Hierarchical modeling and Bayesian statistics for a better consideration of uncertainties when estimating radiation-related risks

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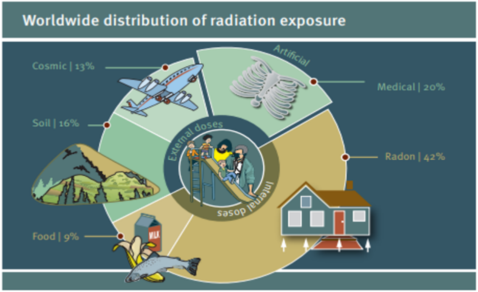
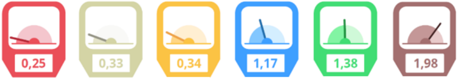
All exposed to ionizing radiations (IR)



UNSCEAR, 2016

Workers (France)
Average individual dose by field of activity (mSv)



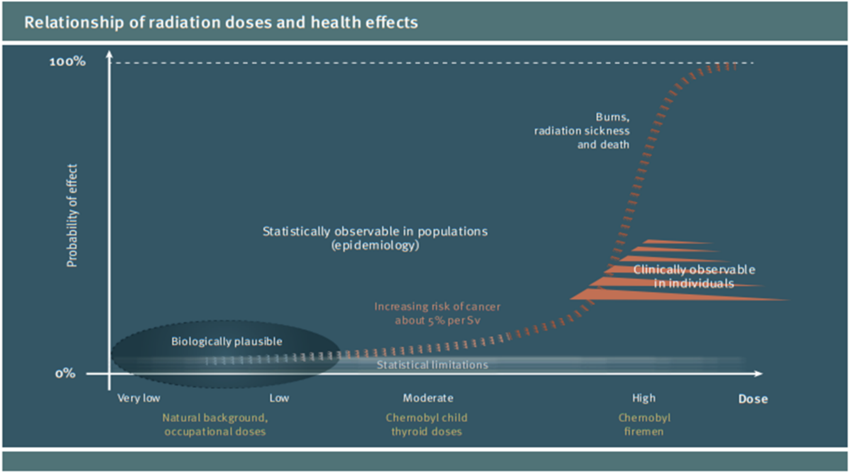
Research Others Medical Nuclear Industry Aviation

French population : average individual dose
4,5 mSv/year (IRSN, 2015)

Workers : average individual dose
0,72 mSv/year

A low and controlled exposure

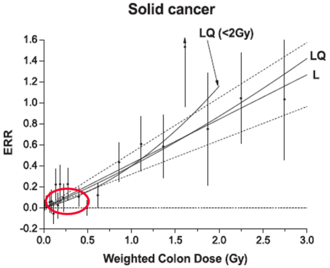
Radiation dose and heath effects



UNSCEAR, 2016

Current issues on stochastic effects

- **Non-threshold linearity of the dose-response relationship for cancers** : discrepancy between epidemiology and radiobiology
- **Multi-exposure situations**
- Taking into account the complexity of biological mechanisms
- Variability factors, individual susceptibility
- Tissue sensitivity, integration of new cancers
- Validity of the assessment of heritable effects, consideration of epigenetic mechanisms



International Radiological Protection system

RESEARCH → SYNTHESIS → RECOMMENDATIONS → RADIATION PROTECTION STANDARDS

RESEARCH

Physics
Dosimetry
Radiochemistry
Genetics
Physiology
Radiobiology
Radiotoxicology
Oncology
Epidemiology
Radioecology

SYNTHESIS

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)

Biological Effects Of Ionising Radiations (NAS, USA)

RECOMMENDATIONS

International Commission on Radiological Protection

ICRP

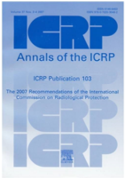
1928

RADIATION PROTECTION STANDARDS

International Atomic Energy Agency

European Community EURATOM

Country



International Commission on Radiological Protection (ICRP)

- Aim
  - "To contribute to an **appropriate level of protection for people and the environment** from the **adverse effects of radiation exposure**, without unduly limiting the desirable human actions that may be associated with such exposure"
  - Avoiding deterministic effects and limiting stochastic effects
- Management tool
  - Strong simplification necessary for the practical application of radiation protection
  - **Radiological detriment** computed from **weighted nominal risk coefficients** of a given terminal event (ex : death by cancer) on a given organ over the entire life
  - Nominal risk coefficients estimated from **dose-response analysis**
- Some priority scientific issues
  - **Effects of prolonged exposures and low dose rates**
  - Non-cancer effects and heritable effects, and contribution to radiological detriment
  - Mechanisms of low-dose effects and integration of these mechanisms into dose-response modeling

