	0.339
	σ (1.12)	-0.0955	-8.5	94	0.196
Number of clusters: 20	β_{age} (0.05)	-0.0001	-0.2	95	0.004
	β_{sex} (1)	0.0085	0.8	94.5	0.09
Mean cluster size: 50	β_{DI} (0.02)	0.1275	637.6	97.6	0.151
	σ (1.12)	0.0002	0	98.6	0.139
Number of clusters: 50	β_{age} (0.05)	-0.0003	-0.5	94.8	0.004
	β_{sex} (1)	0.0082	0.8	96.5	0.088
Mean cluster size: 20	β_{DI} (0.02)	0.0216	107.9	99.9	0.056
	σ (1.12)	0.0476	4.2	99.2	0.111
Number of clusters: 100	β_{age} (0.05)	-0.0004	-0.7	95	0.004
	β_{sex} (1)	0.0193	1.9	95.4	0.097
Mean cluster size: 10	β_{DI} (0.02)	-0.0771	-385.6	96.4	0.089
	σ (1.12)	0.0457	4.1	98.7	0.095

Illustration

- Oral cavity cancer patients, diagnosed between 1997 and 2004, F-up 31/12/2007
- European Deprivation Index, EDI [Pornet JECH, 2012]
  - residential area level, the IRIS (“Ilots Regroupes pour des Indicateurs Statistiques”) ⇔ considered as a proxy for the socio-economic status of the patients.

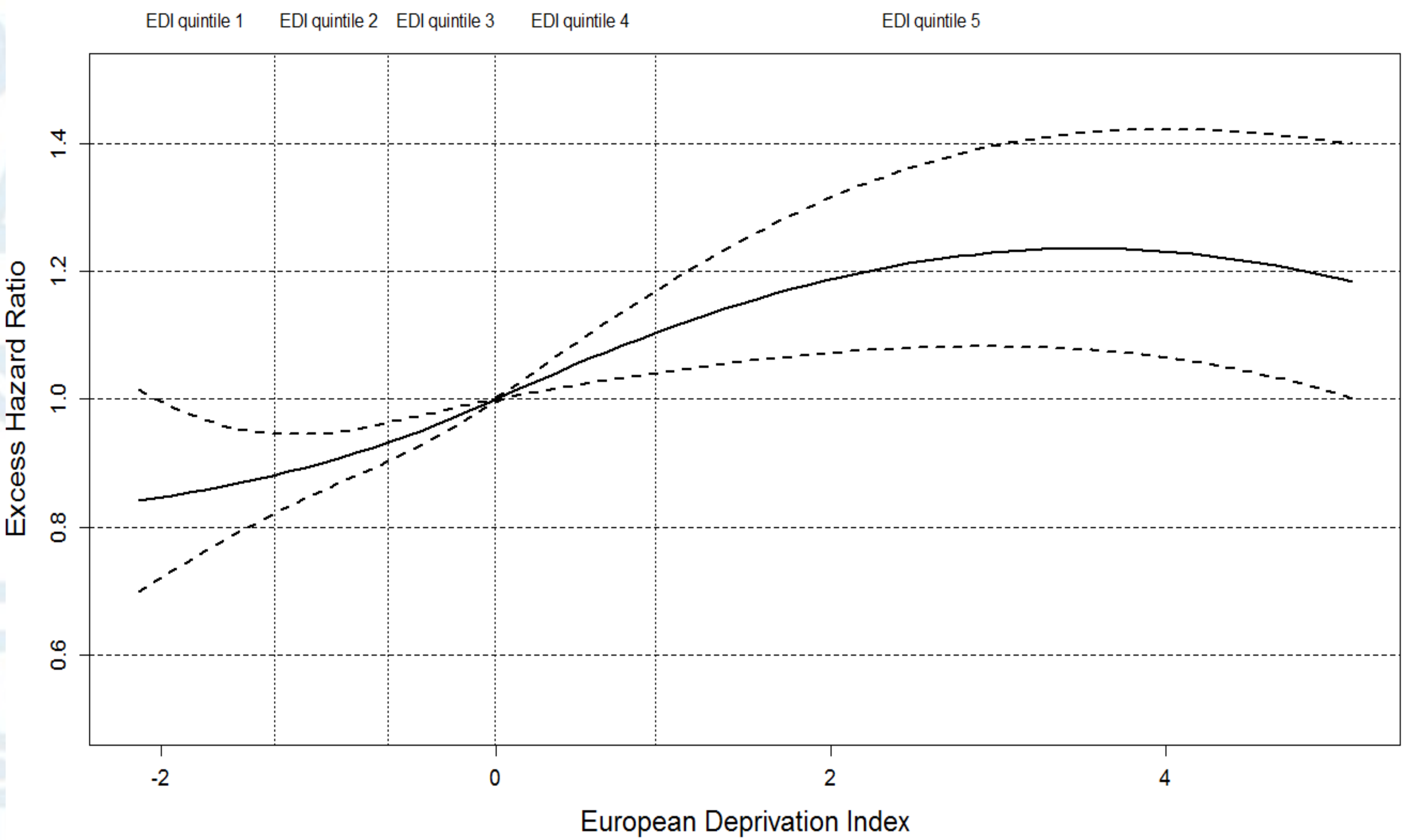
Objective: effect of the EDI on the excess mortality hazard.

