

# Bayesian hierarchical modeling to account for complex patterns of measurement error in cohort studies. Application in radiation epidemiology.

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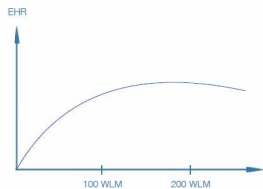
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- Estimation of health risks potentially associated with exposure to one or more pathogens  $\Rightarrow$  one main focus of interest in epidemiological studies
- Measurement error on these exposures (predictor variables) are :
  - ▶ ubiquitous
  - ▶ one of the most important source of input uncertainty

- In retrospective cohort studies :
  - ▶ complex patterns of exposure measurement error
  - ▶ attenuation of the exposure-risk relationship for high exposure values [HertzPicciotto (1993), Stayner (2003)] Effect of measurement error ?



- If not accounted for, exposure measurement error may cause [Carroll et al. (2006)] :
  - ▶ bias in risk estimates
  - ▶ misleading conclusions about the effect of these exposures on the disease risk
  - ▶ a distortion of the exposure-risk relationship

# Standard methods to account for exposure measurement error

- Frequentist functional methods : regression calibration and simulation extrapolation [Carroll et al. (2006); Keogh et al. (2020)]
  - ▶ Lack of flexibility to account for complex measurement error on time-varying exposures
    - Mixture of different types of measurement error
    - Heteroscedastic measurement error
  - ▶ Disjoint steps to estimate "true" exposure and risk parameters
  - ▶ Applicability restricted to cases where a validation sample is available to estimate the expected value of true exposure given observed exposure or the true size of the error
  - ▶ Potential lack of consistency in risk estimates in proportional hazards models [Bartlett and Keogh, 2016]

# The Bayesian structural alternative

- Combination of conditionally independent submodels [Richardson & Gilks (1993)] :
  - ▶ **Disease submodel** : it describes the relation between the "true" unknown exposures and the disease outcome
  - ▶ **Measurement submodel** : it describes the relation between the observed and the "true" unknown exposures
  - ▶ **Exposure submodel** : it describe the probability distribution of the "true" exposures

⇒ Often results in a hierarchical structure

- Flexible approach to describe and account for complex measurement error
- Fitting such a model under the Bayesian paradigm :
  - ▶ Allows for the **joint estimation** of all unknown quantities
  - ▶ Allows to integrate **external information** through the specification of informative priors
  - ▶ **Credible interval** for risk estimates are easily obtained as by-product of Bayesian inference (without asymptotic assumption !)

# Aim of the talk

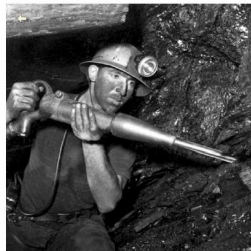
- Present a Bayesian structural approach to account for **complex** exposure measurement error in risk estimates focusing on the following context :
  - ▶ Time-varying exposure variables
  - ▶ Right-censored survival data (outcome variable)

# Motivating case study

## Lung/Kidney cancer and chronic low-dose exposure to radon

- Radon is a radioactive gas which presents the primary source of background radiation
- Radon is the second cause of lung cancer (after tobacco) [Samet and Eradze, 2000]
- Kidney = Main target organ of uranium [ATSDR, 2013]
  - ▶ Is there any association between the risk of death from kidney cancer and cumulative exposure to radon ?

Thanks to annual radiological exposures collected over the entire career, the French cohort of uranium miners is a reference population to study the long-term health effects of chronic low-dose exposure to radon (Inhalation exposure) and define radon exposure thresholds



Source : André De Marles, « Surhomme mineur de Guy DUBOIS »

## The French cohort of uranium miners

- 5086 French uranium miners employed for at least one year at CEA-COGEMA
- Mean follow-up : 39 years (min=0.1,max=67)
- Mean duration of exposure to radon : 13 years (min :1.0, max=41.0)

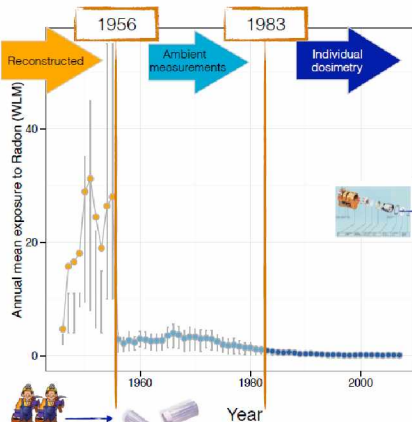
Vital status	Number of miners (%)
Alive	2580 (50.7)
Deceased (Lung cancer)	<b>268</b> (5.3)
Deceased (Kidney cancer)	<b>30</b> (0.6)
Deceased (Other causes)	2166 (42.6)
Lost of follow-up	42 (0.8)

Some characteristics of the cohort at 31st December 2014 (end of follow-up)

⇒ **Highly right-censored survival data + few cases of lung and kidney cancer**

# Radon exposure in the French cohort of uranium miners

MINE	
Henriette	
De 1947	10
à 1950	10
1951	10
1952	10
1953	10
1954	10
1955	10





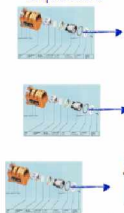
# Different types of measurement error

## Classical measurement error

$$Z_i(t) = X_i(t) \cdot U_i(t)$$

- $U_i(t) \perp X_i(t)$
- $\text{Var}(Z_i(t)) > \text{Var}(X_i(t))$

$Z_i(t)$ : observed exposure



$X_i(t)$ : true exposure

## Berkson error

$$X_i(t) = Z(t) \cdot U_i(t)$$

- $U_i(t) \perp Z(t)$
- $\text{Var}(X_{ij}(t)) > \text{Var}(Z(t))$



$Z(t)$ : fixed exposure

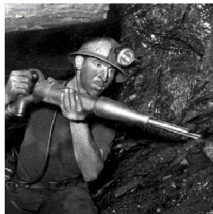
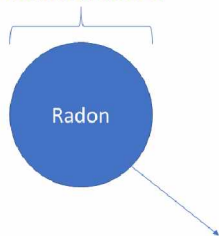
$X_3(t)$ : true exposure

$X_1(t)$ : true exposure

$X_2(t)$ : true exposure

# Applied objective

Measurement error



Source : André De Marles, « Surhomme mineur de Guy DUBOIS »

Obtain a measurement corrected estimation of **lung and kidney** cancer mortality risks as well as their associated uncertainty

## The disease submodel (1/2)

Let's consider **one event of interest** (e.g., death by lung or kidney cancer)

- Disease outcomes :  $(Y_i, \delta_i)$  with  $Y_i = \min(T_i, C_i)$ ,  $T_i$  the age at the time of event for individual  $i = \{1, \dots, N\}$ ,  $C_i$  the age at censorship and  $\delta_i$  the non-censoring indicator
- Modelling the hazard rate of event for miner  $i$  at time  $t \in [0, +\infty[$

$$h_i(t; \beta, \theta) = h_0(t; \theta) \rho(\beta; X_i^{cum}(t))$$

- ▶  $X_i^{cum}(t)$  : 5-year lagged cumulative exposure to radon of individual  $i$  at time  $t$
  - ▶  $h_0(t; \theta)$  : Baseline hazard rate at time  $t$  (i.e., for any unexposed individual)
  - ▶  $\rho(\beta; X_i^{cum}(t))$  : Radiation-related hazard ratio (HR)
  - ▶  $\beta$  : **Unknown risk coefficient**
- Assumption : Non-informative censoring

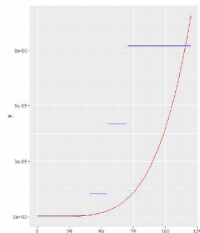
### Contribution to the likelihood of individual $i$ for the disease submodel

$$[(y_i, \delta_i) | \beta, \lambda] \propto h_i(y_i; \beta, \theta)^{\delta_i} S_i(y_i; \beta, \theta) \text{ where } S_i(y_i; \beta, \theta) = \exp\left(-\int_0^{+\infty} h_i(u; \beta, \theta) du\right)$$

## The disease submodel (2/2)

- Modeling the baseline hazard function :

- $h_0(t; \lambda) = \sum_{k=1}^K \lambda_k \mathbb{1}_{t \in I_k}$  with  $\lambda_k > 0$
- $h_0(t; \alpha, \xi) = \xi t^{\alpha-1}$  with  $\xi > 0$ ;  $\alpha > 0$



- Modeling the hazard ratio function :

- $\rho(\beta; X_i^{cum}(t)) = \exp(\beta X_i^{cum}(t)) \Rightarrow$  Cox Model
- $\rho(\beta; X_i^{cum}(t)) = 1 + \beta X_i^{cum}(t) \Rightarrow$  Excess Hazard Ratio (EHR) model
  - Constraint :  $\beta > -\frac{1}{\text{Max}_{i,t}(X_i^{cum}(t))}$

## Exposure period 3 : 1983-2007

- **Classical measurement error** (due to the accuracy of the personal dosimeter) BUT **neglected** in the following as the magnitude of error is much smaller than in earlier periods

⇒ No impact on risk estimates [Hoffmann et al., 2017]

## Exposure period 2 : 1956-1982

### Notations

For year  $t$  in the exposure period  $B=\{1,2\}$  :

- $Z_j^B(t)$  : Estimated mean exposure for all the individuals of mine  $j$
- $T_{ij}^B(t)$  : Effective working time (in months) for individual  $i$  of group  $j$
- $X_{ij}^2(t)$  : "True" exposure for individual  $i$  of group  $j$

### Measurement submodel $\mathcal{M}_1$ = Shared Berkson model

$$X_{ij}^2(t) = Z_j^2(t) \cdot T_{ij}^2(t) \cdot U_i^2$$

- $U_i^2$  : Individual-specific shared Berkson error component (Individual worker practices)
- $U_i^2 \sim^{i.i.d} \mathcal{LN}\left(-\frac{\sigma_2^2}{2}, \sigma_2^2\right) \Rightarrow \mathbb{E}(X_{ij}^2(t) | Z_j^2(t), T_{ij}^2(t)) = Z_j^2(t) \cdot T_{ij}^2(t)$  (Random error)
- Fixed magnitude of the Berkson error :  $\sigma_2 = 0.39$  [Allodji et al., 2012]

## Exposure period 1 : 1946-1955 (1/2)

### A first modelling assumption

#### Measurement submodel $\mathcal{M}_1$ : Shared Berkson model

$$X_{ij}^1(t) = Z_j^1(t) \cdot T_{ij}^1(t) \cdot U_i^1$$

- $U_i^1$  : Individual-specific shared Berkson error component
- $U_i^1 \sim^{i.i.d} \mathcal{LN}\left(-\frac{\sigma_1^2}{2}, \sigma_1^2\right)$
- Fixed magnitude of Berkson error :  $\sigma_1 = 0.93$  [Allodji et al., 2012]

## Exposure period 1 : 1946-1955 (2/2)

### An alternative model

#### Measurement submodel $\mathcal{M}_2$

$$X_{ij}^1(t) = Z_j^1(t) \cdot T_{ij}^1(t) \cdot U_i^1 \quad \text{if } Z_j^1(t) \text{ is unknown}$$
$$\begin{cases} Z_j^1(t) = \zeta_j^1(t) \cdot U_j \\ X_{ij}^1(t) = \zeta_j^1(t) \cdot T_{ij}^1(t) \cdot U_i^1 \end{cases} \quad \text{otherwise (18 mines)}$$

- $U_i^1$  : Individual-specific shared Berkson error component
  - ▶  $U_i^1 \sim^{i.i.d} \mathcal{LN}\left(-\frac{\sigma_1^2}{2}, \sigma_1^2\right)$  with  $\sigma_1 = 0.84$
- $U_j$  : Mine-specific classical error component on  $Z_j^1(t)$  that was retrospectively estimated by experts
  - ▶  $U_j \sim^{i.i.d} \mathcal{LN}\left(-\frac{\sigma_*^2}{2}, \sigma_*^2\right)$  with  $\sigma_* = 0.41$
- $\zeta_j^1(t)$  : "true" mean exposure for all the individuals of group  $j$  at year  $t$

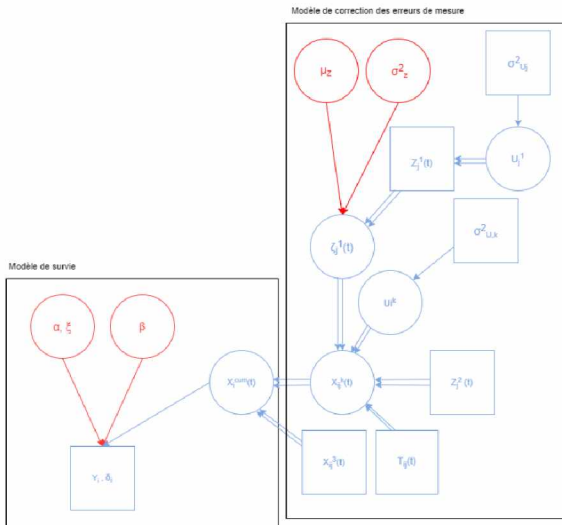
#### Exposure submodel

$$\zeta_j^1(t) \sim^{i.i.d} \mathcal{LN}(\mu_\zeta, \sigma_\zeta^2)$$



# Directed Acyclic Graph

Disease submodel +  $\mathcal{M}_1$  : 1956-82 +  $\mathcal{M}_2$  : 1946-1955



# Prior distributions

- $[\beta]$  :  $\beta \sim \mathcal{N}(0, 10^6)$  left-sided truncated at 0 to guarantee  $h_i > 0$
- $[\alpha]$  :  $\alpha \sim \mathcal{G}(0.01, 0.01)$
- $[\xi]$  :  $\xi \sim \mathcal{G}(1, 1)$
- $[\mu_\zeta]$  :  $\mu_\zeta \sim \mathcal{N}(0, 100)$
- $[\sigma_\zeta]$  :  $\sigma_\zeta \sim \mathcal{G}(0.001, 0.001)$

+ Prior sensitivity analysis for  $\alpha$  and  $\xi$

# Bayesian inference

- Complex joint posterior distribution  $\theta = (\beta, \alpha, \xi, \mu_\zeta, \sigma_\zeta, \zeta, \mathbf{U})$
- More than 198,000 pseudo-observations
- More than 4,000 unknown quantities to estimate  
=> **High dimensional posterior distribution**
  
- Adaptive Metropolis-Within-Gibbs algorithm developed in Python 3.4
  - ▶ (Left-sided truncated) Gaussian random Walk Metropolis-Hastings for  $\beta$  and  $\alpha$
  - ▶ Multiplicative random walk Metropolis-Hastings for  $\zeta, U_i^B$
  - ▶ Gibbs sampling for  $\xi, \mu_\zeta, \sigma_\zeta$
  - ▶ **Block updating** of individual-specific shared Berkson error component  $U_i$  after defining 239 homogeneous groups of miners (hierarchical clustering) based on information on :
    - Mine location
    - Type of mine
    - Job type
  - ▶ Reparametrizations to improve mixing of the chains (e.g.  $\xi$  parameter)
  - ▶ Targeted acceptance rate : About 40% for single parameters and 20% for vectors
  - ▶ Running time : **5 days** for 2 Markov chains, 10,000 iterations for the adaptive phase + 60,000 iterations including 20,000 iterations for the burn-in phase

# Application to the French cohort of uranium miners

## Case 1 : Death by lung cancer and chronic exposure to radon

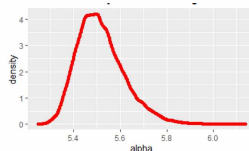
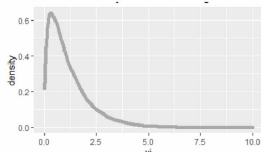
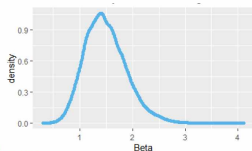
Posterior medians and 95% credible intervals for the hazard ratio of death by lung cancer

Model	HR**	95% CI	WAIC***
Baseline model ( $\beta = 0$ )			6895
$\mathcal{M}_0^*$	2.08	[1.61; 2.72]	6861
$\mathcal{M}_1$ periods 1 & 2	2.30	[1.75; 3.07]	6861
$\mathcal{M}_2$ period 1 + $\mathcal{M}_1$ period 2	2.45	[1.82; 3.37]	6859

\*  $\mathcal{M}_0$  : Disease model **without accounting** for exposure measurement error

\*\* HR : Hazard Ratio for 100 Working Level Months (i.e.,  $1 + \beta \times 100$ )

\*\*\* WAIC : Widely Applicable Information Criterion (conditional)



# Application to the French cohort of uranium miners

## Case 2 : Death by kidney cancer and chronic exposure to radon

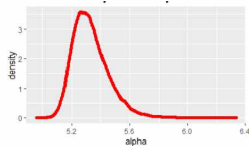
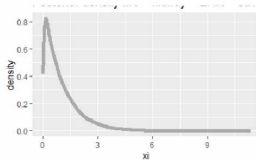
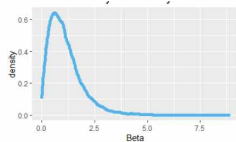
Posterior medians and 95% credible intervals for the hazard ratio of death by kidney cancer

Model	HR**	95% CI	WAIC****
Baseline model ( $\beta = 0$ )			905
$\mathcal{M}_0^*$	2.05	[1.12; 4.51]	905
$\mathcal{M}_1$ periods 1 & 2	2.09	[1.12; 4.49]	908
$\mathcal{M}_2$ period 1 + $\mathcal{M}_1$ period 2	1.95	[1.11; 3.22]	908

\*  $\mathcal{M}_0$  : Disease model **without accounting** for exposure measurement error

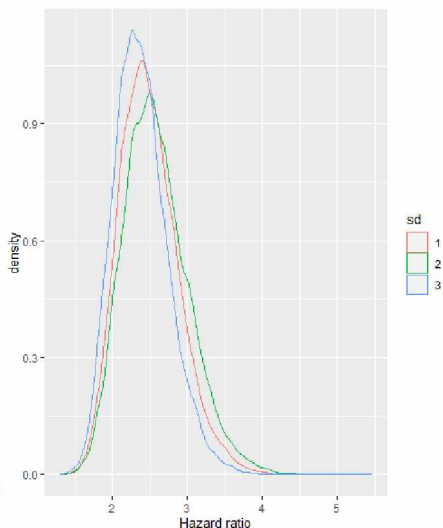
\*\* HR : Hazard Ratio for 100 Working Level Months (i.e.,  $1 + \beta \times 100$ )

\*\*\* WAIC : Widely Applicable Information Criterion (conditional)



# Sensitivity of the hazard ratio posterior distribution to the error variance parameters

## Case 1 : Death by lung cancer and chronic exposure to radon



- $sd=1$ 
  - ▶  $\sigma_1 = 0.84$  (Berkson error);
  - ▶  $\sigma_* = 0.41$  (Classical error)
- $sd=2$ 
  - ▶  $\sigma_1 = 0.84$  (Berkson error);
  - ▶  $\sigma_* = 0.84$  (Classical)
- $sd=3$ 
  - ▶  $\sigma_1 = 0.63$  (Berkson error);
  - ▶  $\sigma_* = 0.31$  (Classical error)

# Conclusions

- We propose different Bayesian hierarchical models to account for **complex** exposure measurement error in risk estimates when working with **time-varying exposure variables** and **right-censored survival data**
- First application of the Bayesian structural approach in radiation epidemiology
  - ▶ (Potentially) improved risk estimates in a **weakly informative context**
  - ▶ Improved considerations of **uncertainties**
- The corrected hazard ratio of death by lung cancer **does not seem to be so sensitive** to measurement error variance parameters

## Limitations & Perspectives

- Adaptive Metropolis-Within-Gibbs algorithm => Very time-consuming to explore high-dimensional posterior distributions
  - ▶ Work under progress to implement a **Metropolis-adjusted Langevin sampler** and compare it to our current adaptive Metropolis-Hastings sampler => First promising results with about 40% reduction in calculation time for an equivalent ESS when updating unknown parameters  $\alpha$  and  $\beta$
  - ▶ Final challenge : Application of the proposed Bayesian structural approach to a joint cohort of about 70,000 uranium miners (French, Czech, German) (Context : RadoNorm European project)
- **Weak signal** in the French cohort of uranium miners to estimate a measurement corrected kidney cancer mortality risk => We plan to define informative prior probability distributions from the Czech cohort of uranium miners
- **Robustness of our models to measurement and/or exposure model misspecification ?**  
=> Simulation studies under progress...
- For each case study, the (conditional) WAIC are very similar for all the considered models. What about estimating the marginal WAIC [Millar R.B., 2018] ?
- **Model validation from a predictive framework** : Which criteria to consider for highly censored survival data ?



## References

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- Hoffmann S, Rage E, Laurier D, Laroche P, Guihenneuc C, Ancelet S. (2017) *Accounting for Berkson and classical measurement error in radon exposure assessment using a Bayesian structural approach in the analysis of lung cancer mortality in the French cohort of uranium miners*. Radiat Res; 187(2) :196-209.

Thank you for your attention !