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

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Outline

Context 1/2

Describe the association between the socio-economic status and the cancer-specific hazard using population-based cancer registry data

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  - Level 1: individual's time-to-event
  - Level 2: cluster (area of residence, hospital, ...)

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- No cause of death information
- Socio-economic level of patients assessed by an ecological measure (area of residence)
- Hierarchical structure of the data
  - Level 1: individual's time-to-event
  - Level 2: cluster (area of residence, hospital, ...)

$\Rightarrow$ Assumption of independence between individual's survival times is violated for individuals living in the same area (same level of deprivation, but also local medical practice, environmental factor...)
$\Rightarrow$ Correct statistical inference requires that the hierarchical structure of the data be taken into account.

Context 2/2

- Cancer-specific hazard without the cause of death?
  $\Rightarrow$ excess hazard regression models
- Correlated data / hierarchical structure?
  $\Rightarrow$ mixed effect models (multilevel models) provide a satisfying and convenient theoretical framework by introducing a random effect at the cluster level.

Mixed effect models have been well developed in the context of overall survival
But lack of tools/development in the context of net survival/excess hazard regression models

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- To evaluate the performances of the proposed approach in an extensive simulation study
- To make available the approach in an user-friendly software (R-package)

Excess hazard regression model 1/2

Classical method used to analyse population-based cancer registry data

The overall mortality hazard λ is split into an excess mortality hazard (due to cancer) λ_E and an expected (or population) mortality hazard λ_P [Estève 1990]:

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

Where

- Covariates $\mathbf{x}$: age at diagnosis a, deprivation, stage at diagnosis, sex, year of diagnosis, ...
- Variables defining the population mortality hazard in the life-table: age $a + t$ and $\mathbf{z}$ (sex, year, region, deprivation, ...)

Excess hazard regression model 2/2

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

- The quantity λ_P is considered known
- The quantity to estimate is λ_E

Many different models have been proposed: more flexible and allowing time-dependent effects using splines [Bolard 2002, Giorgi 2003, Nelson 2007, Remontet 2007, Pohar-Perme 2009, ...]

But nothing has been done to fit an for excess hazard model on correlated data, without losing flexibility (parametric hazard, or piecewise step function [Dupont 2013])

The classical shared frailty hazard-based regression model

In survival analysis, random effect is usually called "frailty"
The frailty, u, can be viewed as a random variable that acts multiplicatively on the baseline hazard [Duchateau 2008, Wienke 2011].

$$\lambda(t; \mathbf{x}_{ij}, u_i) = \lambda_0(t) u_i \exp({}^t\mathbf{x}_{ij}\beta)$$

Each geographical unit i has a frailty value u_i $[= exp(w_i)]$ which is shared by all individuals j observed in unit i

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Usual assumptions:

- Parametric distribution for T (Weibull, piecewise constant,...)
- Gamma distribution for the frailty u

Mainly due to practical reasons (analytical expression of the marginal likelihood)
$\Rightarrow$ No tool for flexible excess hazard

Mixed-effect Excess hazard regression model

The flexible model proposed

$$\boxed{\lambda_E(t, \mathbf{x}_{ij}) = \lambda_0(t; \boldsymbol{\xi}) \cdot \exp(\beta_1 x_1 + f(x_2; \boldsymbol{\beta}_2) + g(t; \boldsymbol{\beta}_3) x_3 + w_i)}$$

Where

- λ_0 is the baseline hazard modelled with (exp of) B-splines (or piecewise or Weibull),
- β_1 the linear and proportional (fixed) effect of x_1,
- f and g are flexible functions (B-splines) allowing for non-linear and non-proportional effects for x_2 and x_3 (defined with $\boldsymbol{\beta}_2$ and $\boldsymbol{\beta}_3$), respectively,
- w_i is the random effect of cluster i, assumed to follow a normal distribution with mean 0 and standard deviation σ

Likelihood function: overview

1. Likelihood of one observation j in cluster i
2. Conditional Likelihood for cluster i
3. Marginal Log-Likelihood for cluster
4. Total Log-likelihood

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Conditional Likelihood for cluster i

For one observation j in cluster i: $\{t_{ij}, \delta_{ij}, \mathbf{x}_{ij}\}$

$$\mathrm{L}_{ij}^{C}(\boldsymbol{\beta}|w_i) = \exp\{-\Lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) - \Lambda_P(a_{ij}+t_{ij}, \mathbf{z}_{ij})\}\left\{\lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) + \lambda_P(t_{ij}, \mathbf{z}_{ij})\right\}^{\delta_{ij}}$$