Strategy of analysis

- Multilevel excess mortality hazard models including
  - covariates age, sex, year of diagnosis and the EDI
  - a random effect associated to the geographical level (normal distribution with mean 0 and standard deviation σ)
  - Non-linear and/or time-dependent effects of age and EDI (quadratic B-splines)

5 models fitted, the final one chosen using the Akaike Information Criteria

Results



EDI quintile 1
EDI quintile 2
EDI quintile 3
EDI quintile 4
EDI quintile 5
Excess Hazard Ratio
0.6
0.8
1.0
1.2
1.4
-2
0
2
4
European Deprivation Index

Illustration package R mexhaz

Package `mexhaz` downloadable here

http://csg.lshtm.ac.uk/tools-analysis/

R Code

```
> library(mexhaz)
> library(statmod)
> data(simdatn1)
```

Data from the package

```
> head(simdatn1)
       age     agecr   depindex IsexH clust vstat  timesurv    popmrate
37.47094 -0.3252906  1.4995788     1    29     1 0.1650722 0.002166154
37.43171 -0.3256829 -0.7932424     1    39     1 0.3027221 0.002166154
38.23911 -0.3176089  1.2784658     1    17     1 0.2277427 0.002361141
38.64260 -0.3135740  1.0052559     1    30     1 0.9837105 0.002583039
39.71695 -0.3028305  1.1485936     1    13     1 0.5851807 0.002840011
40.54103 -0.2945897 -0.3330067     1    40     1 0.2370094 0.002840011
```

```
> summary(simdatn1$age)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  30.30   65.00   72.29   68.49   78.69   84.96
```

```
> summary(simdatn1$depindex)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-2.79300 -0.79320 -0.16970  0.01688  1.11400  2.78100
```

Fitting models

```
> Mod_weib <- mexhaz(formula=Surv(time=timesurv,
event=vstat)~agecr+depindex+IsexH, data=simdatn1, base="weibull")

> Mod_weib
$data
      dame n.obs.tot n.obs expected random n.clust
1 simdatn1      4000  4000        0      0       1

$formula
Surv(time = timesurv, event = vstat) ~ agecr + depindex + IsexH

$Xlevels
named list()

$baseline
  max.time  Bound degree
1   10.001 10.001      3

$knots
NULL
…
```

Fitting models

```
> Mod_weib
…
$coefficients
          Estimates     Std.Err
Lambda   0.28764208 0.009057614
Rho      0.68871903 0.009957415
agecr    5.24235800 0.164759829
depindex 0.07987605 0.014518573
IsexH    0.92337527 0.036346604

$varcov
              [,1]          [,2]          [,3]          [,4]          [,5]
[1,]  8.204037e-05 -4.857398e-05 -0.0003342426 -8.457258e-06 -2.404834e-04
[2,] -4.857398e-05  9.915011e-05  0.0003807724  9.133332e-06  8.244779e-05
[3,] -3.342426e-04  3.807724e-04  0.0271458013  1.821774e-04  4.025224e-04
[4,] -8.457258e-06  9.133332e-06  0.0001821774  2.107890e-04  2.391576e-05
[5,] -2.404834e-04  8.244779e-05  0.0004025224  2.391576e-05  1.321076e-03

$mu.hat
[1] 0

$details
  iter eval nb.param    base nb.quad optim.fct method code    loglik total.time
1   33  207        5 weibull      10       nlm    ---    1 -6230.737       0.18

attr(,"class")
[1] "mod.mxh"
```

