Bayesian contributions to radiation dose estimation in biological retrospective dosimetry.

Sophie Ancelet[1], Gaëtan Gruel[2], Eric Grégoire[2], Aurélie Vaurijoux[2], Laurence Roy [3], Joan Francesco Barquinero Estruch [4]

[1]IRSN, PSE-SANTE/SESANE/LEPID, France (sophie.ancelet@irsn.fr)
[2]IRSN, PSE-SANTE/SERAMED/LRAcc, France
[3]IRSN, PSE-SANTE/SESANE, France
[4]Universitat Autònoma de Barcelona, Facultat de Biociències, Spain

Journée "Big Ideas for Small Data", 13th May 2019

Context

- **Accidents** leading to unplanned exposure of humans to ionizing radiation (IR) have occurred many times
  - **overexposure** in radiotherapy services or occupational settings
  - large-scale **nuclear accidents**
- **Unclear** radiation exposure scenarios and/or **inconsistent** findings
  - workers at risk of exposure **may not wear** their obligatory personal dosimeter
  - workers at risk of exposure **may not store it** correctly after use.

- Estimation of the **absorbed radiation dose** received by an exposed or suspected exposed individual may be crucial to:
  - Optimize patient-centered care
  - Predict the derived health consequences for both early and late effects
  - Perform rapid triage of exposed versus non-exposed persons
  - Clarify unclear radiation exposure scenarios
  - Appease the "worried well" persons

Dose assessment $\Rightarrow$ Proof of exposure by court and professional associations

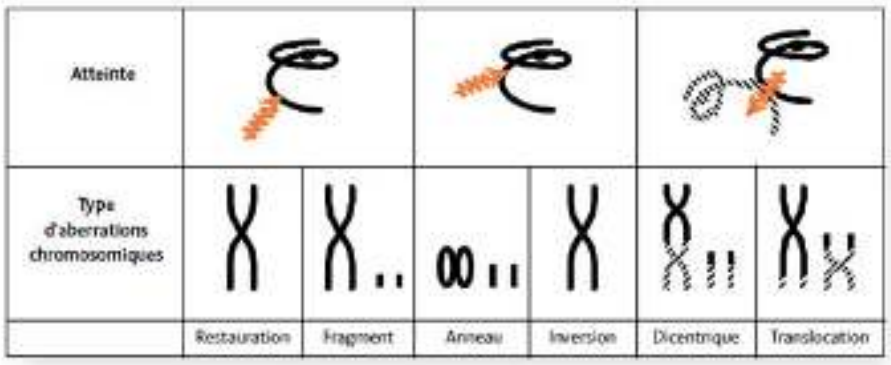
Biological retrospective dosimetry

- It offers the only possibility to estimate the individual absorbed dose
  - even weeks or months after a potential exposure (Kulka et al. (2018)).
  - when a direct measurement of IR exposure is not or no longer possible

Main goal

Estimation of the individual absorbed radiation dose from microscope counting of radiation-related **chromosomal anomalies**

- Radiation exposure causes **chromosomal DeoxyriboNucleic Acid (DNA) lesions** like double-stand breaks
- The broken fragments may repair incorrectly ⇒ **Chromosome aberrations**



The dicentric chromosome assay (DCA)

- Dicentrics have a **low naturally occurring background** frequency
- Frequencies of **dicentrics increase** with the absorbed dose
  $\Rightarrow$ Well-established and highly specific **biological marker** of radiation exposure
- Scoring dicentrics in peripheral human blood lymphocytes : **"gold standard" biological method** for retrospective dose estimation (IAEAb (2011)).

Photo: Olivier Seigneette/Mikael Lafontaa/Mediathèque IRSN

Main questions

Given the number of dicentrics per cell observed in blood lymphocytes:

Question Q1

Can it be stated that a **strictly positive radiation dose** has been received by :

1. **all of the** analyzed cells (whole-body irradiation)?
2. **only a fraction** of the analyzed cells (partial irradiation)?
3. **none** of the analyzed cells ? (Relevant for **unclear exposure scenarios**)

Main questions

Given the number of dicentrics per cell observed in blood lymphocytes:

Question Q1

Can it be stated that a **strictly positive radiation dose** has been received by :

1. **all of the** analyzed cells (whole-body irradiation)?
2. **only a fraction** of the analyzed cells (partial irradiation)?
3. **none** of the analyzed cells ? (Relevant for **unclear exposure scenarios**)

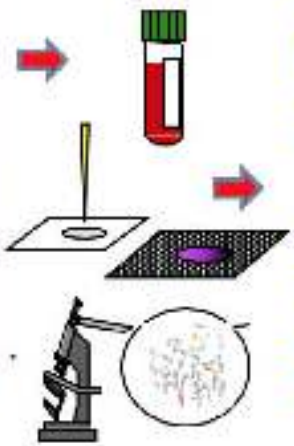
Question Q2

What is the **estimated absorbed dose** and the **uncertainty associated** to this estimation?

4 real radiation accident victims (2006-2013)
In-vivo data provided by IRSN/LRAcc

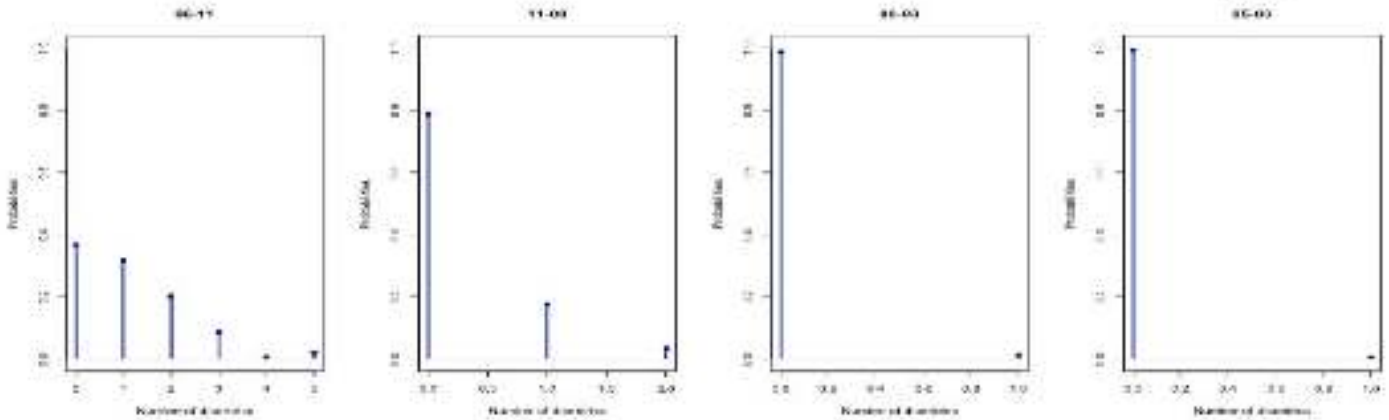
Id	Circumstances of accident	Clinical signs	Physical dosimetry
06-11	Exposure to γ-rays	Vomiting (4h30), nausea, hair loss, Lymphocytes: 0.8×10^{-3}	No
11-08	Medical context; 10 minutes located next to a γ-source (Co 60)	Hematopoetic syndrom 7 days after exposure	No
08-03	Put the γ-source (Ir) in his hand then in his pocket (10 minutes to 1 hour) -> Hand burn	lymphocytes: 1.05×10^{-3}	0.25 Sv
05-03	Exposure head and chest : 15-30 seconds Shoulders 5cms away from the X source Neck 20cms away from the X source	Erythema (collarbone) Lymphocytes: 2.39×10^{-3}	0.045 Sv