$\Rightarrow$ The assessment of the risk of stochastic effects in the current radiation protection system is mainly based on knowledge from **epidemiological studies**

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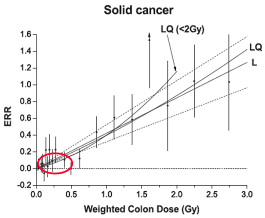
Radiation epidemiology

Some priority scientific issues

- **Identification and estimation** of the effects of :
  - chronic or repeated exposures at **low doses** and characterization of the form of the dose-response relationship for cancer risk
  - exposure during childhood
  - non-cancer effects associated with exposure to low and moderate doses

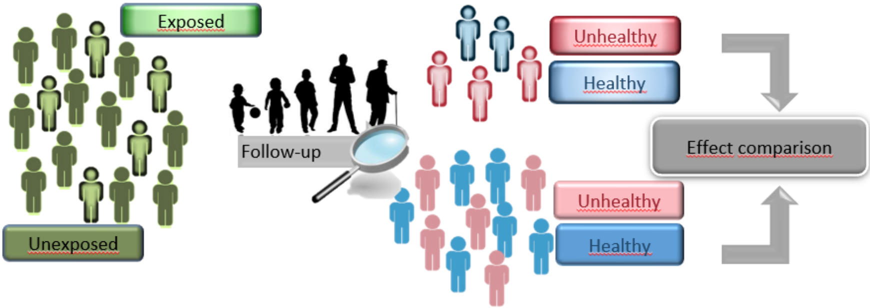
Main statistical aims

- Estimate the magnitude of the association (and its uncertainty) between one (several) exposure(s) to ionizing radiations (IR) and a given disease
  - **(Probabilistic) modelling and statistical learning**
- Identify the existence of an association between one (several) exposure(s) to ionizing radiations (IR) and a given disease
  - **Statistical hypothesis testing/model selection**
- Characterize the shape of dose-response relationships
  - **Model selection/Model averaging**



Radiation epidemiology : an observational science

- First step : Build, validate and maintain **large databases over the long term**, in compliance with health data confidentiality constraints



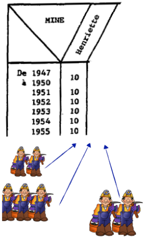
Is the occurrence of the event different in individuals exposed to IR compared to unexposed or less exposed individuals?

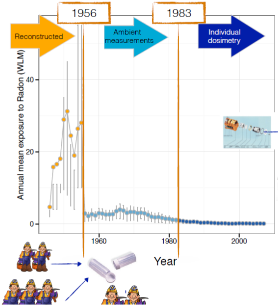
Many sources of uncertainty

- **Exposures** (measurement/estimation, left-censored value due to detection limits, missing data, ...)
- **Organ dose** estimation
- **Right-censored survival data** (competing risks...)
- **Baseline risk for rare diseases** (but not only)
- Cause of death
- Multifactorial diseases (e.g., cancer)
- Confounding factors
- **Shape of the dose-reponse/exposure-risk model**
- **Individual variability**
- ...

Exposure uncertainty

- **Uncertainty on radiological exposure values** (predictor variables) is :
  - ubiquitous
  - one of the most important source of input uncertainty in epidemiological studies





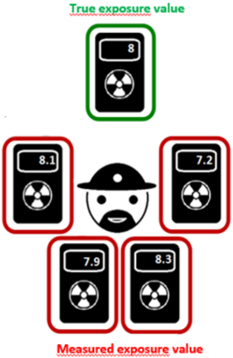
Uncertainty in assessing radon and decay products exposure among uranium miners 7

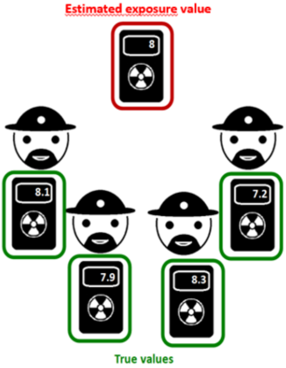
Table 2. Sources and magnitude of uncertainty for exposure to radon (^{222}Rn) and its decay products (RDP) (%).

	Periods			
Sources	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.