- Gauss-Legendre quadrature to approximate the cumulative excess hazard $\Lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) = \int_0^t \lambda(u, \mathbf{x}_{ij}, w_i)\ \mathrm{d}u$
- Last term of the exponential can be omitted (does not depend on the $\boldsymbol{\beta}$s)

For cluster i:

$$\mathrm{L}_{i}^{C}(\boldsymbol{\beta}|w_i) = \prod_{j=1}^{n_i}\left\{\mathrm{L}_{ij}^{C}(\boldsymbol{\beta}|w_i)\right\}$$

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Marginal Likelihood for cluster *i*

We assume a normal distribution for the random effect, with mean=0 and variance=σ^2, $\phi(w, 0, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left\{-\frac{w^2}{2\sigma^2}\right\}$

For cluster *i*

$$\mathrm{L}_i^M(\boldsymbol{\beta}, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{+\infty} \mathrm{L}_i^C(\boldsymbol{\beta}|w) \exp\left\{-\frac{w^2}{2\sigma^2}\right\} \mathrm{d}w$$

- Problem : How to evaluate this likelihood ?
- A solution is to use the Gauss-Hermite Quadrature (GHQ)

Definition

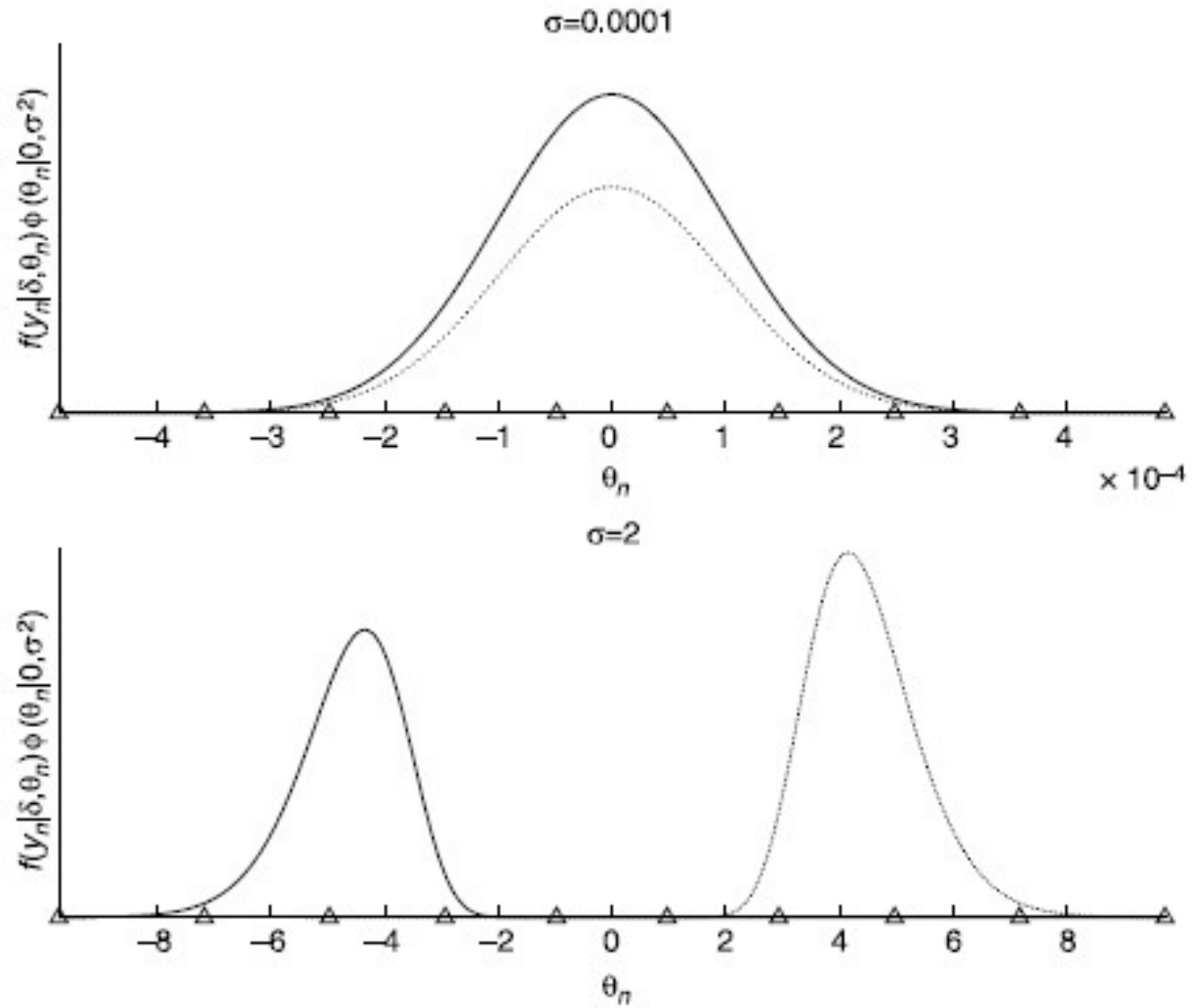
Gauss-Hermite Quadrature

$$\int_{-\infty}^{\infty} f(v) \exp\{-v^2\} \, \mathrm{d}v \approx \sum_{k=1}^{Q} \rho_k^H \cdot f(x_k^H)$$

- Nodes $= x_k^H$
- Weights $= \rho_k^H$

The nodes and weights depend only on Q (not on the integrand f...)

Illustration of the GHQ



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

A refinement of the GHQ : the **adaptive** GHQ