Conventional cytogenetics



n_0: Number of peripheral blood lymphocytes analysed

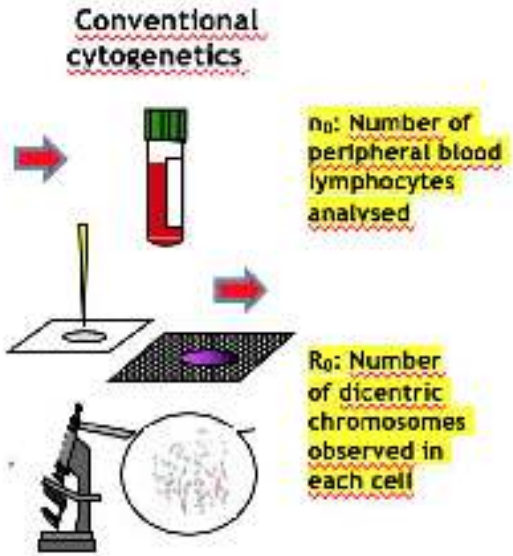
R_0: Number of dicentric chromosomes observed in each cell



8 suspected exposed individuals (2006-2013)
In-vivo data provided by IRSN/LRAcc

4 real suspected individuals (2006-2013)
From IRSN/LRAcc

Id	Circumstances of accident	Clinical signs	Physical dosimetry
06-63	Exposure to γ-rays (10-15 minutes)	No	No
06-70	Spent the night 25 centimeters away from a γ-source	No	No
06-13	Colleague of 06-11	No	No
06-15	Colleague of 06-11	No	No

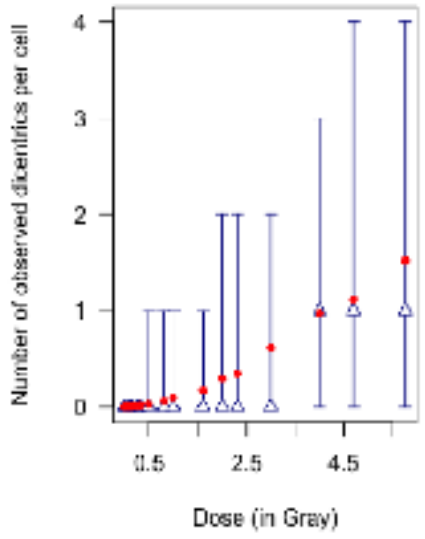


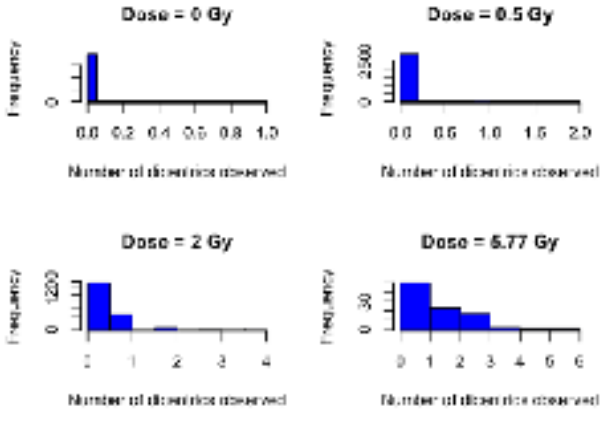
For some of them, no dicentric was observed...

Calibration data (Cobalt 60) - In-vitro data provided by IRSN/LRAcc

In-vitro irradiation of blood samples - various healthy donors - different doses

Number of analyzed cells	Dose (Gray)	Number of dicentrics
19194	0	21
1676	0.05	3
1552	0.10	6
481	0.15	3
1057	0.24	11
1768	0.30	38
1187	0.33	18
2919	0.50	83
1538	0.80	100
869	1	90
1525	1.6	269
1844	2	545
352	2.31	122
784	3	482
534	4	521
341	4.70	381
94	5.77	143





Dose-response model $\mathcal{M}_A$ for in-vivo data
Exposed and suspected exposed individuals

Let's consider a given individual with n_0 analyzed cells:

- D_0 : **Unknown** absorbed dose (in Gray) received by each cell
- R_k: Number of dicentrics observed in each cell k ($k = 1, \ldots, n_0$)

In case of LOW-LET radiation and homogeneous irradiation

$$(\mathcal{M}_A) \qquad R_k \sim^{i.i.d} Poisson(\lambda_0)$$
$$\lambda_0 = A + \alpha D_0 + \beta D_0^2$$

- $\theta = (A, \alpha, \beta)$: **unknown parameters** with $A > 0$, $\beta > 0$, $\alpha > -2\sqrt{A\beta}$
- A: background expected number of dicentrics per cell at dose $D_0 = 0$
- $Y_0 = \sum_{k=1}^{n_0} R_k \sim Poisson(n_0\lambda_0)$

Non-identifiable model $\Rightarrow$ External data required to estimate $\theta = (A, \alpha, \beta)$

Dose-response model $\mathcal{M}_C$ for calibration data

Let's consider a given experimental (in-vitro) irradiation i $\in \{1, \ldots, I\}$

- D_i: **Fixed** absorbed dose (in Gray) received by each cell
- $Z_{i,l}$: Number of dicentrics observed in **each cell l** $\in \{1, \ldots, n_i\}$ at dose D_i

In case of LOW-LET radiation and homogeneous irradiation

At a given dose D_i:

$$(\mathcal{M}_C) \qquad Z_{i,l} \sim^{i.i.d} Poisson(\lambda_i)$$
$$\lambda_i = A + \alpha D_i + \beta D_i^2$$

$$\Rightarrow Y_i = \sum_{l=1}^{n_i} Z_{i,l} \sim Poisson(n_i \lambda_i)$$

where Y_i is the total number of dicentrics observed at dose D_i and n_i the total number of analyzed cells