Fitting models

```
> Mod_pw <- mexhaz(formula=Surv(time=timesurv,
event=vstat)~agecr+depindex+IsexH, data= simdatn1,
base="pw.cst", knots=c(1,3,5,8))

> Mod_bs3_2 <- mexhaz(formula=Surv(time=timesurv,
event=vstat)~agecr+depindex+IsexH , data=simdatn1,
base="exp.bs", degree=3, knots=c(1,5))
```

```
base can be weibull, pw.cst, exp.bs (degree 1 2 or 3, knots)
```

Predicting and plotting the results

Predicting

```
> fitweibpred <- pred.mexhaz(Mod_weib, t=10, nb.time=1000,
    data.val = data.frame(agecr=0, depindex=0, IsexH=0))
> fitpwpred <- pred.mexhaz(Mod_pw, t=10, nb.time=1000,
    data.val = data.frame(agecr=0, depindex=0, IsexH=0))
> fitbspred <- pred.mexhaz(Mod_bs3_2, t=10, nb.time=1000,
    data.val = data.frame(agecr=0, depindex=0, IsexH=0))
```

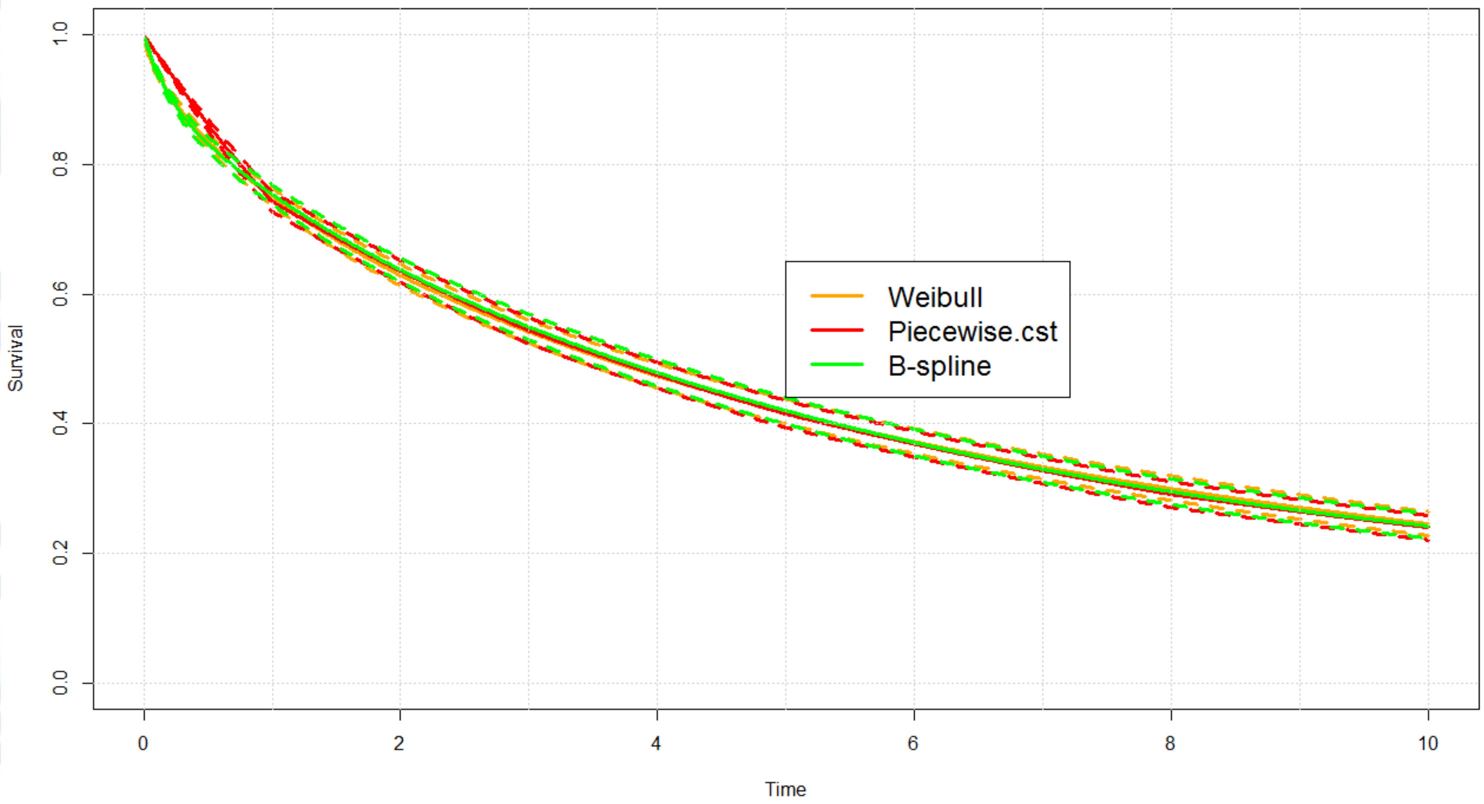
Reference group

Plotting

```
> graph.mexhaz(fitweibpred, type = "survival", col="orange",
lwd=3)
> graph.mexhaz(fitpwpred, type = "survival", points = T,
col="red", lwd=3)
➢ graph.mexhaz(fitbspred, type = "survival", points = T,
  col="green", lwd=3)
```

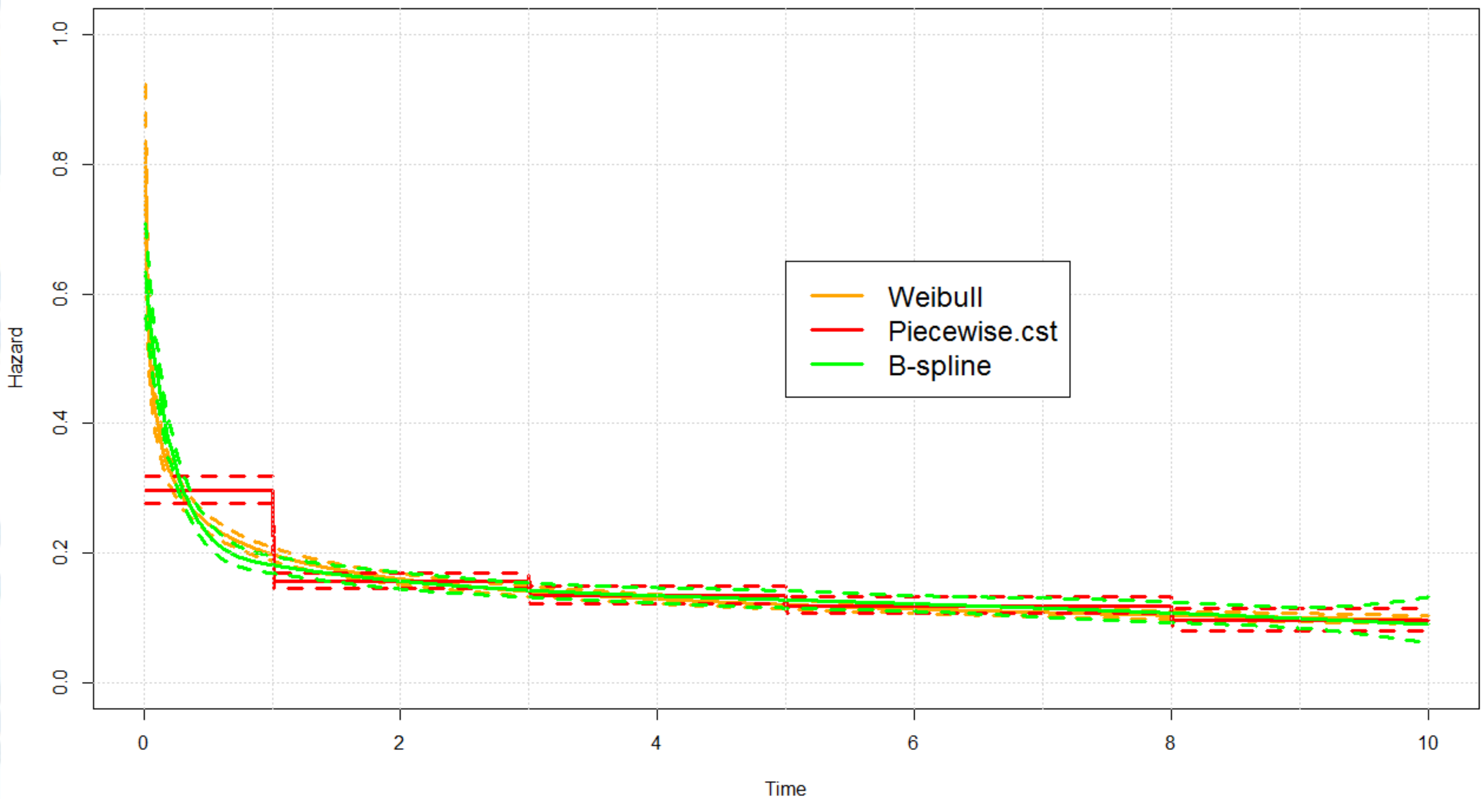
type can be survival or hazard

Survival



Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Time
Weibull
Piecewise.cst
B-spline