Basic idea:

- The quadrature locations are rescaled and translated so that they cover the region where the integrand varies most, i.e. around its mode
- To transform the integrand to obtain a new quadrature formula in which the new nodes and the corresponding weights depend on the integrand (and so on the cluster i)

Laplace approximation

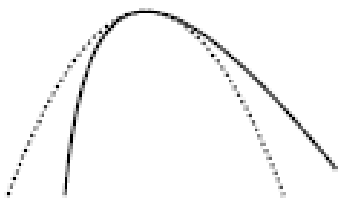
Let g be a strictly positive, unimodal function with mode μ_g and let us define l such that $l(x) = \log\{g(x)\}$.

In a neighbourhood of μ_g:

$$l(x) \approx l(\mu_g) + (x - \mu_g) l'(\mu_g) + \frac{(x - \mu_g)^2}{2} l''(\mu_g)$$

- μ_g extremum $\Rightarrow l'(\mu_g) = 0$
- μ_g maximum $\Rightarrow l''(\mu_g) < 0$

$$g(x) \approx g(\mu_g) \underbrace{\exp\left\{\frac{(x - \mu_g)^2}{2} l''(\mu_g)\right\}}_{\propto \phi(x, \mu_g, \sigma_g)} \quad \text{with} \quad \sigma_g = \frac{1}{\sqrt{-l''(\mu_g)}}$$



The **adaptive** GHQ 1/2

Define and use LAPLACE approximation on :

$$g_i(w, \boldsymbol{\beta}, \sigma) = \mathrm{L}_i^C(\boldsymbol{\beta}|w)\phi(w, 0, \sigma) \quad \Rightarrow \quad \left\{ \begin{array}{l} \mu_i \\ \sigma_i \end{array} \right.$$

We have :

$$\mathrm{L}_i^M(\boldsymbol{\xi}, \boldsymbol{\beta}, \sigma) = \int_{-\infty}^{\infty} \underbrace{\frac{g_i(w, \boldsymbol{\beta}, \sigma)}{\phi(w, \mu_i, \sigma_i)}}_{f_i^{\mathrm{A}}(w, \boldsymbol{\beta}, \sigma)} \phi(w, \mu_i, \sigma_i) \, \mathrm{d}w$$

Using the GHQ, we approximate :