Answering Q_2 - Estimation of the dose

- Fit $\mathcal{M}_C$ to **calibration data** using maximum likelihood estimation
- Plug $\hat{\theta} = (\hat{A}, \hat{\alpha}, \hat{\beta})$ into $\mathcal{M}_{\mathcal{A}}$
- Derive point estimate $\hat{D}_0$ of the absorbed dose D_0 (inverse regression)

$$\hat{D}_0 = g(\hat{A}, \hat{\alpha}, \hat{\beta}) = \frac{-\hat{\alpha} + \sqrt{\hat{\alpha}^2 + 4\hat{\beta}(\hat{\lambda_0} - \hat{A})}}{2\hat{\beta}}$$

where $\hat{\lambda_0} = \frac{Y_0}{n_0}$

Answering Q_2 - Estimation of the dose

Id	Circumstances of accident	MLE for the dose D_0
06-11	Exposure to γ-rays	4.40
11-08	Medical context; 10 minutes located next to a γ-source (Co 60)	1.88
08-03	Put the γ-source (Ir) in his hand then in his pocket (10 minutes to 1 hour) -> Hand burn	0.23
05-03	Exposure head and chest : 15-30 seconds Shoulders 5cms away from the X source Neck 20cms away from the X source	0.11
06-63	Exposure to γ-rays (10-15 minutes)	0.15
06-70	Spent the night 25 centimeters away from a γ-source	0.25

Id	Circumstances of accident	MLE for the dose D_0
06-13	Colleague of 06-11	0.02
06-14	Colleague of 06-11	0.02
06-15	Colleague of 06-11	-0.03
06-16	Colleague of 06-11	0.02
04-14	Positive dosimeter	-0.03
13-09	Positive dosimeter	-0.03

Potential drawbacks:

- If $\hat{\lambda_0} = \frac{Y_0}{\eta_0} = 0$ then $\hat{D}_0 < 0$ (Context: Small signal in the data)
- Prior information on the dose not accounted for
- Modular approach : Disjoint estimation of θ and D_0

Answering Q_2 - Derive a 95% confidence interval on $\hat{D}_0$

- Approach 1: **Multivariate delta-method**

$$\sigma^2_{\hat{D}_0} = \sigma^2_{\hat{A}} \left(\frac{\partial g}{\partial A}\right)^2_{A=\hat{A}} + \sigma^2_{\hat{\alpha}} \left(\frac{\partial g}{\partial \alpha}\right)^2_{\alpha=\hat{\alpha}} + \sigma^2_{\hat{\beta}} \left(\frac{\partial g}{\partial \beta}\right)^2_{\beta=\hat{\beta}} + \sigma^2_{\hat{\lambda_0}} \left(\frac{\partial g}{\partial \lambda_0}\right)^2_{\lambda_0=\frac{Y_0}{n_0}}$$
$$+ 2\left(\frac{\partial g}{\partial A}\right)_{A=\hat{A}} \left(\frac{\partial g}{\partial \alpha}\right)_{\alpha=\hat{\alpha}} cov(\hat{A}, \hat{\alpha}) + 2\left(\frac{\partial g}{\partial \alpha}\right)_{\alpha=\hat{\alpha}} \left(\frac{\partial g}{\partial \beta}\right)_{\beta=\hat{\beta}} cov(\hat{\alpha}, \hat{\beta})$$
$$+ 2\left(\frac{\partial g}{\partial A}\right)_{A=\hat{A}} \left(\frac{\partial g}{\partial \beta}\right)_{\beta=\hat{\beta}} cov(\hat{A}, \hat{\beta})$$

$\Rightarrow$ **Asymptotical 95% confidence interval** on dose estimate: $\hat{D}_0 \pm 1.96\hat{\sigma}_{D_0}$

- Approach 2: **Bootstrap**

Potential drawbacks:

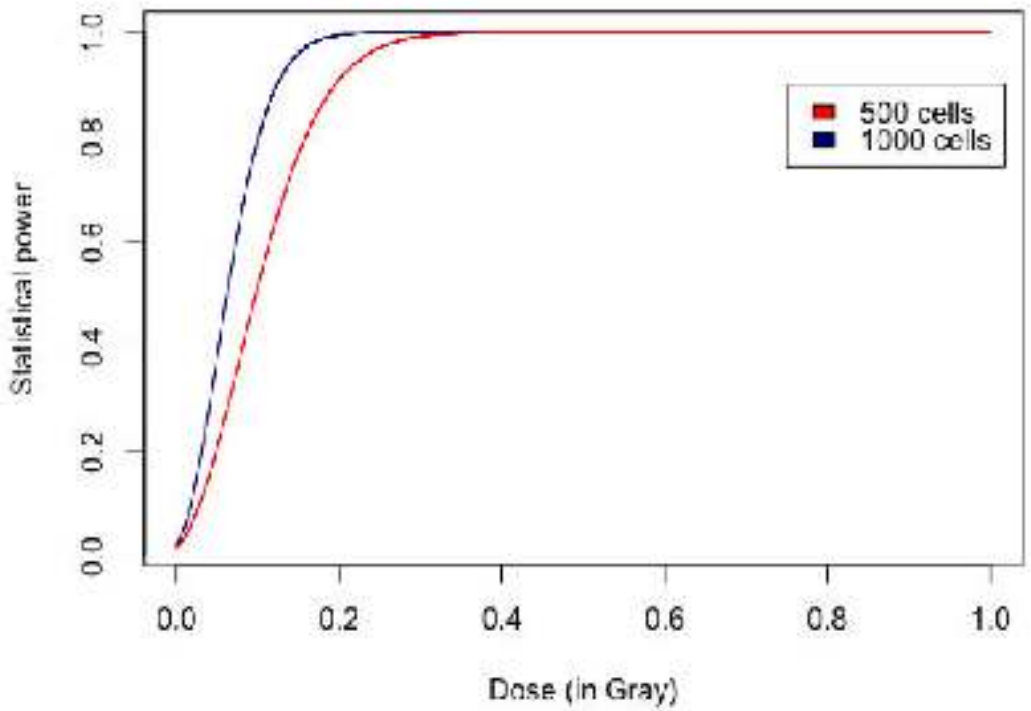
- Is the asymptotic assumption correct?
- Bootstrap $\Rightarrow$ Strong data redundancy if small signal in data
- Uncertainty on the dose estimation may depend on the statistical method used to compute the confidence interval

Answering Q1 - Strictly positive absorbed dose received?