Exposure uncertainty





Classical measurement error

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

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

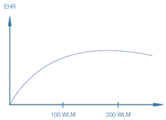
Berkson error

$X_{ji}(t) = Z_j(t) \cdot U_{ji}(t)$

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

Exposure uncertainty

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



- If not accounted for, exposure uncertainty 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

$\Rightarrow$ It is important to account for exposure uncertainty in risk estimation [ICRP103 (2007) ; UNSCEAR (2012)]

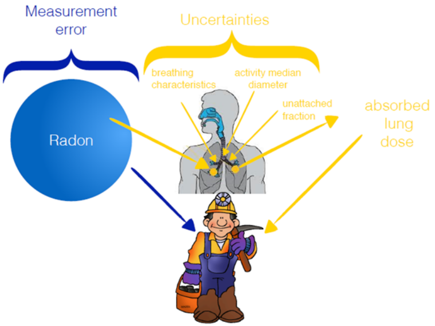
Standard methods to account for exposure uncertainty in risk estimates

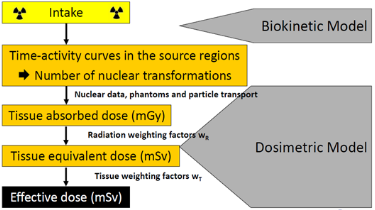
- Exposure measurement error $\Rightarrow$ Frequentist functional methods : regression calibration and simulation extrapolation [Carroll et al. (2006) ; Keogh et al. (2020)]
  - Lack of flexibility to account for complex measurement error on time-varying exposures
    - Mixture of different types of 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]

Dose uncertainty

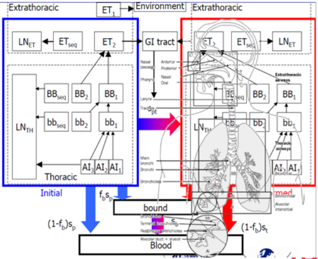
- The health effects of IR are associated with **radiation dose** rather than with radiation exposure [Preston et al. (2013) ; Birchall and Marsh (2005)].
- The values of radiation dose do not only depend on the exposure to radioactive material, but also on the exposure conditions.
- The calculation of radiation doses involves further uncertainties

Dose uncertainty





ICRP66 Human Respiratory Tract Model (HRTM)



Dose uncertainty

Journal of Radiological Protection

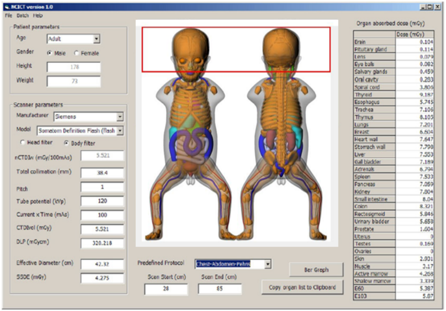
PAPER

NCICT: a computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans

To cite this article: Choonsik Lee *et al* 2015 *J. Radiol. Prot.* 35 891

NCICT : National Cancer Institute dosimetry system for CT

=> Radiation transport **Monte Carlo simulation** within ICRP reference pediatric and adult **computational anatomic phantoms**



Dose uncertainty

- The **input** parameters of dosimetric models are **uncertain** ⇒ The estimation of radiation doses is uncertain when estimating the health effects of radiation exposure
- If not accounted for, dose uncertainty may cause :
  - bias in risk estimates
  - misleading conclusions about the effect of these exposures on the disease risk
  - a distortion of the dose-response relationship
- However, they are most often neglected in epidemiological studies !
- NB : The dosimetric models are **black box** for epidemiologists/statisticians (but dose calculations from these models are fast)

⇒ It is important to account for dose uncertainty in risk estimation [ICRP103 (2007) ; UNSCEAR (2012)]

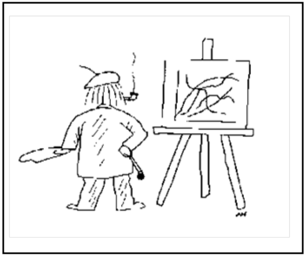
Standard methods to account for dose uncertainty in risk estimates

- Step 1 : Simulate plausible dose values using 2-dimensional Monte-Carlo algorithm [Simon et al. (2015)]
- Step 2 :
  - Plug-in of dose point estimates (i.e., empirical mean, median or other quantiles derived from the simulated dose distributions) in dose-response models
  - Monte-Carlo Maximum Likelihood [Stayner et al. (2007)] : Estimate the risk coefficient β and its uncertainty by maximizing the estimated average likelihood from a grid of fixed values for β
- Asymptotical confidence intervals

Model uncertainty

- In radiation epidemiology, different radiation-related risk models may fit **similarly well** to a given dataset.
- Usual practice ignores such a model uncertainty by selecting **a single model**
  $\hookrightarrow$ Some excess risks may be wrongly declared as significant or non-significant.