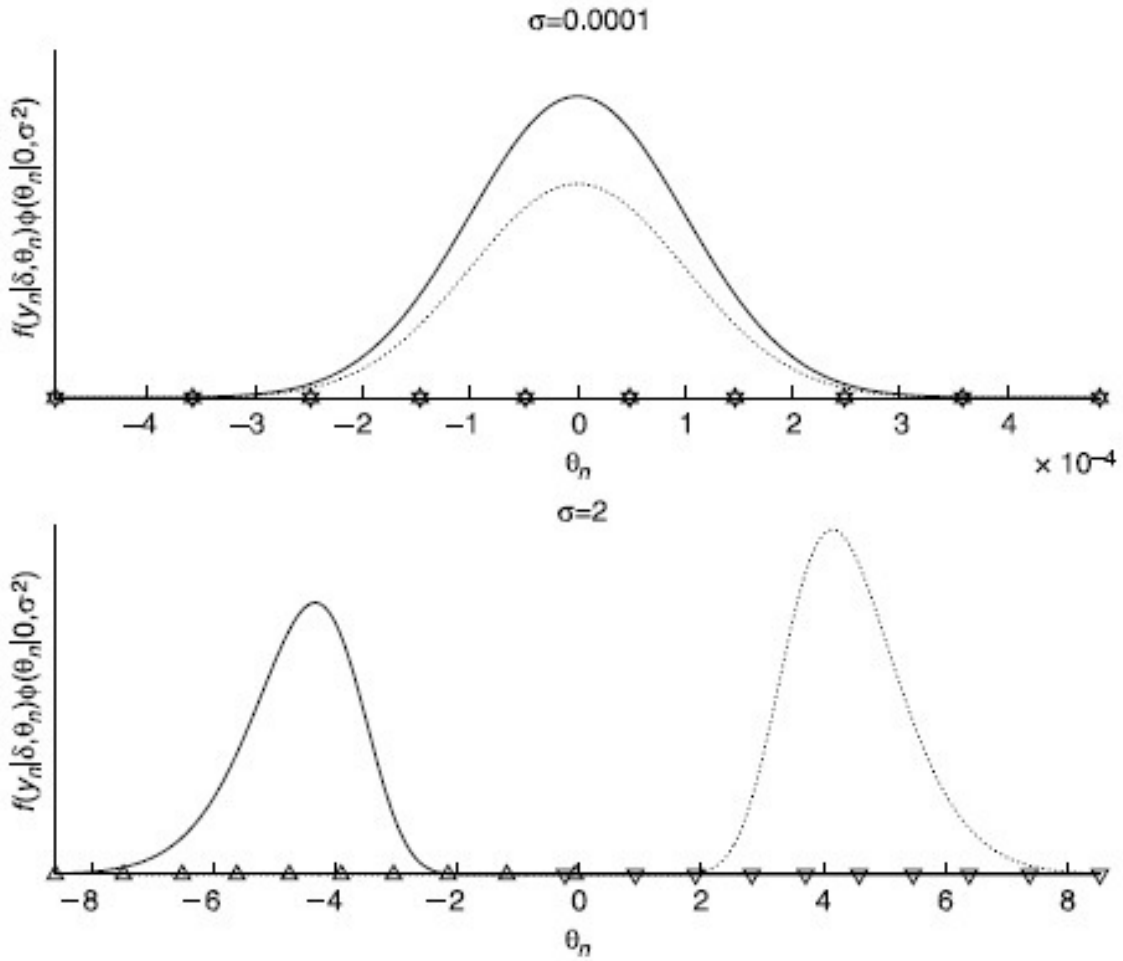
$$\mathrm{L}_i^M(\boldsymbol{\xi}, \boldsymbol{\beta}, \sigma) \approx \sum_{k=1}^{Q} \rho_k^N(\mu_i, \sigma_i) \cdot f_i^{\mathrm{A}}\left(x_k^N(\mu_i, \sigma_i), \boldsymbol{\beta}, \sigma\right)$$

The **adaptive** GHQ 2/2

The modified nodes and weights are given (as functions of the original ones) by:

$$\begin{cases} x_k^N(\mu_i, \sigma_i) = \mu_i + \sigma_i \sqrt{2} \cdot x_k^H \\ \rho_k^N(\mu_i, \sigma_i) = \rho_k^H \cdot \sigma_i \sqrt{2} \exp\{x_k^{H^2}\} \end{cases}$$

Illustration of the Adaptive GHQ



More accurate approximation than GHQ and it needs less quadrature points
Tuerlinckx F et al., British Journal of Mathematical and Statistical Psychology, 2006

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Finally

Log-likelihood for cluster i

$$\ell_i^M(\boldsymbol{\beta}, \sigma) \approx \log\left\{\sum_{k=1}^{Q} \rho_k^N(\mu_i, \sigma_i) \cdot f_i^{\mathrm{A}}\left(x_k^N(\mu_i, \sigma_i), \boldsymbol{\beta}\right)\right\}$$

Total Log-likelihood

$$\ell(\boldsymbol{\beta}, \sigma) \approx \sum_{i=1}^{D} \ell_i^M(\boldsymbol{\beta}, \sigma)$$

To estimate the parameters $(\widehat{\boldsymbol{\beta}}, \widehat{\sigma})$, use a standard optimisation routine (such as the Newton-Raphson algorithm) on the quantity $\ell(\boldsymbol{\beta}, \sigma)$