Hypothesis testing: $H_0 : D_0 = 0$ vs $H_1 : D_0 = d_1$ (with $d_1 > 0$)

- Test statistic: $Y_0 = \sum_{k=1}^{n_0} R_k$
- Under H_0, $Y_0 \sim Poisson(n_0 A)$
- Critical region: $[y_0^*, +\infty]$ with $y_0^* = 0.95$ quantile of $Poisson(n_0 \hat{A})$
  - y_0^* is called "Decision threshold"
- If $y_0^{obs} > y_0^*$, H_0 is rejected with error (of the first kind) $= 0.05$
- Statistical power: $1 - Frd_{H_1}(y_0^*)$ where Frd_{H_1} cumulative distribution function of a Poisson distribution with intensity $= n_0(\hat{A} + \hat{\alpha} d_1 + \hat{\beta} d_1^2)$
  - Detection Limit: The smallest value of dose d_1 from which the statistical power of the test is greater or equal to 0.95

Answering Q1 - Strictly positive absorbed dose received?



Answering Q1 - Strictly positive absorbed dose received?

Id	n_i	y_i	y_{lc}	DL
06-11	139	155	1	0.21
11-08	451	112	2	0.25
08-03	1024	13	1	0.14
05-03	500	3	2	0.23
06-63	500	4	2	0.23
06-70	356	5	2	0.30

Id	n_i	y_i	y_{lc}	DL
06-13	602	1	2	0.19
06-14	500	1	2	0.23
06-15	505	0	2	0.22
06-16	508	1	2	0.22
04-14	503	0	2	0.23
13-09	507	0	2	0.22

DL = Detection Limit

Potential drawbacks:

- Binary answer to Q_1: Rejection of H_0 or not
- **D_0 is unknown !** : Statistical power?
- **The statistical power** may be very small for small doses D_0...
- Uncertainty on the estimation of the background expected number of dicentrics per cell A not accounted for
- Does not allow to test if **only a fraction** of the analyzed cells have received a strictly positive radiation dose

Aim of the work

- Can **Bayesian statistical methods** offer relevant alternative answers to questions Q_1 and Q_2 in biological retrospective dosimetry ?

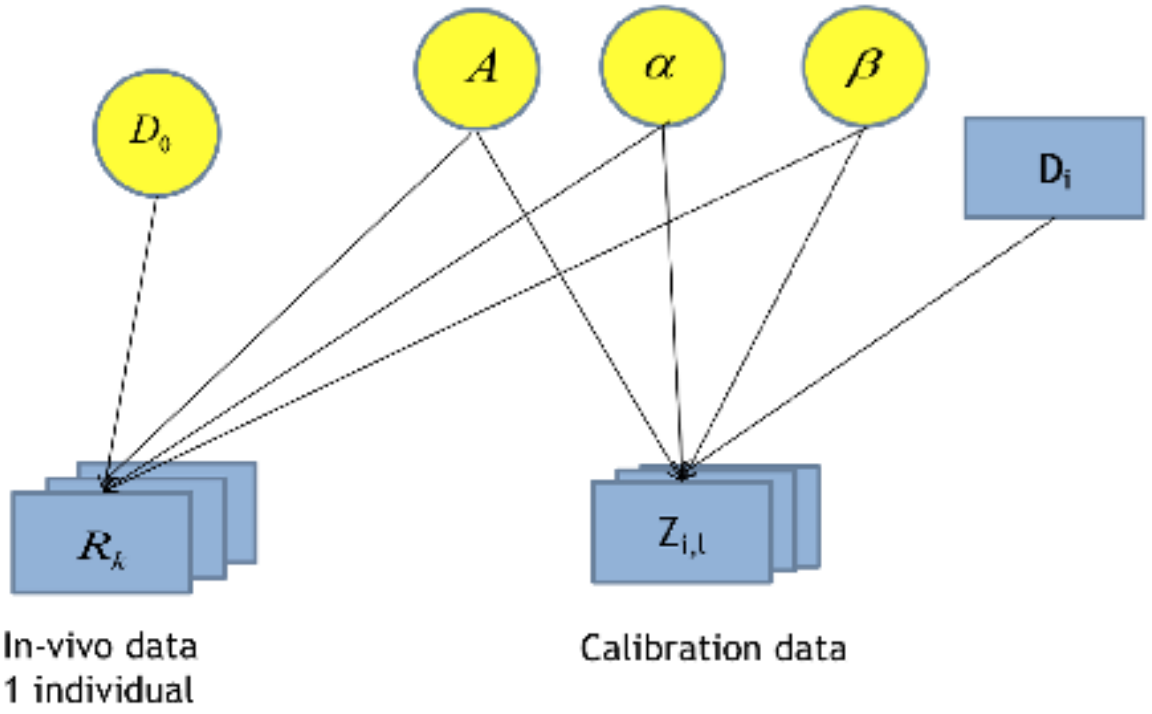
- To account for **expert knowledge** when assigning a prior distribution on the unknown absorbed dose D_0
- To propose a **unique, flexible and coherent framework** allowing to simultaneously answer to questions Q_1 and Q_2

IRSN

Which model?

Approach 1: the one previously described....

Directed Acyclic Graph of the full model ($\mathcal{M}_A + \mathcal{M}_C$)



- $\theta = (A, \alpha, \beta)$: shared parameters
- Possibility for the in-vivo data to be accounted for when fitting A, α, β
- The Bayesian framework allows fitting this model in one step

The prior distributions

- $A \sim Unif\,[0, +\infty[$
- $\alpha \sim Unif\,[-2\sqrt{A\beta}, +\infty[$
- $\beta \sim Unif\,[0, +\infty[$
- Prior probability distribution on D_0
  - $D_0 \sim Unif\,(0, 10) \Rightarrow$ Vague prior
  - $D_0 \sim Gamma(a, b) \Rightarrow$ Informative prior

Using expert knowledge to define an informative Gamma prior D_0

- Hyperparameters a and b of the Gamma prior may be fixed by expert knowledge given the accident scenario

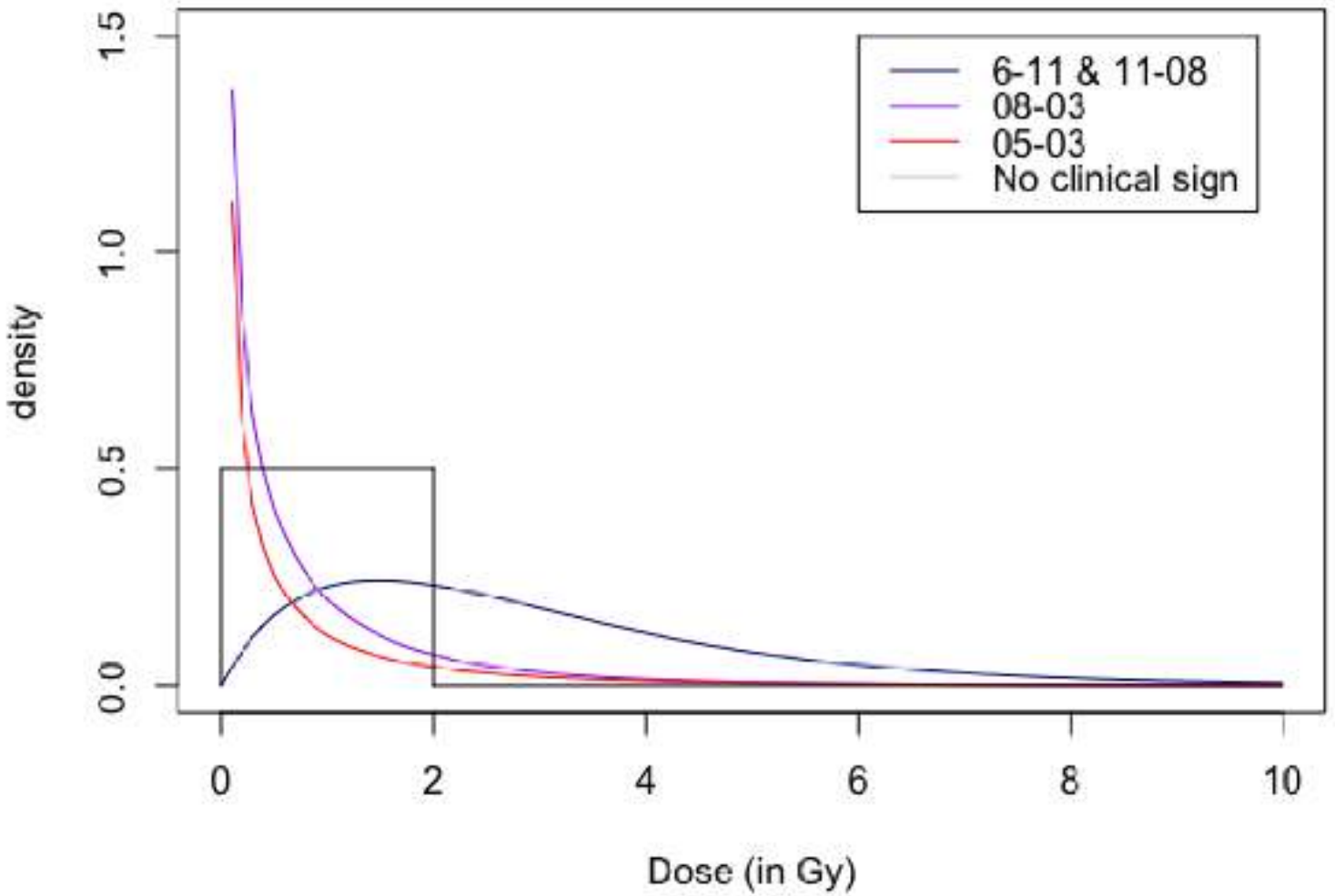
Id	Circumstances of accident	Clinical signs	Physical dosimetry	Prior distribution on D_0
06-11	Exposure to γ-rays	Vomiting (4h30), nausea, hair loss, Lymphocytes: 0.8×10^{9}	No	D_0.median=2.5 D_0max = 10 (q99-10) D_0~Gamma(a=1.98 , b=0.66)
11-08	Medical context: 10 minutes located next to a γ-source (Co 60)	Hematopoetic syndrom 7 days after exposure	No	D_0.median=2.5 D_0max = 10 (q99-10) D_0~Gamma(a=1.98 , b=0.66)
08-03	Put the γ-source (Ir) in his hand then in his pocket (10 minutes to 1 hour) -> Hand burn	lymphocytes: 1.05×10^{9}	0.25 Sv	D_0.median=0.25 D_0max = 5 (q99-5) D_0~Gamma(a=0.4, b=0.6)
05-03	Exposure head and chest : 15-30 seconds Shoulders 5cms away from the X source Neck 20cms away from the X source	Erythema (collarbone) Lymphocytes: 2.39×10^{9}	0.045 Sv	D_0.median=0.045 D_0max = 5 (q99-5) D_0~Gamma(a=0.2, b=0.44)