Model uncertainty $\rightarrow$ Uncertainty by ignorance/Epistemic uncertainty



Example : Modelling the radiation-related leukaemia excess risk

ERR models	Form of $\mathrm{ERR}_{\theta_2,i}$
UNSCEAR (2006)	$(\alpha d_i + \beta d_i^2) exp(\kappa log(a_i/55))$
Qexp	$\beta d_i^2 exp(\gamma d_i) exp(\kappa log(a_i/55))$
Sigmoid	$\frac{A}{exp(B)+\left(\frac{1}{d_i}\right)^{exp(C)}} exp(\kappa log(a_i/55))$
Spline	$[\alpha_1 d_i + \alpha_2 (d_i - d_k) 1_{(d_i \geq d_k)}] exp(\kappa log(a_i/55))$
Little (2008)	$(\alpha d_i + \beta d_i^2) exp(\kappa_1 log(a_i/55) + \kappa_2 log(e_i/25))$
Littleexp (2008)	$(\alpha d_i + \beta d_i^2) exp(\gamma d_i) exp(\kappa_1 log(a_i/55) + \kappa_2 log(e_i/25))$
BEIRVII (2006)	$\beta_{(s_i+1)} (d_i + \theta d_i^2) exp(\gamma e_i' + \delta log(t_i/25) + \phi e_i' log(t_i/25))$
EAR models	Form of $\mathrm{EAR}_{\theta_2,i}$
UNSCEAR (2006)	$(\alpha d_i + \beta d_i^2) exp(\kappa_1 s_i + \kappa_2 log(t_i/25))$
Littleexp (2008)	$(\alpha d_i + \beta d_i^2) exp(\gamma d_i) exp(\kappa_1 s_i + \kappa_2 log(t_i/25))$
BEIRVII (2006)	$\beta_{(s_i+1)} (d_i + \theta d_i^2) exp(\gamma e_i' + \phi e_i' log(t_i/25))$
Schneider (2009)	$(1 + \alpha \tilde{s}_i)(\beta d_i + \delta d_i^2) exp(\gamma_1 (e_i - 41) + \gamma_2 log(a_i/60))$
Schneiderexp (2009)	$(1 + \alpha \tilde{s}_i)(\beta d_i + \delta d_i^2) exp(\gamma d_i) exp(\gamma_1 (e_i - 41) + \gamma_2 log(a_i/60))$
Preston (2004)	$\beta_{(s_i+1)} (\alpha d_i + \delta d_i^2) exp(\gamma[\mathrm{ecat}_i] + \tau[\mathrm{ecat}_i] log(t_i/25))$

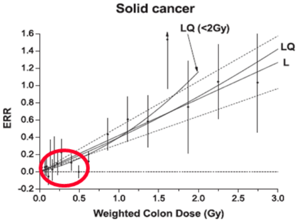
FRENCH COHORT OF URANIUM MINERS
5086 URANIUM MINERS (31/12/2014)

Mean follow-up : 39 years
Mean duration of exposure to radon: 13 years
268 deaths by lung cancer
30 deaths by kidney cancer
Alive: 2580 miners (50.7%)
Mean cumulative total absorbed lung dose among exposed miners (post-55 cohort): 133.9 mGy

FRENCH CT COHORT
100 560 CHILDREN (31/12/2016)

Mean age at entry in the cohort (1st scanner) : 3,4 years
Mean follow-up : 9,5 years
Mean cumulative brain dose : 24 mGy
Mean cumulative red bone marrow dose : 9 mGy
75 central nervous system tumors
39 leukaemia
41 lymphoma

low dose & low risks



Approximated **statistical power** at level = 0.05 of the following hypothesis test:

$$H_0: \exp(\beta)=1 \quad \text{vs} \quad H_1: \exp(\beta)\neq 0$$

where $\exp(\beta)$ is the hazard ratio (for 1 mSv) of death by radiation-induced solid cancer from a cohort of nuclear workers (Cox model)

$exp(\beta)$	1.0001	1.0005	1.0009	1.001	1.003	1.005	1.007	1.009	1.015
P_{2003}	8%	8%	15%	15%	56%	89%	99 %	100%	100%
P_{2014}	5.85%	10.22%	21.76%	23.2%	97%	100%	100%	100%	100%

Aim

- **Promote the use of hierarchical (also called multilevel models) modeling and Bayesian statistical methods** when estimating radiation-related risks at low doses

- Why hierarchical modeling ?
  - **Flexible modelling approach** to describe and simultaneously account for several and heterogeneous sources of uncertainty
  - Benefit of **"borrowing strength"** in the inference of multiple groups of data

- Why Bayesian statistics ?
  - Allows for the joint inference of all unknown quantities (e.g., true exposure/dose and risk parameters) when fitting complex models like hierarchical models
  - Allows to integrate external information through the specification of informative priors or transfer/sequential learning
  - Credible intervals (i.e., for risk estimates) are easily obtained as by-product of Bayesian inference (without asymptotic assumption !)
  - . . .

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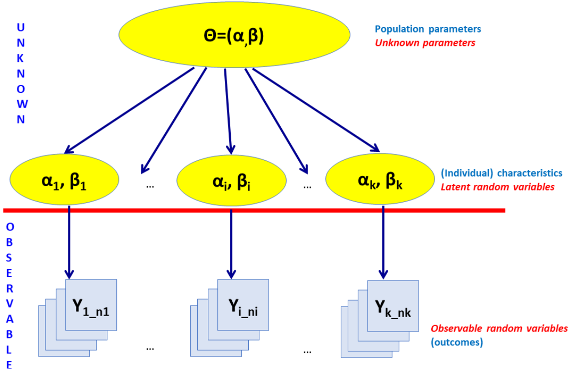
What is a hierarchical (probabilistic) model ?

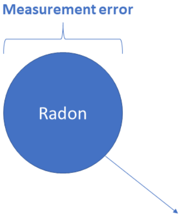
- Main idea : **Think conditionally** to build complexity !



- Combination of conditionally independent submodels
- Each sub-model describes one source of uncertainty
- Many latent layers can be combined

Case study 1 : Lung 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]
- 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»

Obtain a measurement corrected estimation of lung cancer mortality risk as well as its associated uncertainty

Building a Bayesian hierarchical model

Work in collaboration with Julie Fendler (IRSN), Chantal Guihenneuc (Univ. Paris Cité), Sabine Hoffmann (Univ. Ludwig Maximilians)

- Two (or three) conditionally independent submodels [Richardson & Gilks (1993)]
  - **Disease submodel** : it describes the relation between the "true" unknown exposures/doses 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

- Specific context :
  - Heteroscedastic measurement error components
  - Time-varying exposure covariates
  - Right-censored survival data (outcome variable)
  - Weak signal in the data (low dose/exposure and low radiation-related risks)

$\Rightarrow$ New models are required

The disease submodel $\mathcal{M}_0$ (1/2)

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

- Disease outcomes : (Y_i, δ_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 δ_i the non-censoring indicator
- Modelling the hazard rate of event for individual i at time $t \in [0, +\infty[$

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

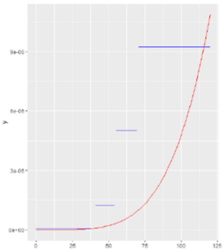
  - $X_i^{cum}(t)$: 5-year lagged cumulative exposure to radon of individual i at time t
  - $h_0(t; \theta)$: Baseline hazard rate at time t (i.e., for any unexposed individual)
  - $\rho(\beta; X_i^{cum}(t))$: Radiation-related hazard ratio (HR)
  - **β : Unknown risk coefficient**
- Assumption : Non-informative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

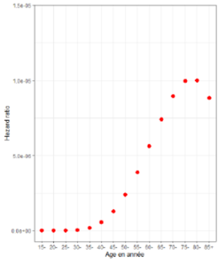
Contribution to the likelihood of individual i for the disease submodel

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

The disease submodel $\mathcal{M}_0$ (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 $\xi > 0$ (scale parameter) and $\alpha > 0$ (shape parameter)





- Modeling the hazard ratio function :
  1. $\rho(\beta; X_i^{cum}(t)) = exp(\beta X_i^{cum}(t)) \Rightarrow$ Cox Model
  2. $\rho(\beta; X_i^{cum}(t)) = 1 + \beta X_i^{cum}(t) \Rightarrow$ Excess Hazard Ratio (EHR) model
     - Constraint : $\beta > -\frac{1}{X_i^{cum}(t)}$

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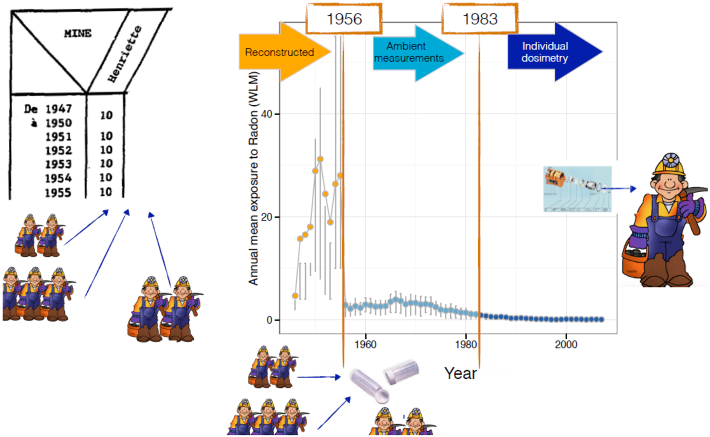
Estimation of annual radon exposure in the French cohort of uranium miners



Measurement submodel $\mathcal{M}_1$

For an individual i working in mine m at time t :

Berkson error components only

$$\begin{cases} \underbrace{X^1_{im}(t)}_{\textit{true exposure}} = \underbrace{Z^1_m(t)}_{\textit{estimated mean exposure}} \cdot \underbrace{T_{im}(t)}_{\textit{effective working time}} \cdot \underbrace{U^1_i(t)}_{\textbf{Berkson error}} & \text{period 1 : 1945-1955} \\ X^2_{im}(t) = Z^2_m(t) \cdot T_{im}(t) \cdot U^2_i(t) & \text{period 2 : 1956-1982} \\ X^3_{im}(t) = Z^3_{im}(t) \quad \text{[Hoffmann et al., 2017]} & \text{period 3 : post 1983} \end{cases}$$

with $Z^1_m(t) \perp\!\!\!\perp U^1_i(t)\ \forall i, m, t$ and $\mathbf{U}^k_i = \left(U^k_i(t_1), \ldots, U^k_i(t_{ik})\right)^T \sim \mathcal{LN}(-\frac{\sigma^2_k}{2} 1_{t_{ik}}, \sigma^2_k \Gamma_{t_{ik}})$

$\Rightarrow E[\mathbf{U}^k_i] = 1_{t_{ik}}\ \forall k \in \{1, 2\}$

$$1_{t_{ik}} = (1, ..., 1)^T \text{ et } \Gamma_{t_{ik}} = \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \rho \\ \rho & \cdots & \rho & 1 \end{bmatrix}, \rho \in [0; 1[.$$

- $\mathbf{U}^k_i$: Shared Berkson error (individual worker practices)
- Fixed magnitudes of Berkson error : $\sigma_1 = 0.93$, $\sigma_2 = 0.39$ [Allodji et al., 2012]

An alternative hierarchical model to describe exposure measurement error in period 1945-1955

Measurement submodel $\mathcal{M}_2$: A mixture of Berkson and classical error for period 1

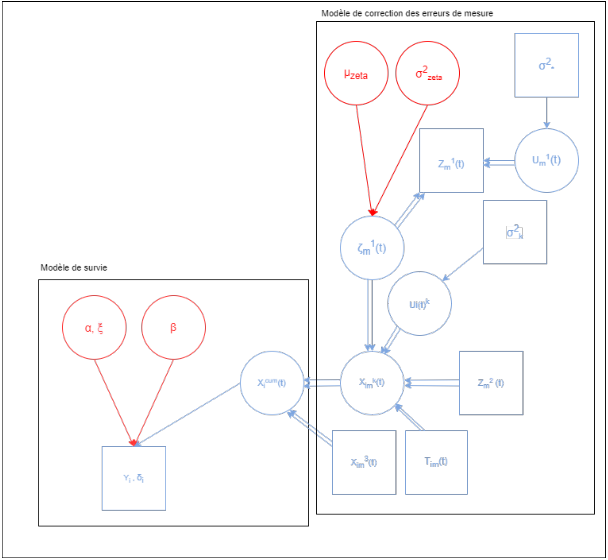
$$\begin{cases} \bullet\ Z_m^1(t) = \zeta_m^1(t) \cdot \underbrace{U_m(t)}_{\text{classical error}} & \text{if } Z_m^1(t) \text{ is known, period 1 : 1945-1955} \\ X_{im}^1(t) = \underbrace{\zeta_m^1(t)}_{\textit{true mean exposure}} \cdot T_{im}(t) \cdot \underbrace{U_i^1(t)}_{\text{Berkson error}} & \\ X_{im}^1(t) = Z_m^1(t) \cdot T_{im}(t) \cdot U_i^1(t) & \text{if only } \left(Z_m^1(t) \cdot T_{im}(t)\right) \text{ is known} \\ \bullet X_{im}^2(t) = Z_m^2(t) \cdot T_{im}(t) \cdot U_i^2(t) & \text{period 2 : 1956-1982} \\ \bullet X_{im}^3(t) = Z_{im}^3(t) & \text{period 3 : post 1983} \end{cases}$$

- $U_m(t) \sim^{i.i.d} \mathcal{LN}(-\frac{\sigma_*^2}{2}, \sigma_*^2) \qquad \forall t$
- Fixed magnitudes of errors : $\sigma_* = 0.41$ and $\sigma_1 = 0.84$ [Allodji et al., 2012]

Exposure submodel

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

Directed Acyclic Graph



Prior distributions and fixed parameters

- $[\beta]$: $\beta \sim \mathcal{N}(0, 10^6)$ left-sided truncated at 0 to guarantee $h_i > 0$
- $[\boldsymbol{\alpha}]$: $\alpha \sim \mathcal{G}(0.01, 0.01)$
- $[\xi]$: $\xi \sim \mathcal{G}(1, 1)$
- $[\boldsymbol{\lambda}]$: $\lambda_j \sim \mathcal{G}(\alpha_{0j}, \lambda_{0j})$ for each component j, of $\boldsymbol{\lambda}$, $j = 1, \ldots, 4$ based on the lung cancer mortality in the general French male population between 1968 and 2005 or $\lambda_j \sim Unif(0, 1) \forall j$
- $[\mu_\zeta]$: $\mu_\zeta \sim \mathcal{N}(0, 100)$
- $[\tau_\zeta] = [\frac{1}{\sigma_\zeta^2}]$: $\tau_\zeta \sim \mathcal{G}(0.001, 0.001)$

\+ Prior sensitivity analysis for α and ξ

- No validation sample to estimate the expected value of true exposure given observed/estimated exposure or the true magnitude/variance of the error components => σ_1, σ_2, σ_* [Allodji et al., 2012] and ρ must be fixed...

\+ Impact of these choices on risk estimates must be evaluated

Bayesian inference

- Complex joint posterior distribution $\theta = (\beta, \alpha, \xi, \mu_\zeta, \tau_\zeta, \zeta, \mathrm{U})$
- More than 198,000 pseudo-observations
- More than $40,000$ unknown quantities to estimate
  => **High dimensional posterior distribution**

- Adaptive Metropolis-Within-Gibbs algorithm developed in Python 3.4 + cluster HPC
  - (Left-sided truncated) Gaussian random Walk Metropolis-Hastings for β and α
  - Multiplicative random walk Metropolis-Hastings for ζ, $\mathbf{U}_i^k$ and $\mathbf{U}_m$
  - Gibbs sampling for ξ, μ_ζ, τ_ζ
  - Block updating of shared Berkson error component $\mathbf{U}_i$ after defining 239 homogeneous groups of miners (hierarchical clustering) based on information on mine location, type of min, job type
- Reparametrizations to improve mixing of the chains (e.g. ξ 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 ($\Rightarrow$ Effective Sample Size >4000)

Impact of the correlation parameter ρ on Bayesian inference

		HR* 100WLM	IC** 95%	WAIC
EHR	$\rho = 0$	2.14	1.65 ;2.81	6860
	$\rho = 0.2$	2.16	1.66 ;2.86	6860
	$\boldsymbol{\rho = 0.4}$	**2.21**	**1.70 ;2.94**	**6858**
	$\rho = 0.6$	2.23	1.68 ;2.99	6859
	$\rho = 0.8$	2.17	1.66 ;2.89	6862
	$\rho = 0.99$	2.13	1.63 ;2.80	6863
Cox	$\rho = 0$	1.32	1.18 ;1.48	6971
	$\rho = 0.2$	1.33	1.18 ;1.50	6870
	$\boldsymbol{\rho = 0.4}$	**1.33**	**1.18 ;1.52**	**6870**
	$\rho = 0.6$	1.35	1.18 ;1.54	6872
	$\rho = 0.8$	1.35	1.20 ;1.55	6875
	$\rho = 0.99$	1.19	1.08 ;1.35	6886

Results provided by the disease submodel combined with the $\mathcal{M}_1$ measurement error submodel

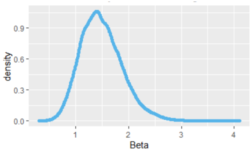
*HR : *Posterior median* of the hazard ratio for 100 Working Level Months of death by lung cancer (i.e., $1 + \beta \times 100$), **IC : 95% credible interval

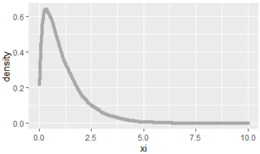
Uncorrected and measurement corrected estimation of lung cancer mortality risk and associated uncertainty

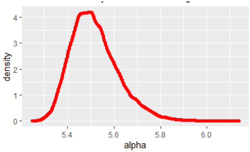
		HR* 100WLM	IC** 95%	WAIC***
Baseline model ($\beta = 0$)				6895
$\mathcal{M}_0$		2.06	1.60 ;2.70	6861
$\mathcal{M}_1$		2.21	1.70 ;2.94	6858
$\mathcal{M}_2$	$\sigma_1 = 0.84$; $\sigma_* = 0.41$	2.38	1.78 ; 3.26	6855
	$\sigma_1 = 0.84$; $\sigma_* = 0.82$	2.50	1.81 ;3.46	6854
	$\sigma_1 = 0.63$; $\sigma_* = 0.31$	2.32	1.73 ;3.13	6857

Results provided by the EHR disease submodel $\mathcal{M}_0$ (i.e., **without accounting for exposure measurement error**) and the measurement submodels $\mathcal{M}_1(\rho = 0.4)$ and $\mathcal{M}_2(\rho = 0.4)$ combined with $\mathcal{M}_0$

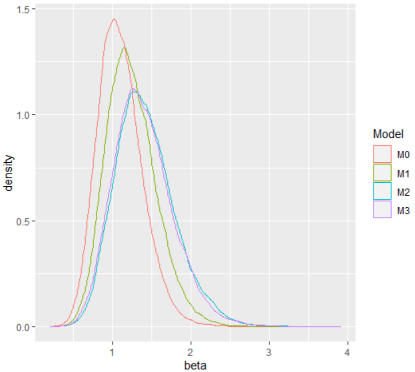
Some posterior probability distributions :







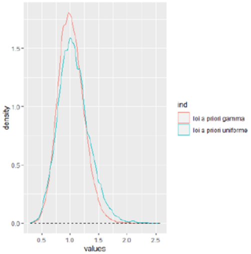
Impact of exposure measurement error on the instantaneous excess risk β ($\rho = 0.4, \sigma_1 = 0.84, \sigma_* = 0.41$)



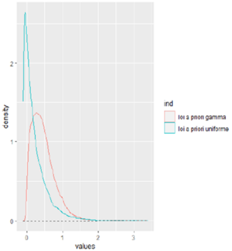
Posterior density of the excess risk coefficient β (per 100 WLM) of death by lung cancer in the French cohort of uranium miners

Application on the French cohort of uranium miners
Prior sensitivity

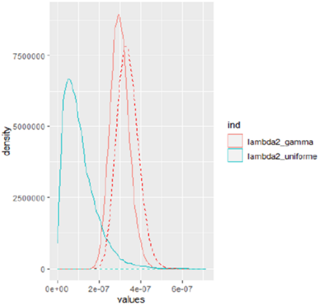
Influence of the prior density assigned on the baseline risk $\boldsymbol{\lambda}$ on the posterior density of the risk coefficient β in the French cohort of uranium miners



Lung cancer



Leukaemia



Influence of the prior density (dotted lines) on the posterior density (solid line) when estimating the baseline risk of leukaemia between 55 and 65 years in the French cohort of uranium miners

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Limitations & Perspectives

- Adaptive Metropolis-Within-Gibbs algorithm are time-consuming to explore high-dimensional posterior distributions $\Rightarrow$ Which alternative bayesian learning algorithm ?
  - Work under progress to implement a Metropolis-adjusted Langevin sampler and compare it to our current adaptive Metropolis-Hastings sampler $\Rightarrow$ First promising results with about 40% reduction in calculation time for an equivalent ESS when updating unknown parameters α and β
- Robustness of our models to measurement and/or exposure model mispecification ?
  $\Rightarrow$ Simulation studies under progress...

MEMBRE DE ETSON

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