Overview of the different simulated scenarios 1/2

Aim: to evaluate the performances of the proposed approach in different scenarios, in terms of its ability to estimate

- the baseline excess hazard
- the fixed effects of covariates defined **both** at the individual level and at the cluster level (including time-dependent effect)
- the variance of the random effect

Overview of the different simulated scenarios 2/2

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

- scenario A: Balance-Design: N patients by cluster is fixed
- scenario B: UnBalance-Design: N patients by cluster is variable

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

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

Simulation study (I)

Design of the 1000 simulated dataset, with 1000 patients in each

- Age (25% [30, 65], 35% [65, 75], 40% [75, 85], with an uniform law in each age-class)
- Sex (Binomial distribution with P(sex=man)=0.5
- Cluster (the cluster ID (D = 10, 20, 50, 100))
- Deprivation Index (DI) defined at the cluster level (Normal(0,sd=1.5))

In scenarios A, Balance-Design: the number of patients by cluster is **exactly** equal to 10, 20, 50 or 100

In scenarios B, UnBalance-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 and 10 patients on average).

Simulation study (II)

- To simulate the time to death due to cancer T_1

$$\lambda_E(t, \text{Age}_{ij}, \text{Sex}_{ij}, \text{DI}_i) = \lambda_0(t) \exp\{\beta_{\text{Age}}\text{Age}_{ij} + \beta_{\text{Sex}}\text{Sex}_{ij} + \beta_{\text{DI}}\text{DI}_i + w_i\}$$

  - Weibull baseline hazard $\lambda_0(t) = \lambda\rho t^{\rho-1}$ ($\lambda = 0.25$; $\rho = 0.7$)
  - Age effect ($\beta_{\text{Age}} = 0.05$ for 1 year increase)
  - Sex effect ($\beta_{\text{Sex}} = 1$, Men vs. women)
  - DI effect ($\beta_{\text{DI}} = 0.02$ for 1 unit increase)
  - Random effect w_i: Normal distribution with mean 0 and standard deviation $\sigma = 0.25$ or 0.5 or 1

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  - Random effect w_i: Normal distribution with mean 0 and standard deviation $\sigma = 0.25$ or 0.5 or 1
- To simulate the time to death due to other causes T_2 : yearly piecewise exponential law using mortality rates from the population lifetable
- $\Rightarrow$ Final time $T = \min(T_1, T_2)$, with the corresponding vital status δ

Simulation study (III)

For the scenario **NPH**, two different Weibull baseline hazards for men and women:

- 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).

$\Rightarrow$ the Hazard Ratio between Men vs. Women is time-dependent

For the scenario **Robustness** The random effect was drawn from a normal distribution with $\sigma = 0.5$ **but**

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

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

Simulation study (IV)

The model used to analyse the data

- in scenarios balance- and unbalance- Design and Robustness

$$\lambda_E(t, \mathrm{Age}_{ij}, \mathrm{Sex}_{ij}, \mathrm{DI}_i) = \lambda_0(t) \exp\{\beta_{\mathrm{Age}}\mathrm{Age}_{ij} + \beta_{\mathrm{Sex}}\mathrm{Sex}_{ij} + \beta_{\mathrm{DI}}\mathrm{DI}_i + w_i\}$$

With $\lambda_0(t)$ modelled either as a Weibull or using a cubic B-spline (1 knot at 1 year)

- in scenarios NPH

$$\lambda_E(t, \mathrm{Age}_{ij}, \mathrm{Sex}_{ij}, \mathrm{DI}_i) = \lambda_0(t) \exp\{\beta_{\mathrm{Age}}\mathrm{Age}_{ij} + \beta_{\mathrm{Sex}}(t)\mathrm{Sex}_{ij} + \beta_{\mathrm{DI}}\mathrm{DI}_i + w_i\}$$

With $\lambda_0(t)$ and $\beta_{\mathrm{Sex}}(t)$ modelled using a cubic B-spline (1 knot at 1 year)

Overview of simulation results

Scenarios balance-Design, unbalance-Design and NPH

- Fixed-effect estimates of individual-level covariates unbiased and CP $\approx 95\%$ whatever number and size of clusters, the level of heterogeneity simulated and the level of unbalance
- Same performances with B-spline instead of Weibull for the baseline hazard
- With small number of clusters (10 or 20), bias and CP less than 95% for cluster-level covariate (β_{DI}) and std.dev (σ) of the random effect
- RMSEs for β_{DI} and σ $\searrow$ when the number of clusters $\nearrow$
- Time-dependent effects correctly estimated

Scenario Robustness

- Fixed effect estimates of individual-level covariates unbiased and CP $\approx 95\%$
- Bias and bad CP for cluster-level covariate
- Bad CP for σ

Simulation results

What about neglecting the hierarchical structure of the data ?

Simulation condition	Parameters (True value)	Weibull mixed				Weibull fixed			
		Bias	Percentage Bias	CP[a]	RMSE[b]	Bias	Percentage Bias	CP[a]	RMSE[b]
Number of clusters: 10 Cluster size: 100	λ (0.25)	0.0019	0.8	90.2	0.045	0.0209	8.4	53.8	0.051
	ρ (0.7)	-0.0014	-0.2	93.8	0.023	-0.0454	-6.5	45.9	0.054
	β_{age} (0.05)	-0.0002	-0.5	93.8	0.004	-0.0038	-7.6	76.5	0.005
	β_{sex} (1)	0.0053	0.5	93.9	0.085	-0.074	-7.4	82.2	0.119
	β_{DI} (0.02)	0.0095	47.6	88.1	0.157	0.0072	36.2	40.2	0.147
	σ (0.5)	-0.0673	-13.5	78	0.146	NA	NA	NA	NA
Number of clusters: 20 Cluster size: 50	λ (0.25)	-0.0005	-0.2	92.9	0.033	0.0212	8.5	63	0.04
	ρ (0.7)	-0.0004	-0.1	94.8	0.022	-0.0506	-7.2	33.3	0.056
	β_{age} (0.05)	0	0	94.7	0.004	-0.0042	-8.4	73.9	0.006
	β_{sex} (1)	0.0073	0.7	95.7	0.082	-0.0825	-8.2	80.7	0.119
	β_{DI} (0.02)	-0.0033	-16.4	92.5	0.08	-0.0063	-31.4	52.4	0.074
	σ (0.5)	-0.0311	-6.2	87.7	0.096	NA	NA	NA	NA
Number of clusters: 50 Cluster size: 20	λ (0.25)	-0.0021	-0.8	93.2	0.026	0.021	8.4	72.3	0.034
	ρ (0.7)	-0.0011	-0.2	95.5	0.023	-0.0537	-7.7	29.3	0.058
	β_{age} (0.05)	-0.0002	-0.3	95.6	0.004	-0.0044	-8.9	73.2	0.006
	β_{sex} (1)	0.012	1.2	95.1	0.085	-0.0845	-8.5	81.3	0.12
	β_{DI} (0.02)	0.0007	3.6	94.7	0.069	-0.0008	-4.2	70	0.063
	σ (0.5)	-0.013	-2.6	92.6	0.073	NA	NA	NA	NA
Number of clusters: 100 Cluster size: 10	λ (0.25)	-0.0018	-0.7	94.7	0.022	0.0218	8.7	77.1	0.031
	ρ (0.7)	-0.0005	-0.1	96.1	0.023	-0.0547	-7.8	25.6	0.058
	β_{age} (0.05)	0.0001	0.2	94.8	0.004	-0.0043	-8.7	73.7	0.005
	β_{sex} (1)	0.008	0.8	95.1	0.086	-0.0896	-9	78.9	0.122
	β_{DI} (0.02)	-0.0033	-16.5	94.3	0.045	-0.0049	-24.5	80.3	0.041
	σ (0.5)	-0.0038	-0.8	95.3	0.064	NA	NA	NA	NA

Illustration

Based on data from two population-based cancer registries in France (Calvados and Manche)

- Oral cavity cancer patients, diagnosed between 1997 and 2004 in a French region and followed up to 31/12/2007
- European Deprivation Index, EDI [Pornet JECH, 2012], defined at the residential area level, the IRIS (Ilots Regroupés pour des Indicateurs Statistiques)
  $\Leftrightarrow$ considered as a proxy for the patients socio-economic status (**continuous** variable)

Objective: effect of the EDI on the excess mortality hazard

Illustration - The data

- We analysed 2461 cancer patients
- Patients alive at 5 years were censored
- Distribution of patients per cluster (IRIS): 329 IRIS with 1 patient, 337 IRIS with 2-5 patients, 100 IRIS with 6-10 patients, 31 IRIS with more than 10 patients (max=21)
- EDI : from -3.45 for the most affluent to 8.98 for the most deprived