For individuals for which no clinical sign was observed: $D_0 \sim Unif(0, 2)$

$\Rightarrow$ **Not enough informative ! To improve!**

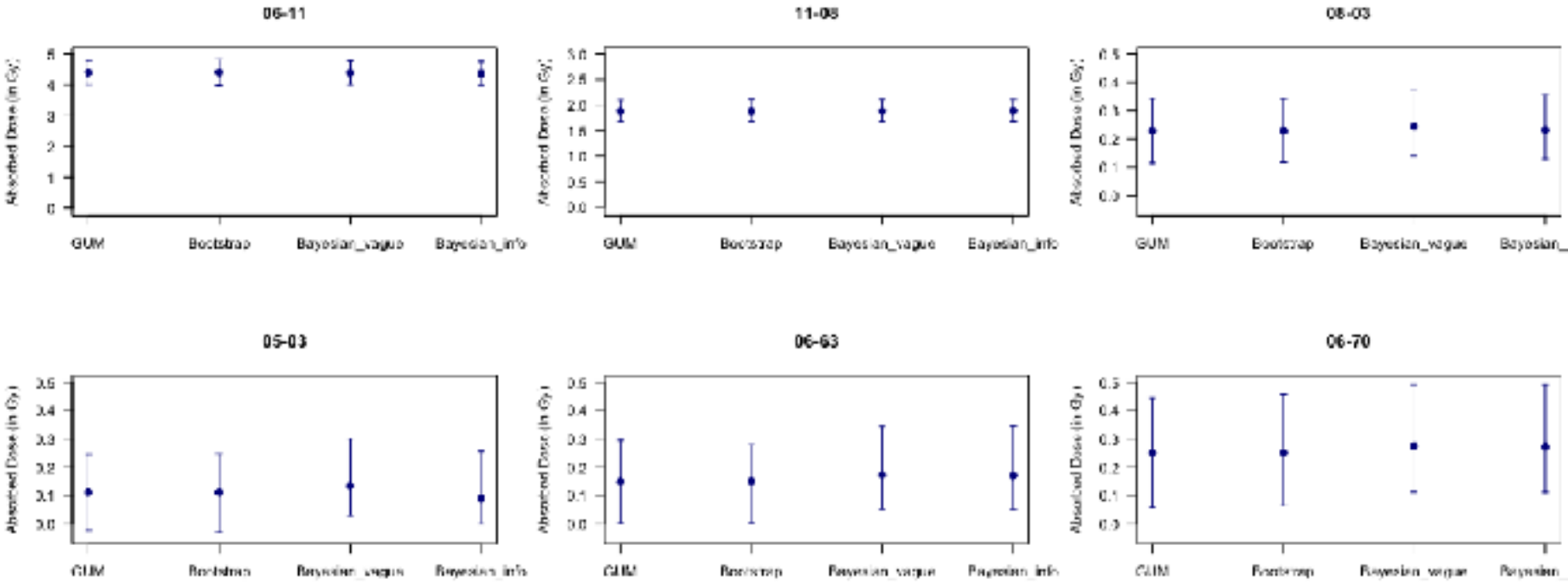
IRSN

Using expert knowledge to define an informative Gamma prior on D_0



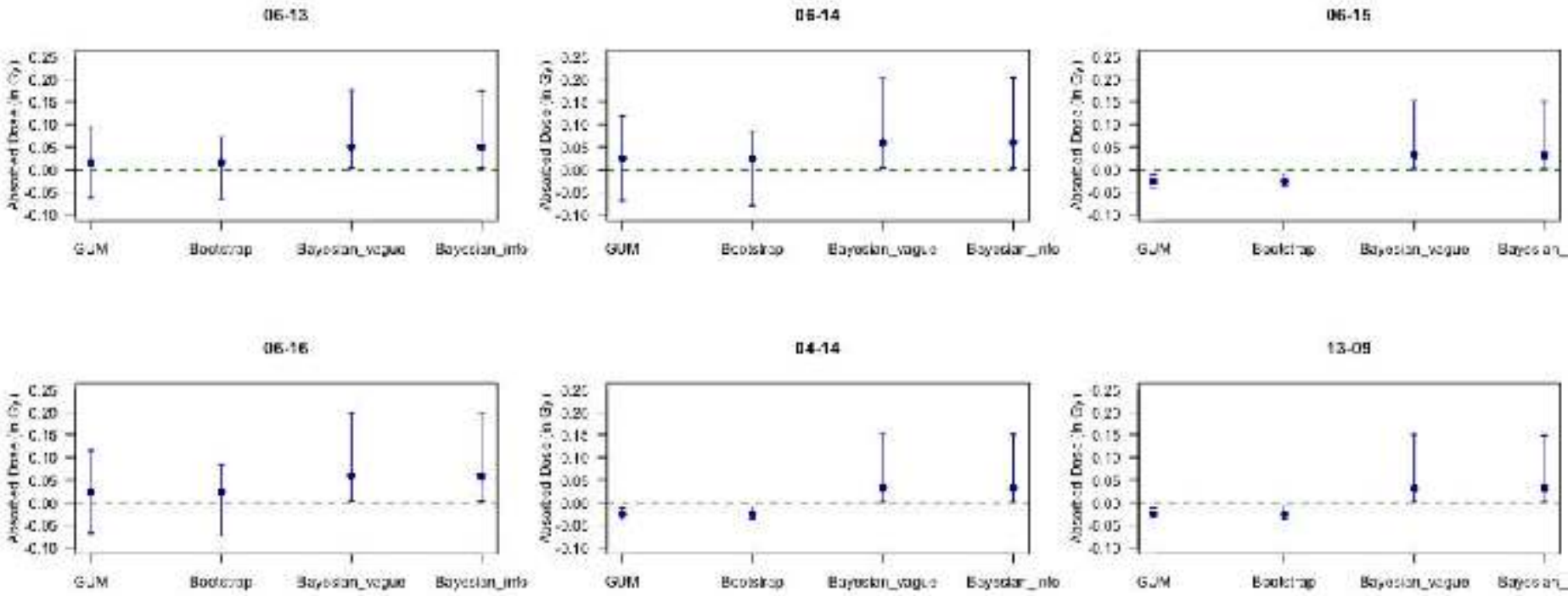
Answering Q_2 - Bayesian estimation of the dose

MCMC algorithm - Package R "rjags"



GUM= Multivariate Delta-Method

Answering Q_2 - Bayesian estimation of the dose



BUT...

Given the prior distribution assigned to D_0, we are assuming that $D_0 > 0$

$\Rightarrow$ **Is this assumption relevant for all the considered individuals?**

Answering Q_1 and Q_2 under the Bayesian framework

Question Q_1

Can it be stated that a **strictly positive radiation dose** has been received by :

1. **all of the** analyzed cells (whole-body irradiation)?
2. **only a fraction** of the analyzed cells (partial irradiation)?
3. **none** of the analyzed cells ? (Relevant for **unclear exposure scenarios**)

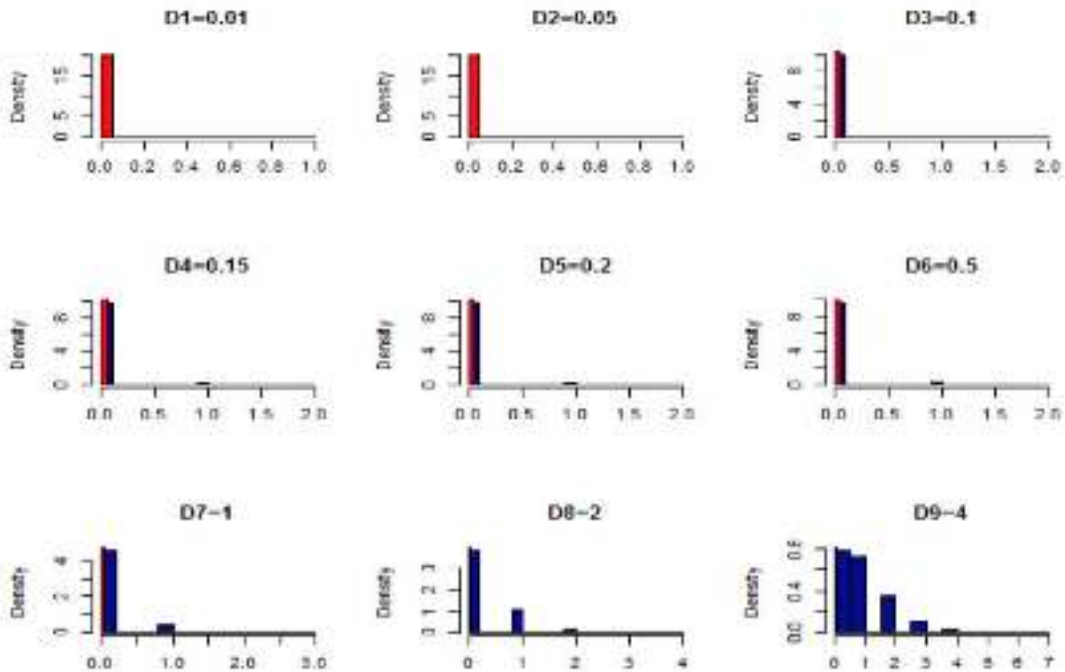
The **above sub-questions 1 and 3** can be formalized as :

A Bayesian model selection problem

$\mathcal{M}_0 : R_k \sim^{i.i.d} Poisson(A)$ vs $\mathcal{M}_A : R_k \sim^{i.i.d} Poisson(A + \alpha D_0 + \beta D_0^2)$

given in-vivo data **and** calibration data following model $\mathcal{M}_C$ $(D_0 > 0)$

Answering Q_1 and Q_2 under the Bayesian framework



$Poisson(A)$

$Poisson(A + \alpha D_0 + \beta D_0^2)$ $\quad with\ D_0 > 0$

	Bayesian inference	
	Post.mean	Credible interval at 95%
A	0.001	[0,0006; 0.0015]
α	0.040	[0.032; 0.048]
β	0.048	[0.044; 0.052]

Answering Q_1 and Q_2 under the Bayesian framework

$\Rightarrow$ A Bayes factor (Jeffreys, 1939) can be efficiently approximated (e.g., Monte-Carlo estimate)

But what about **sub-question 2 about partial irradiation**?

Idea: using a mixture model (Kamary et al. (2014) - arXiv)

Let's consider a given individual - potentially exposed - with n_0 analyzed cells:

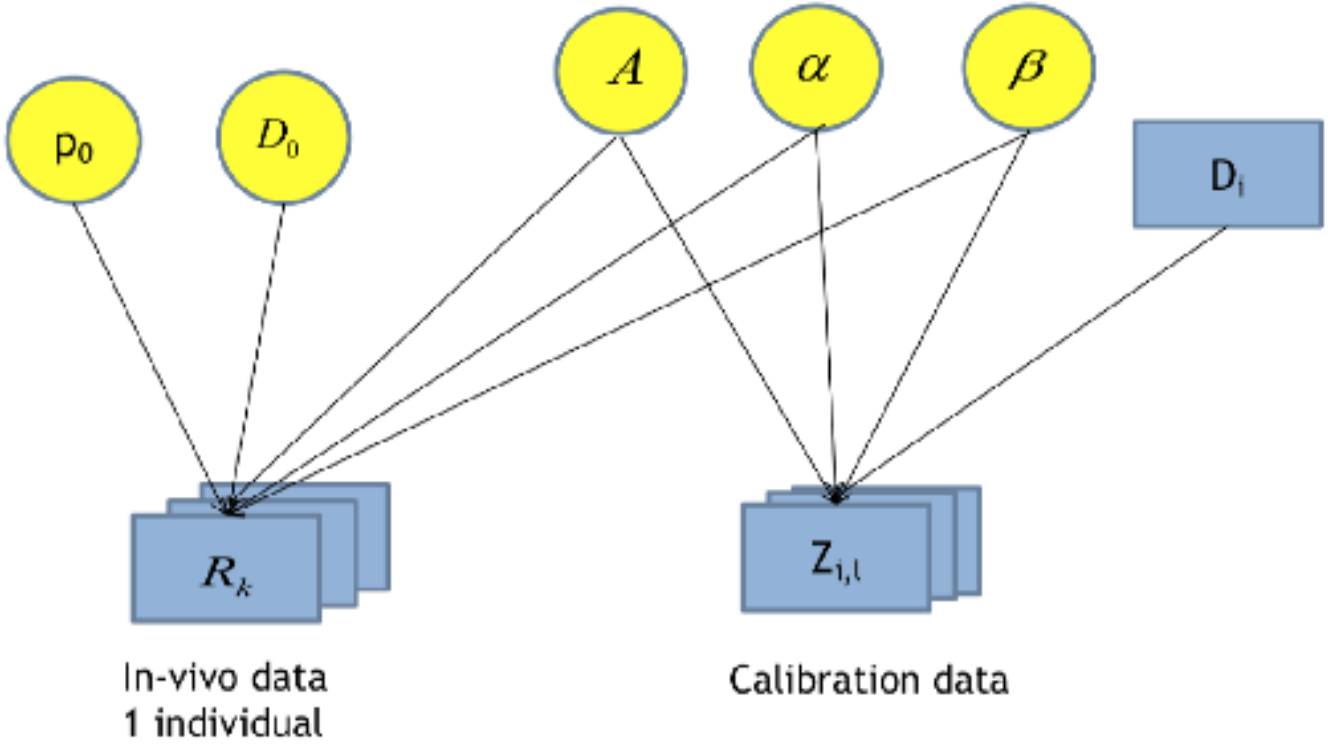
- p_0: **unknown** probability for each cell to have received a dose > 0
- D_0 : **unknown** absorbed dose (in Gray) received by each irradiated cell

A mixture model for in-vivo data (LOW LET + homogeneous irradiation)

$$\mathcal{M}_{mix}: \quad R_k \sim^{i.i.d} (1-p_0)Poisson(A) + p_0 Poisson(A + \alpha D_0 + \beta D_0^2)$$

- $D_0 > 0$ and $p_0 \in [0,1]$
- $\theta = (A, \alpha, \beta)$: unknown parameters with $A > 0$, $\beta > 0$, $\alpha > -2\sqrt{A\beta}$
- A: **common parameter** shared by both mixture components
- p_0 can also be interpreted as the proportion of irradiated cells
- D_0 and p_0 assumed to be identical for each irradiated cell
- $\mathcal{M}_0$ and $\mathcal{M}_A$ are very special cases of the mixture model

Directed Acyclic Graph of the full model ($\mathcal{M}_{mix} + \mathcal{M}_C$)



- $\theta = (A, \alpha, \beta)$: shared parameters
- The Bayesian framework allows fitting this model in one step

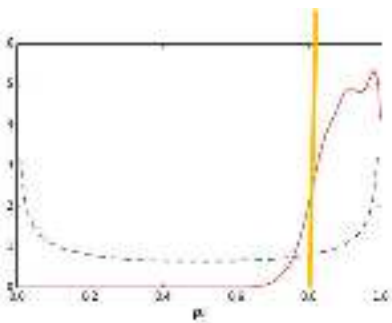
Answering to Q_1 and Q_2 with $\mathcal{M}_{mix}$ (1/2)