Hazard


Weibull
Piecewise.cst
B-spline
Hazard
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time

Fitting models

A more complex model

Mixed effect excess hazard model with time-dependent effects of age and sex

```
> Mod_bs2_2mixnphnlin <- mexhaz(formula=Surv(time=timesurv,
event=vstat)~agecr+agecr2+agecr2plus+depindex+IsexH +
nph(agecr), data=simdatn1, base="exp.bs", degree=2,
knots=c(1,5),        expected="popmrate", random="clust)
```

Fitting models

A more complex model

Mixed effect excess hazard model with time-dependent effects of age and sex

```
> Mod_bs2_2mixnphnlin <- mexhaz(formula=Surv(time=timesurv,
event=vstat)~agecr+agecr2+agecr2plus+depindex+IsexH +
nph(agecr), data=simdatn1, base="exp.bs", degree=2,
knots=c(1,5),        expected="popmrate", random="clust)
```

Time-dependent effect of age

Non-linear effect of age

Population Mortality (➔Excess hazard)

Random effect

Mixed effect excess hazard model with time-dependent and non-linear effect of age

```
> Mod_bs3_2mixnph$coeff

                Estimates    Std.Err
Intercept      -0.62191746 0.07206795
bs.t1          -1.22686527 0.09341339
bs.t2          -1.57346208 0.09537244
bs.t2+1        -1.92228078 0.18534268
bs.t2+5        -2.40496565 0.29110156
agecr           4.97906020 0.81490223
agecr2         -0.70339439 2.36511496
agecr2plus     -0.46487937 8.36499588
depindex        0.09310733 0.03102677
IsexH           1.02323714 0.04381095
agecr*bs.t1     0.07001013 0.88029371
agecr*bs.t2    -0.83266897 0.80540855
agecr*bs.t2+1  -0.62992813 1.31420479
agecr*bs.t2+5  -0.87023423 1.71588347
clust (sd)      0.21440181 0.03150999
```

Conclusion/discussion

- We proposed an approach to fit a flexible excess hazard model, allowing for a random effect defined at the cluster level and time-dependent and/or non-linear effects of covariates
  - Numerical integration techniques
    - Adaptive Gauss-Hermite quadrature to calculate the cluster-specific marginal likelihood
    - Gauss-Legendre quadrature for the cumulative hazard
  - Flexible functions (B-splines) used for the baseline and the time-dependent effects
- Good performances shown by simulation
- R package available http://csg.lshtm.ac.uk/tools-analysis/

- Extension to more than one random effect

References

- **Charvat H, Remontet L, Bossard N, Roche L, Dejardin O, Rachet B, Launoy G, Belot A. A multi-level excess hazard model to estimate net survival on hierarchical data allowing for non-linear and non-proportional effects of covariates. In revision in Statistics In Medicine**
- Duchateau,L; Janssen,P. The frailty model. Springer 2008
- Wienke,A. Frailty models in survival analysis. Chapman & Hall/CRC Biostatistics Series 2011
- Therneau,T; Grambsch,P. Modeling survival data, Extending the Cox model. Springer 2000.
- Liu,L; Huang,X. The use of Gaussian quadrature for estimation in frailty proportional hazard model. Statistics In Medicine 2008.
- Rondeau,V; Commenges,D; Joly,P. Maximum penalized likelihood estimation in frailty models. Lifetime Data Analysis 2003.
- Vaida,F; Xu,R. Proportional hazards models with random effects. Statistics In Medicine 2000.
- Liu,Q; Pierce,D. A note on Gauss-Hermite quadrature. Biometrika 1994.
- Kuss,O; Blankenburg,T; Haerting, J. A relative survival model for clustered responses. Biometrical Journal 2008.
- Dupont C, et al. Description of an approach based on maximum likelihood to adjust an excess hazard model with a random effect. Cancer Epidemiology (2013), http://dx.doi.org/10.1016/j.canep.2013.04.001
- Tuerlinckx F et al., Statistical inference in generalized linear mixed models: A review. British Journal of Mathematical and Statistical Psychology, 2006

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE