A hierarchical Bayesian approach to account for exposure measurement error - An application to radiation epidemiology

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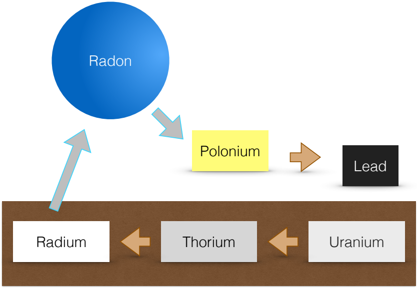
Context

- Radon is a radioactive gas which presents the primary source of background radiation
- It is known to be the second leading cause of lung cancer [Samet and Eradze, 2000] responsible for about 2% of cancer deaths in Europe [Darby et al., 2005]

Cohorts of uranium miners present an important source of information on the association between radon and lung cancer



Context

- Exposure measurement error may cause bias in risk estimates, a distortion in the exposure-risk relationship and a loss in power
- Regression calibration is the most popular method to correct for measurement error [Buonaccorsi et al., 2015]:
  - Requires a validation sample or measurement error variance is assumed to be known
  - It is difficult to correct heteroscedastic measurement error and measurement error in time-varying exposure variables
  - Disjoint steps to estimate true exposure and the risk parameters

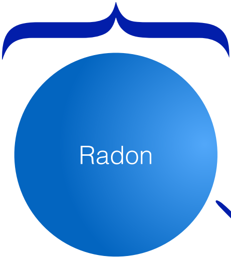
Context

The hierarchical Bayesian approach provides a natural and flexible way of combining exposure and parameter uncertainty in a coherent framework

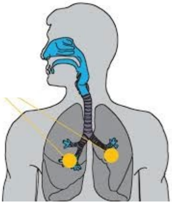
- Allows to take into account exposure uncertainty in risk estimation
- Flexible approach to account for
  - Heteroscedastic measurement error variances
  - Measurement error in time-varying exposures
  - Different types of measurement error simultaneously
  - Uncertainty in measurement error variance estimates
- Natural conditional reasoning in the Bayesian framework

Aim

Measurement error



Obtain a measurement
corrected estimate of
the lung cancer risk associated
with cumulative exposure to Radon



The French Uranium Miners' Cohort

1946

5086 uranium miners
employed for at least one year at CEA-COGEMA

31/12/2007

mean cumulated exposure:
36.61 WLM
(0.003 - 960.11)

mean follow-up:
35 years (0.1-60)

alive:
n = 2924

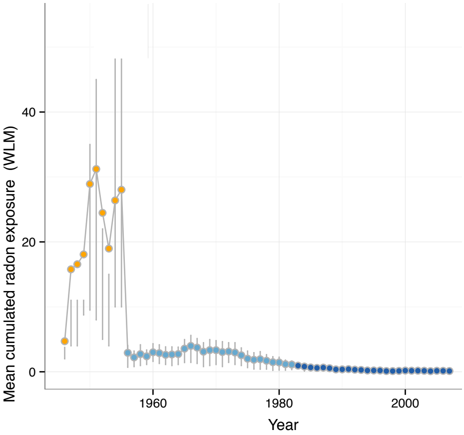
deceased:
n = 1935

deceased by lung cancer
n = 211 (11%)

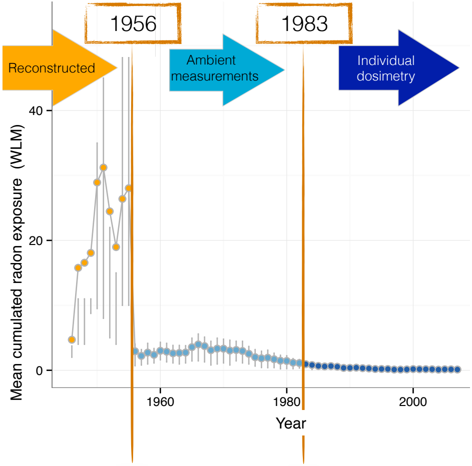
> 85 ans
n = 187

lost to follow-up
n = 40

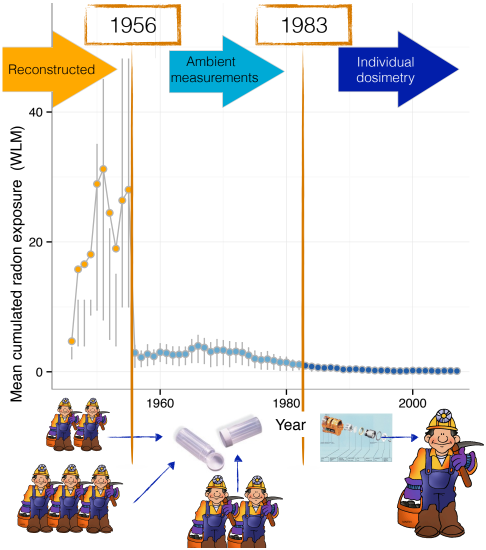
Radon Exposure in the Cohort



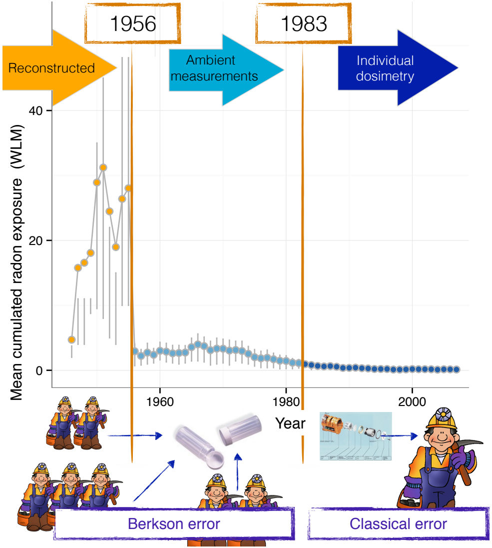
Radon Exposure in the Cohort



Radon Exposure in the Cohort



Radon Exposure in the Cohort



Modelling measurement error

[Richardson and Gilks, 1993] propose to account for measurement error using conditional independence models:

- **disease model:** $[Y_i|\boldsymbol{X_i}, \beta]$
- **measurement model:**
  $[\boldsymbol{Z_i}|\boldsymbol{X_i}, \sigma]$ for classical error
- **exposure model:** $[\boldsymbol{X_i}|\boldsymbol{V_i}, \pi]$ for classical error

where Y_i is the outcome, $\boldsymbol{X_i}$ denotes the vector of true exposure, $\boldsymbol{Z_i}$ the vector of observed exposure and $\boldsymbol{V_i}$ potential additional covariates for miner i

Modelling measurement error

[Richardson and Gilks, 1993] propose to account for measurement error using conditional independence models:

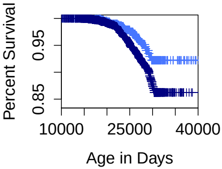
- **disease model:** $[Y_i|\boldsymbol{X_i}, \beta]$
- **measurement model:**
  $[\boldsymbol{X_i}|\boldsymbol{Z_i}, \sigma]$ for Berkson error

where Y_i is the outcome, $\boldsymbol{X_i}$ denotes the vector of true exposure, $\boldsymbol{Z_i}$ the vector of observed exposure

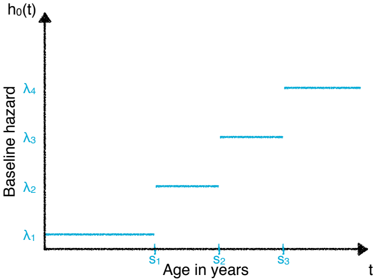
The disease model

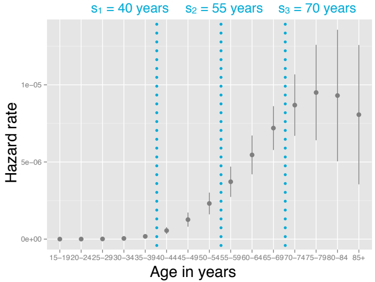
- $Y_i = \min(T_i, C_i)$, $\delta_i = \mathbb{1}_{[T_i < C_i]}$

$$h_i(t) = h_0(t) \left(1 + \beta \sum_{q=1}^{Q} X_{iq}(t)^{t_j - 5} \right)$$



- Describe $h_0(t)$ by a piecewise constant hazard model





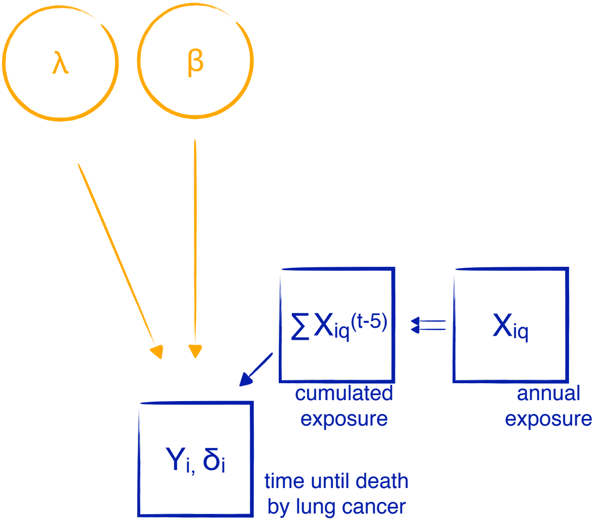
The measurement model

- Berkson model 1946 -1982:
  $X_{iq}^{B} = Z_{iq}^{B} \cdot U_{iq}$ where
  $\mathbb{E}(U_{iq}|Z_{iq}^{B}) = 1$
- Classical model after 1983:
  $Z_{iq}^{c} = X_{iq}^{c} \cdot U_{iq}$ where
  $\mathbb{E}(U_{iq}|X_{iq}^{c}) = 1$
- $U_{iq} \sim \mathcal{LN}\left(-\frac{\sigma_{p_{iq}}^2}{2}, \sigma_{p_{iq}}^2\right)$
- Measurement error characterisation in the cohort [Allodji et al., 2012]: Assume different error variances $\sigma_{p_{iq}}^2$ for the periods p 1946-1955, 1956-1974, 1975-1977, 1978-1982 and 1983-2007

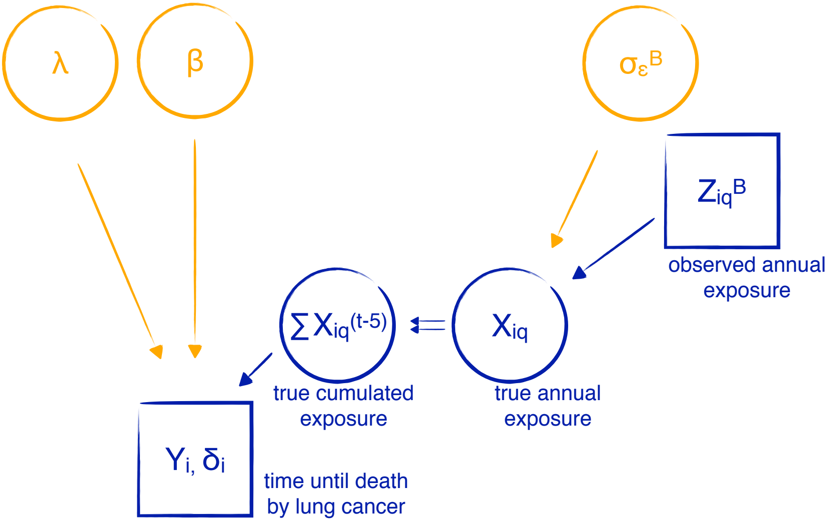
The exposure model

- True radon exposure is often found to be log normally distributed [Heid, 2002]
- [Zettwoog, 1981] and [Le Gac et al., 1981] identified distinct lognormal distribution according to type of work/ type of mining technique in French uranium mines
- Elicitation of priors concerning the means μ_x and the standard deviations σ_x is difficult

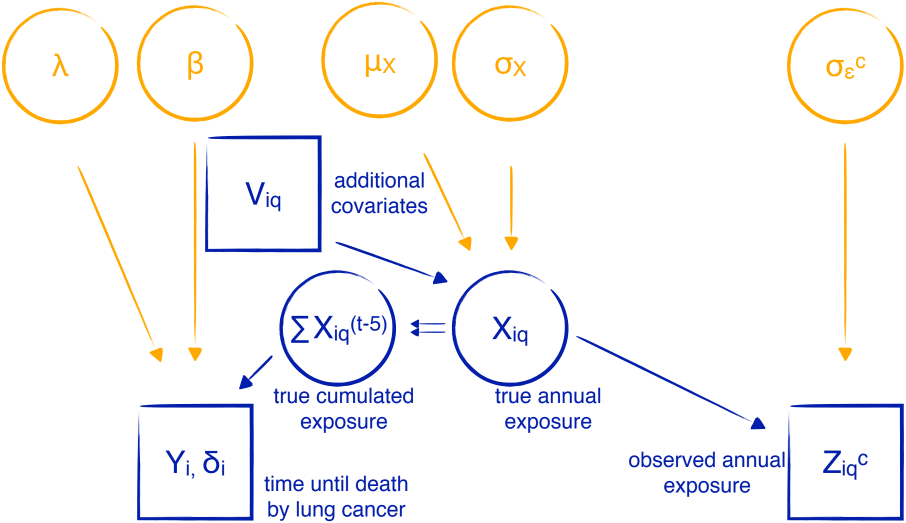
Integrating measurement error



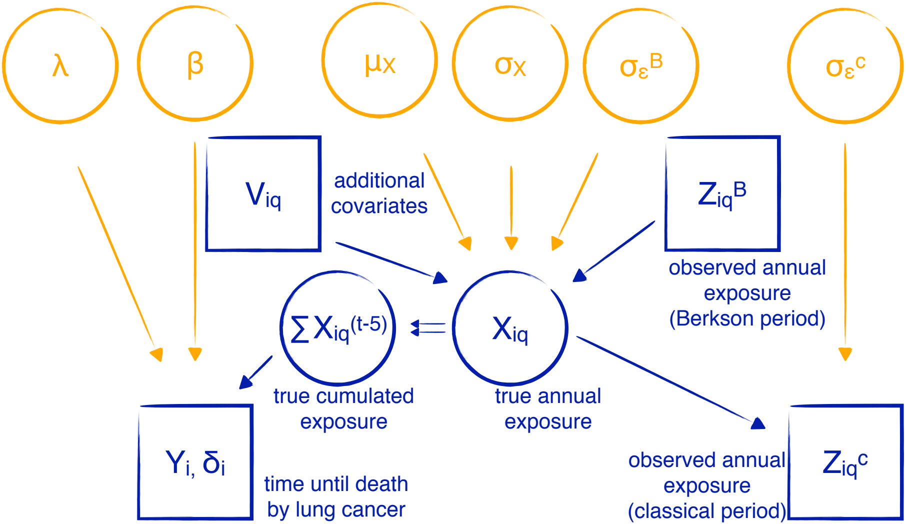
Integrating Berkson measurement error



Integrating classical measurement error



Integrating both types of measurement error



Bayesian inference

$$[\boldsymbol{\theta}|y,Z] \propto [\beta][\boldsymbol{\lambda}]\prod_{i=1}^{n}\left[y_i|\sum_{q=1}^{Q_i}X_{iq},\beta,\lambda\right]$$

$$\cdot\,[\boldsymbol{\sigma}_{\epsilon}^{B}]\prod_{i=1}^{n}\prod_{q=1}^{Q_i^B}\left[X_{iq}^{B}|Z_{iq}^{B},\boldsymbol{\sigma}_{\epsilon}^{B}\right]$$

$$\cdot\,[\mu_x][\sigma_x][\sigma_{\epsilon}^{c}][X_{iq}|V_{iq},\mu_x,\sigma_x]\prod_{i=1}^{n}\prod_{q=1}^{Q_i^c}\left[Z_{iq}^{c}|X_{iq}^{c},\sigma_{\epsilon}^{c}\right]$$

Bayesian inference

$$[\boldsymbol{\theta}|y, Z] \propto [\beta][\boldsymbol{\lambda}]\prod_{i=1}^{n}\left[y_i|\sum_{q=1}^{Q_i} X_{iq}, \beta, \lambda\right]$$

$$\cdot [\boldsymbol{\sigma}_{\epsilon}^{B}]\prod_{i=1}^{n}\prod_{q=1}^{Q_i^B}\left[X_{iq}^{B}|Z_{iq}^{B}, \boldsymbol{\sigma}_{\epsilon}^{B}\right]$$

$$\cdot [\mu_x][\sigma_x][\sigma_{\epsilon}^{c}][X_{iq}|V_{iq}, \mu_x, \sigma_x]\prod_{i=1}^{n}\prod_{q=1}^{Q_i^c}\left[Z_{iq}^{c}|X_{iq}^{c}, \sigma_{\epsilon}^{c}\right]$$

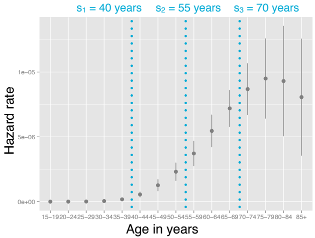
- Adaptive Metropolis-Hastings algorithm developed and tested in Python to sample from the joint posterior distribution with Gibbs steps to update μ_x and σ_x
- Model comparison based on Deviance Information Criterion (DIC)

Updating latent exposures

- Create homogeneous groups of miners based on information on mine location, type of mine and type of work
- Multiple correspondance analysis ⇒ hierarchical clustering
- Result: 334 groups for Berkson period
- Update $\log(X)$ instead of X in order to respect the constraint $X > 0$ and to improve convergence

Prior distributions

- $[\beta]$: $\beta \sim \mathcal{N}(0, 10^4)$
  truncated at $-\frac{1}{\max_i \sum_j X_{ij}}$ (to guarantee $h_i > 0$)
- $[\boldsymbol{\lambda}]$: $\lambda_j \sim \mathcal{G}(\alpha_{0j}, \lambda_{0j})$ for each component j, $j = 1, \ldots, 4$



- $[\boldsymbol{\sigma}_\epsilon]$: No validation sample available, fix values at $\hat{\sigma}_{\epsilon 1} = 0.94$, $\hat{\sigma}_{\epsilon 2} = 0.47$, $\hat{\sigma}_{\epsilon 3} = 0.42$, $\hat{\sigma}_{\epsilon 4} = 0.33$, $\hat{\sigma}_{\epsilon 5} = 0.10$
  estimates [Allodji et al., 2012]
  or alternatively $\sigma_{\epsilon p} \sim \mathcal{N}(\hat{\sigma}_p, 0.02)$ for $p \in \{1, 2, 3, 4, 5\}$

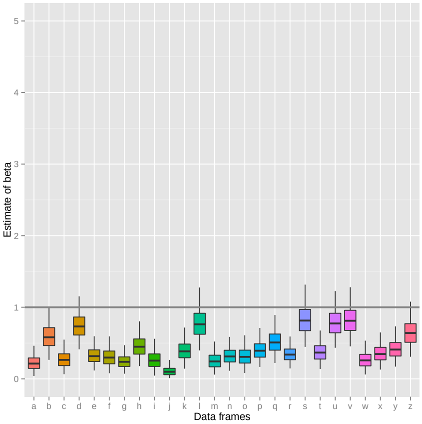
Preliminary simulation study

- n = 1000 miners
- X is time dependent: Use a method based on piecewise exponential variables proposed by [Hendry, 2014]
- $\beta = 1$
- $\sigma^2_{\epsilon 1} = 0.8$ and $\sigma^2_{\epsilon 2} = 0.3$
- Random censoring (exponential distribution)
- For classical error: μ_x and σ_x are supposed to be known
- Flat prior distributions

Classical error $\sigma_1^2 = 0.3$ $\sigma_2^2 = 0.5$ $\beta = 1$

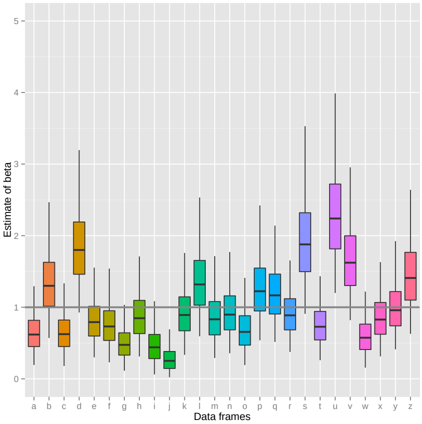
Uncorrected risk estimate:

$\beta_{median} = 0.42$ [0.17, 0.76]
with cover probability 0.20

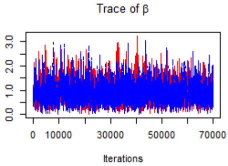


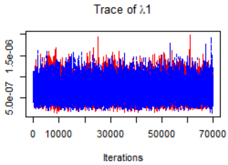
Corrected risk estimate:

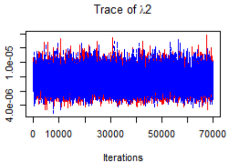
$\beta_{median} = 1.01$ [0.42, 1.96]
with cover probability 0.957

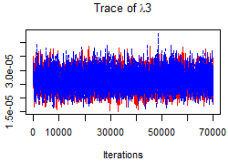


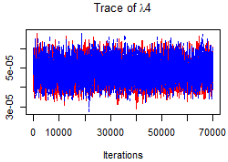
Classical error $\sigma_1^2 = 0.3$ $\sigma_2^2 = 0.5$ $\beta = 1$

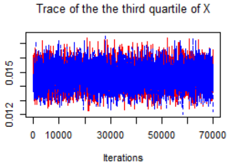


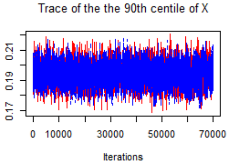






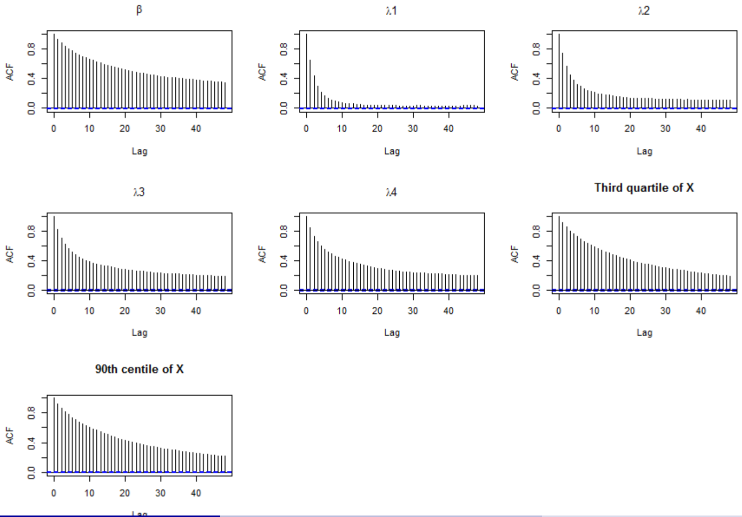






Classical error $\sigma_1^2 = 0.3$ $\sigma_2^2 = 0.5$ $\beta = 1$

Effective sample size: 543.52 for 70 000 iterations (burnin of 25 000)



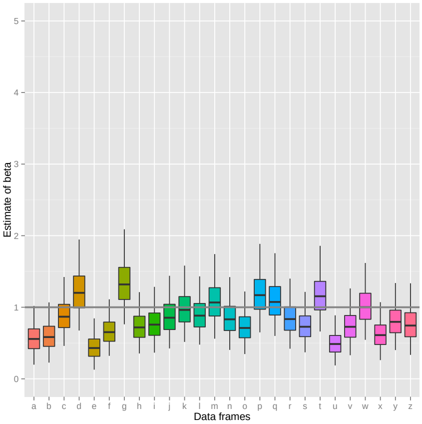
Berkson error $\sigma_1^2 = 0.8$ $\sigma_2^2 = 0.3$ $\beta = 1$

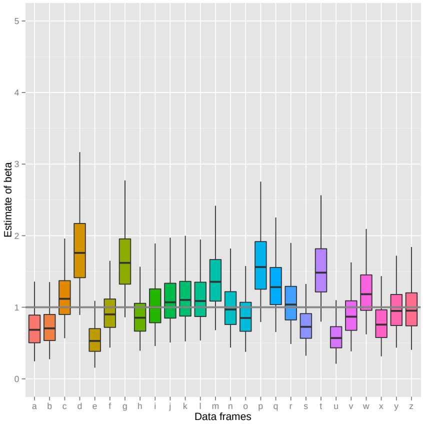
Uncorrected risk estimate:

$\beta_{median} = 0.83$ [0.42, 1.40]
with cover probability 0.90

Corrected risk estimate:

$\beta_{median} = 1.04$ [0.49, 1.90]
with cover probability 1





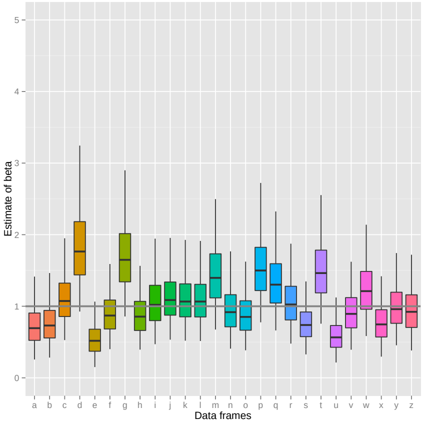
Results when σ_ϵ is estimated

Classical error:

$\beta_{median} = 0.98$ [0.41, 1.89]
with cover probability 0.92

Berkson error:

$\beta_{median} = 1.05$ [0.50, 1.94]
with cover probability 1

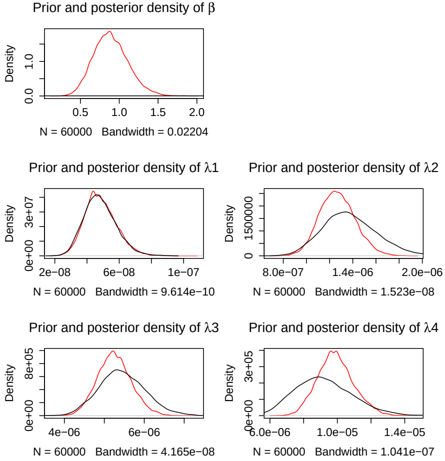


Application to the data of the cohort

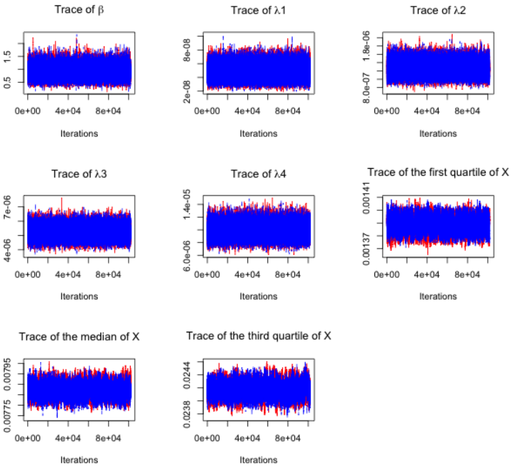
Model	DIC
Intercept only	5458.41
linear	5433.21
piecewise linear	5426.58

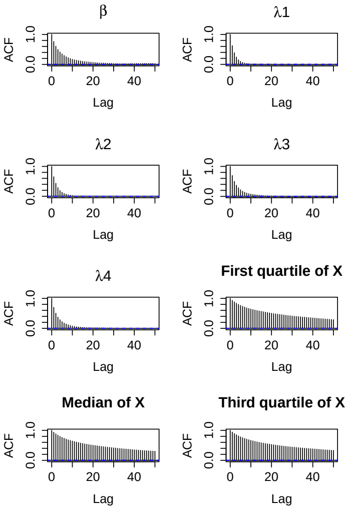
Model	β_1	β_2
Linear without measurement error	0.89 (0.23) [0.49;1.37]	
Linear with Berkson measurement error	0.92 (0.23) [0.51; 1.40]	
Piecewise linear without measurement error	1.48 (0.35) [0.84;2.21]	0.31 (0.23) [0.01;0.86]
Piecewise linear with Berkson measurement error	1.48 (0.35) [0.86; 2.21]	0.30 (0.24) [0.002; 0.88]

ESS = 42 864 for β

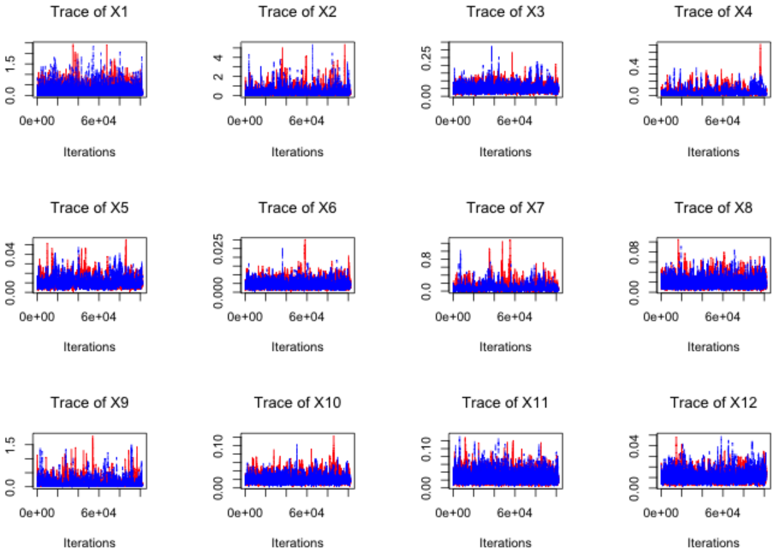


Checking the convergence of the full model





Checking the convergence of the full model



Discussion

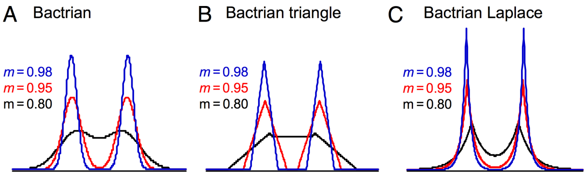
- Bayesian approach flexible, possible to account for external information
- Taking Berkson type measurement error into account does not seem to substantially change the risk associated with cumulative exposure to radon [Küchenhoff et al., 2007]
- Non linearity persists when measurement error is accounted for [Stayner et al., 2003]
- Further research is needed to compare the proposed methodology with classical methods for measurement error correction
- Use Bayes factors instead of DIC

Perspectives: Is the Metropolis Hastings appropriated?

Effective sample size small due to autocorrelations

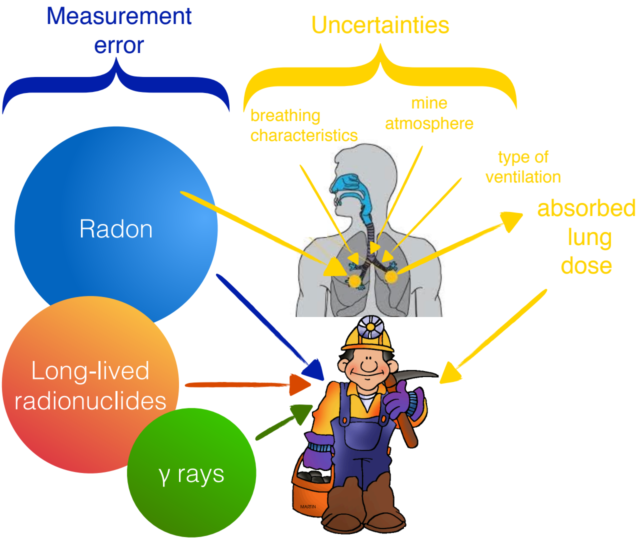
⇒ Possible remedies:

- Use alternative proposal distributions [Yang and Rodrigues, 2013] ?



- Use Hamiltonian dynamics:
  - No-U-Turn sampler?
  - Use second derivatives ?
  - Randomly selecting number of leapfrog steps
- INLA ?

Perspectives: Integrating dose uncertainties



Thank you for your attention

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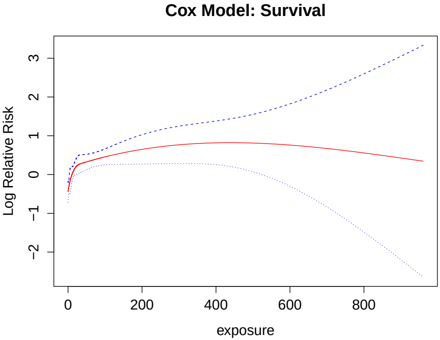
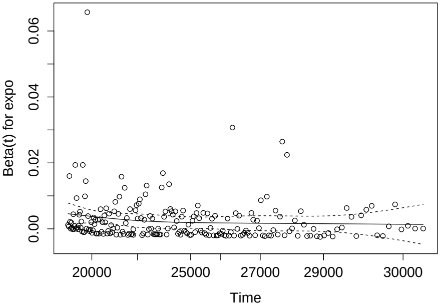
Checking the model assumptions

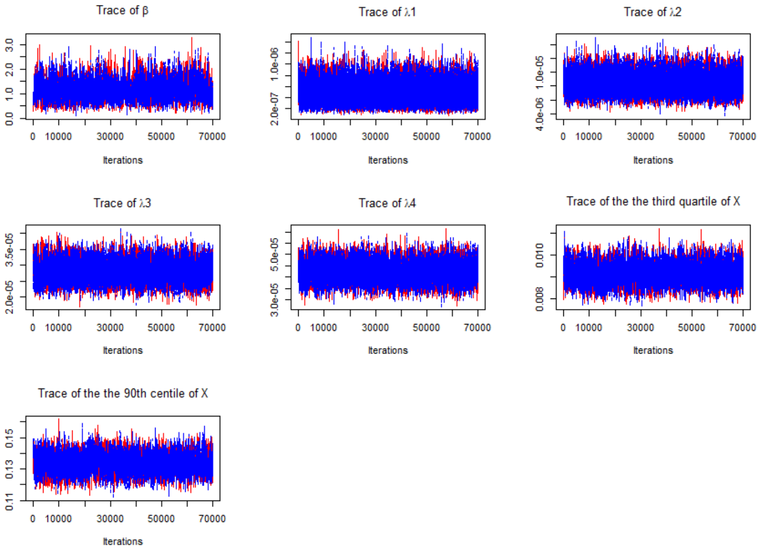
Test linear model against linear-quadratic model:
$p = 0.006 < 0.05$

Proportional hazards assumption
Harrell test: $p = 0.16 > 0.05$



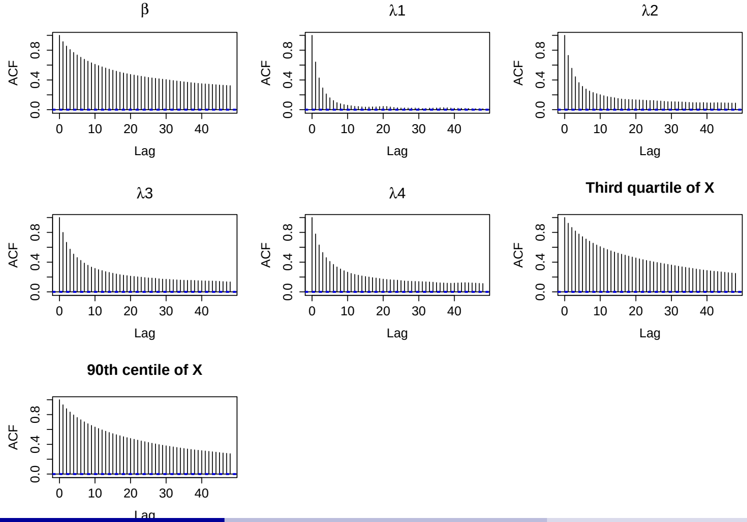


Berkson error $\sigma_1^2 = 0.3$ $\sigma_2^2 = 0.5$ $\beta = 1$



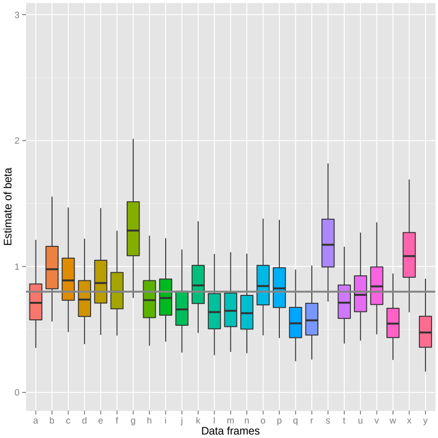
Berkson error $\sigma_1^2 = 0.3$ $\sigma_2^2 = 0.5$ $\beta = 1$

Effective sample size: 561.89 for 70 000 iterations (burnin of 25 000)

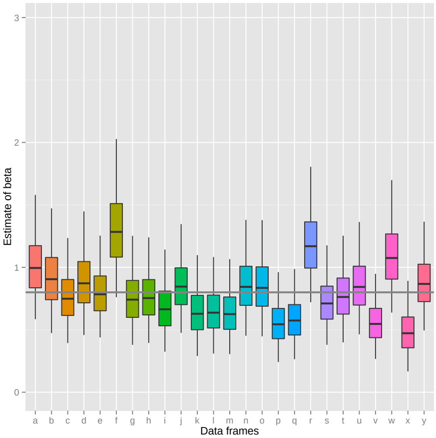


Berkson error $\sigma_1^2 = 0.2$ $\sigma_2^2 = 0.1$ $\beta = 0.8$

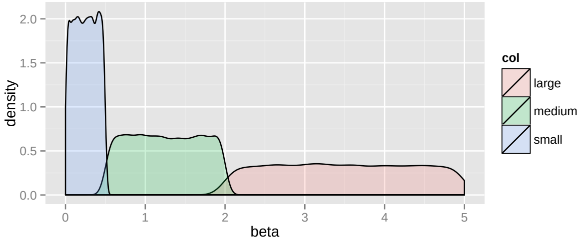
- $\beta_{median} = 0.85$ [0.47, 1.38] with cover probability 0.98

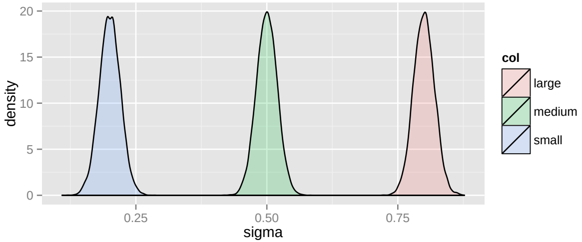


- $\beta_{median} = 0.86$ [0.47, 1.39] with cover probability 0.97



Perspectives: More extensive simulation studies

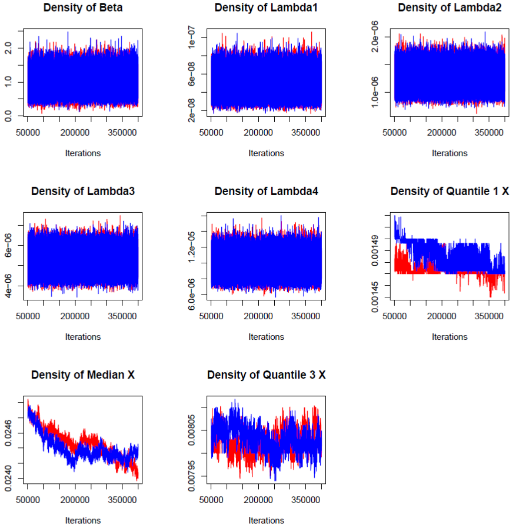




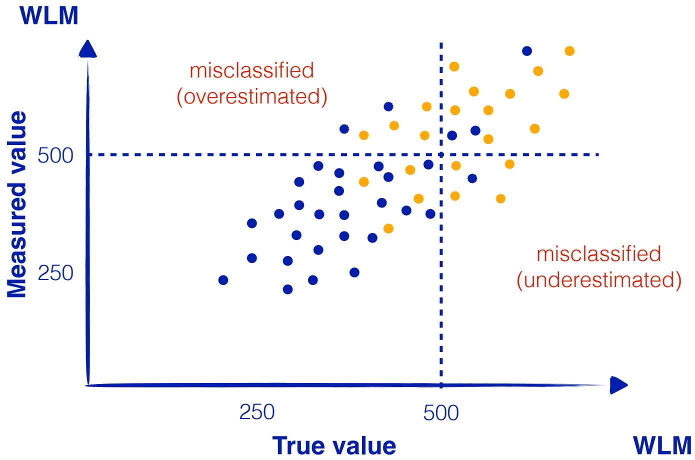
Integrating measurement error

Model	β_1	β_2	λ_1 in 10^{-8}	λ_2 in 10^{-6}	λ_3 in 10^{-6}	λ_4 in 10^{-6}
Linear without	0.89 (0.23)		4.85 (0.97)	1.27 (0.15)	5.25 (0.42)	9.90 (1.15)
measurement error	[0.49;1.37]		[3.15 ;6.94]	[0.99;1.58]	[4.46; 6.12]	[7.92;12.14]
Linear with Berkson	0.92 (0.23)		4.82 (0.96)	1.26 (0.15)	5.24 (0.42)	9.88 (1.09)
measurement error	[0.51; 1.40]		[3.13 ;6.87]	[0.98 ;1.58]	[4.44;6.09]	[7.91;12.11]
Piecewise linear without	1.48 (0.35)	0.31 (0.23)	4.81 (0.96)	1.23 (0.15)	5.02 (0.41)	9.39 (1.04)
measurement error	[0.84;2.21]	[0.01;0.86]	[3.12 ;6.82]	[0.95;1.53]	[4.26; 5.87]	[7.47;11.55]
Piecewise linear with Berkson	1.48 (0.35)	0.30 (0.24)	4.86 (0.98)	1.23 (0.15)	5.03 (0.41)	9.39 (1.02)
measurement error	[0.86; 2.21]	[0.002; 0.88]	[3.06 ;6.93]	[0.95 ;1.55]	[4.24;5.87]	[7.49;11.44]

Convergence when updating X instead of $\exp(X)$



Misclassification in Poisson regression



Simulate survival times with time-varying covariates

- [Hendry, 2014] proposes to write the hazard of individual j at time t as $h_j(t) = h_0(t) \cdot \lambda_i = [\frac{\partial g^{-1}(t)}{\partial t}] \cdot \exp(X_i(t) \cdot \beta)$
- You have to choose a baseline hazard $h_0(t) = \frac{\partial [g^{-1}(t)]}{\partial t}$ with $g(0) = 0, g(t) \nearrow$ and $g^{-1}(t)$ differentiable
- Calculate $\{\lambda_{ij}\}_{j=1}^{t}$ for every subject i at time j and generate V_i as truncated piecewise exponential with rates $\lambda_{i1}, \ldots, \lambda_{iJ}$
- Calculate $T_i = g(V_i)$
- Define a censoring indicator $\delta_i{}_{i=1}^{n}$, where $\delta_i \in \{0, 1\}$
- Delete all data lines of individual i that are greater than T_i

$\Rightarrow$ **Validated method of data simulation with the function** *phreg* **from the R package** *eha*

Characterisation of the error periods in the French cohort of uranium miners

Sources	Periods 1956–74	1975–77	1978–82	1983–99
Natural variations of air-borne radon gas concentration	30.0	21.2	21.2	0.0
Precision of the measurement device	20.0	20.0	20.0	10.0
Approximation of equilibrium factor	29.4	29.4	11.8	0.0
Operator in charge of air samples	2.0	2.0	2.0	0.0
Estimation of working time	4.0	4.0	8.0	0.0
Record-keeping and data transcription	1.5	1.5	1.5	1.0
Combined relative standard uncertainty[a]	46.8	41.7	32.6	10.1

[a] Estimated using the root sum square (RSS) method.

Effect modifying variables

- Single most important effect modifying variable in the French cohort of uranium miners:
  Period before 1956 or after 1956: After this variable is included in the model, time since exposure and exposure rate are no longer significant [Vacquier, 2008]
- Attenuation of exposure-response curves in occupational studies at high exposure levels is a general known phenomenon [Stayner et al., 2003]
- In the Colorado plateau uranium miners cohort, the inverse exposure-rate effect is weakened after measurement error correction [Stram, 1999]

Comparing different disease models

Model	DIC
Intercept only	5458.41
Excess relative risk model $X_i^{\text{cum}}(t)$	5433.39
Excess relative risk model $X_i^{\text{cum}}(t) \cdot \exp(A_i(t))$	5436.02
Cox-like model $X_i^{\text{cum}}(t)$	5443.64
Cox-like model $X_i^{\text{cum}}(t) \cdot \exp(A_i(t))$	5445.03

Model	β	γ	λ_1 in 10^{-8}	λ_2 in 10^{-6}	λ_3 in 10^{-6}	λ_4 in 10^{-6}
ERR $X_i^{\text{cum}}(t)$	0.89 (0.23)	-	4.85 (0.97)	1.27 (0.15)	5.25 (0.42)	9.90 (1.07)
	[0.49;1.37]	-	[3.15 ;6.94]	[0.99;1.58]	[4.46; 6.12]	[7.92;12.14]
ERR $X_i^{\text{cum}}(t) \cdot$	0.85 (0.23)	0.14 (0.32)	4.87 (0.98)	1.28 (0.15)	5.28 (0.43)	9.94 (1.07)
$\exp(A_i(t))$	[0.45; 1.34]	[-0.53; 0.71]	[3.13 ;6.91]	[0.99 ;1.60]	[4.49;6.15]	[7.92;12.17]

Effect of calendar period on baseline hazard

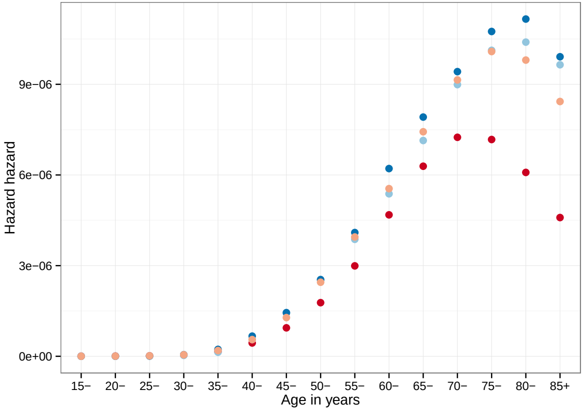


Figure: Hazard of lung cancer mortality in French males for the following periods: 1968-1977 (red), 1978-1987 (orange), 1988-1997 (blue), 1998-2005 (lightblue)

Smoking as effect modifying factor

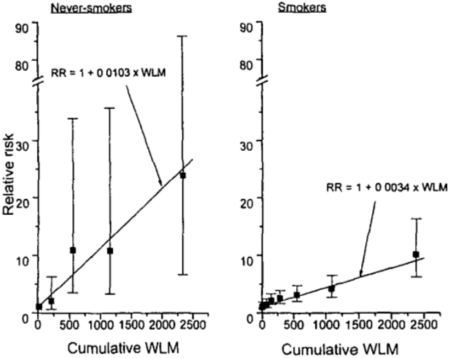
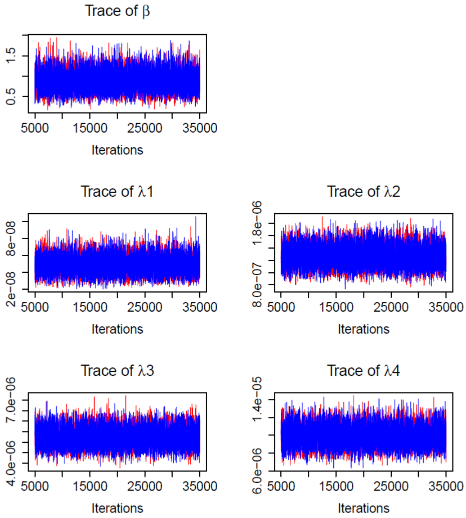


Figure 3. Relative risk (RR) of lung cancer with cumulative radon exposure among lifelong non-smokers and others in the six cohort studies of underground miners for which smoking information was available (based on [18]). Although the increase in relative risk per unit exposure is higher for never smokers than for smokers, the increase in absolute risk will be higher for smokers, as they have much higher rates of lung cancer.

Convergence disease model



Regression calibration

- Basic idea: Replace **X** by the regression of **X** on (**Z**, **W**) where **W** are predictors measured without error
- Algorithm:
  - Using replication, validation or instrumental data, estimate the regression of **X** on (**Z**,**W**)
  - Replace the unobserved **X** by its estimate and run a standard analysis to obtain parameter estimates
  - Adjust the resulting standard errors to account for exposure uncertainty using either the bootstrap or a sandwich method