Illustration - strategy of analysis

Multilevel excess mortality hazard models including

- covariates age, sex, year of diagnosis and the EDI
- a random effect defined at the cluster level (normal distribution with mean 0 and standard deviation σ)
- Non-linear and/or time-dependent effects of age and EDI (quadratic B-splines)

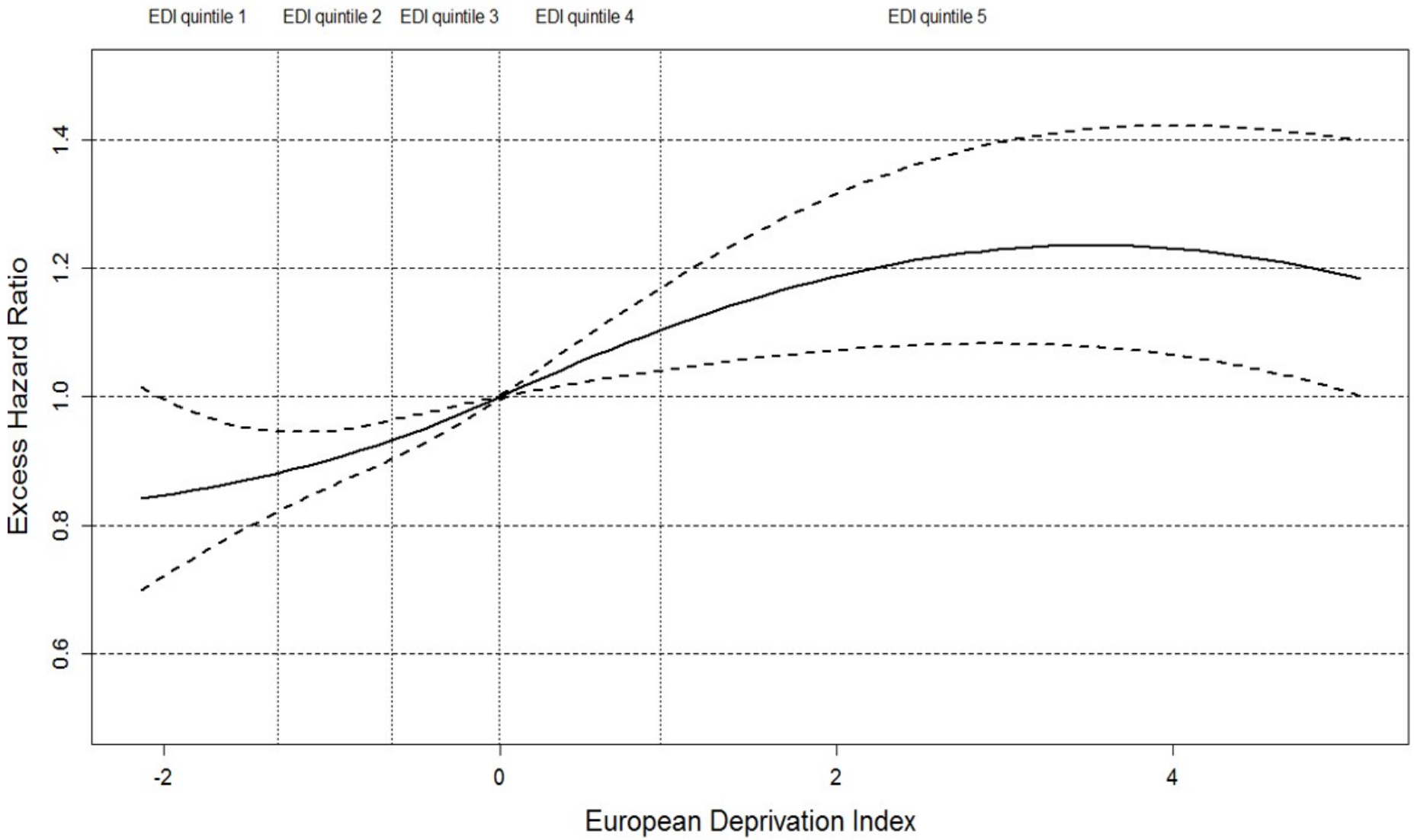
$\Rightarrow$ Five models were fitted, the final one was chosen using the Akaike Information Criterion

Illustration - results 1/2

Parameters estimated from the five models

	Parameter estimates (Standard Errors)				
	Model 1 (AIC = 7754.048)	Model 2 (AIC = 7754.473)	Model 3 (AIC = 7715.413)	**Model 4 (AIC = 7709.038)**	Model 5 (AIC = 7712.898)
Covariates					
Sex (ref=women)	0.37 (0.075)	0.36 (0.076)	0.35 (0.076)	0.34 (0.076)	0.34 (0.076)
Year of diagnosis	0.09 (0.011)	0.09 (0.011)	0.08 (0.011)	0.09 (0.011)	0.09 (0.011)
Age at diagnosis	0.01 (0.002)	NLIN	NLIN-NPH	NLIN-NPH	NLIN-NPH
EDI	0.04 (0.013)	0.04 (0.013)	0.04 (0.013)	NLIN	NLIN-NPH
Standard deviation σ	0.09 (0.108)	0.11 (0.097)	0.10 (0.099)	0.06 (0.15)	0.07 (0.143)

Illustration - results 2/2



R-package mexhaz

A R-package was developed: mexhaz, Mixed-effect EXcess HAZard model (available on the CRAN website https://cran.r-project.org/)
The mexhaz package allows

- to fit flexible hazard regression model
  - with/without introducing λ_P (i.e. to estimate overall or excess hazard)
  - with different baseline hazards: piecewise step function, Weibull or B-splines
  - with non-linear and/or time-dependent effect(s) of covariate(s)
  - with/without a random effect defined at the cluster level

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  - at several time points for one vector of covariates
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- to plot the hazard and the corresponding survival

R-package mexhaz

A R-package was developed: mexhaz, Mixed-effect EXcess HAZard model (available on the CRAN website https://cran.r-project.org/)
The mexhaz package allows

- to fit flexible hazard regression model
  - with/without introducing λ_P (i.e. to estimate overall or excess hazard)
  - with different baseline hazards: piecewise step function, Weibull or B-splines
  - with non-linear and/or time-dependent effect(s) of covariate(s)
  - with/without a random effect defined at the cluster level
- to predict hazard and the corresponding survival
  - at several time points for one vector of covariates
  - for several vectors of covariates at one time point
- to plot the hazard and the corresponding survival

R-package mexhaz - Example of code

- **Estimation**

```
Mod1 <- mexhaz(formula=Surv(time=timesurv, event=vstat)~
agecr+depindex+IsexH+nph(agecr), data=simdatn1,
base="exp.bs", degree=3, knots=c(1,5), expected="popmrate",
random="clust")
```

R-package mexhaz - Example of code

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random="clust")
```

- **Prediction** at several time points for one vector of covariates

```
Pred_Mod1 <- predMexhaz(Mod1, time.pts=seq(0.1,10,by=0.1),
data.val=data.frame(agecr=0,depindex=0.5,IsexH=1),
conf.int="delta")
```

R-package mexhaz - Example of code

- **Estimation**

```
Mod1 <- mexhaz(formula=Surv(time=timesurv, event=vstat)~
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conf.int="delta")
```

- **Plot**

```
plot(Pred_Mod1, which="hazard")
```

Conclusions

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 on the CRAN website

Ongoing Work and Perspectives

- Application for 18 cancers on French data and English Data
- Extension to more than one random effect
- Use of this model to distinguish individual deprivation from contextual effect
- Extension to crossed and nested random effects

Population-based Time-to-event Analysis International conference

http://csg.lshtm.ac.uk/pta2016

31 August-2 September 2016

Cancer Survival Group

International Conference, London, 2016

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Population-based Time-to-event Analyses (PTA)

The conference, co-organised by the ***Cancer Survival Group*** and the ***Centre for Statistical Methodology*** at the ***London School of Hygiene and Tropical Medicine*** (LSHTM), will take place from Wednesday 31st of August to Friday 2nd September 2016.

Venue

The meeting will be held at the London School of Hygiene and Tropical Medicine, in the School's Manson Lecture Theatre, which is in the main building on Keppel Street.

Themes of the conference

The conference will focus on three main areas of time-to-event analyses, all of which concentrate on population-based data and translational epidemiology:

1. Recent methodological developments in competing risks and net survival
2. Hierarchical and correlated data in survival and longitudinal analysis
3. Causal inference in longitudinal settings with time-dependent confounding

The conference will include invited speakers as well as oral or poster communications. At the end of the conference, a **panel** will summarise the main important methods and discussions highlighted during these three days and, will point to the **future in methodological developments** regarding advanced time-to-event analyses of population-based data

Questions

Any questions?
I have one

- Would you be able to explain (intuitively) the main difference between Gauss-Hermite quadrature and the Adaptive Gauss-Hermite quadrature?
- And how the Adaptive Gauss-Hermite quadrature works?

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