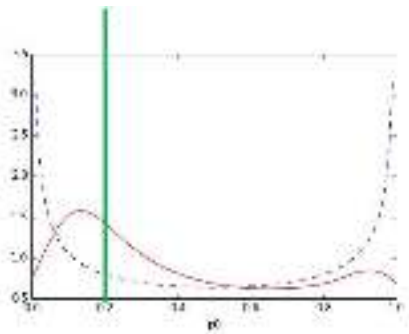
- If $p_0 = 0$, model $\mathcal{M}_0$ is selected given the available count data
  - $\Rightarrow$ Response to Q_1 is NO= "There is no evidence that a strictly positive radiation dose has been received".
- If $p_0 = 1$, model $\mathcal{M}_A$ is selected given the available count data
  - $\Rightarrow$ Response to Q_1 is YES= "A strictly positive radiation dose has been received **by all the analyzed cells"**.
- If $p_0 \in]0, 1[$, neither model $\mathcal{M}_0$ nor model $\mathcal{M}_A$ is selected given the available count data
  - $\Rightarrow$ Response to Q_1 is YES= "A strictly positive radiation dose has been received **BUT only by a fraction of the analyzed cells" (partial body exposure)**.
  - The fraction of the body irradiated is defined as (IAEA report 2001):

$$F_0 = \frac{p_0 \times exp(D_0/\tilde{D})}{(1-p_0) + p_0 \times exp(D_0/\tilde{D})} \qquad \tilde{D} \sim Unif(2.7, 3.5)$$

Answering to Q_1 and Q_2 with $\mathcal{M}_{mix}$ (2/2)

- Posterior distribution on p_0 $\Rightarrow$ Probabilistic answer to Q_1
- $\Rightarrow$ Decision criterion to define the range of acceptance, rejection and indecision conclusions





- Let's c_1, c_2, U be fixed decision thresholds (to calibrate by simulation)
- Compute $\pi_1 = P(p_0 > c_1 | Y_i, R_k)$ and $\pi_2 = P(p_0 < c_2 | Y_i, R_k)$
  - If $\pi_1 > U \Rightarrow$ YES= "There is **strong evidence** that a strictly positive radiation dose has been received **by all of the analyzed cells"**.
  - If $\pi_2 > U \Rightarrow$ NO= "There is no evidence that a strictly positive radiation dose has been received".
  - Else YES= "A strictly positive radiation dose has been received **BUT only by a fraction of the analyzed cells" (partial body exposure)**.

The prior distributions

- $A \sim Unif[0, +\infty[$
- $\alpha \sim Unif[-2\sqrt{A\beta}, +\infty[$
- $\beta \sim Unif[0, +\infty[$
- $D_0 \sim Gamma(a, b)$ or $D_0 \sim Unif(0, 10)$
- $p_0 \sim Beta(c, d)$

- Hyperparameters a,b,c,d may be fixed by expert knowledge given the accident scenario
- Default choice (Rousseau and Mengersen (2011)): c=0.5,d=0.5

Bayesian inference

Adaptive Metropolis-Hastings algorithm

- Block updating for (A, α, β) using a Gaussian random walk (20% acceptation rate)
- Gaussian random walk for D_0 (40% acceptation rate)
- For the mixture weight p_0:
  - Iteration t: Independent proposal $\Rightarrow p_0^{cand} \sim Beta(0.5, 0.5)$
  - Iteration t+1: Random walk $\Rightarrow p_0^{cand} \sim Beta(1 + p_0^t, 2 - p_0^t)$
  - 40% acceptation rate
- Implemented in Python (2.7.10) (100000 iterations = 30 seconds)

Asymptotic consistency of the proposed mixture testing procedure

- Proved by Kamary et al. (2014) in the specific case of embedded mixture components
  - "If one model is indeed correct, the posterior medians of the corresponding weight in the mixture settles very quickly near the boundary values of 1 as the sample size increases"

Remark

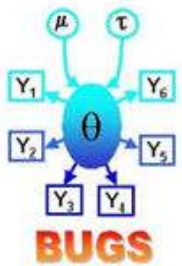
- Equivalent formulation of $\mathcal{M}_{mix}$ pointing out the latent allocation variables

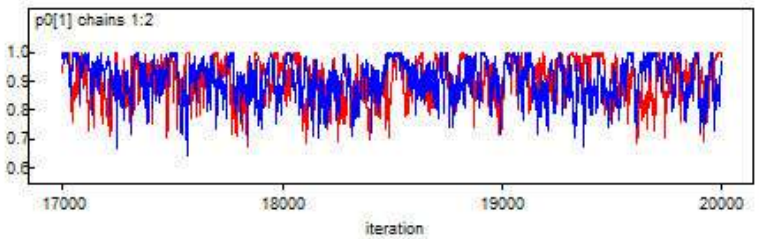
$$\mathcal{M}_{mix}: \quad R_k \sim^{i} Poisson(\lambda_k) \quad \text{with} \quad \lambda_k = A + \alpha D_{0k} + \beta D_{0k}^2$$
$$D_{0k} = \gamma_k \times D_0 \quad \text{with} \quad \gamma_k \sim Bern(p_0)$$

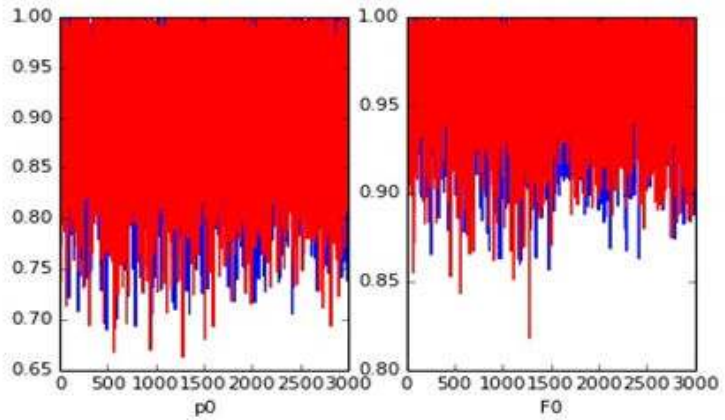
- Easy implementation in WinBUGS or JAGS but inefficient Gibbs sampler!!!

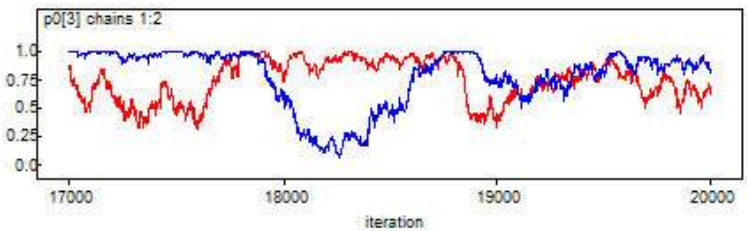
Convergence diagnostics on the weight p_0

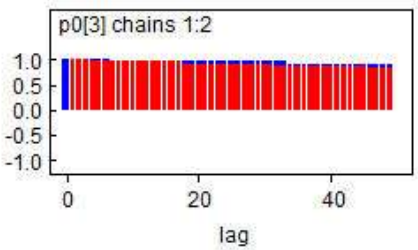
Gibbs sampler (Left) vs Adaptive Metropolis-Hastings (Right)

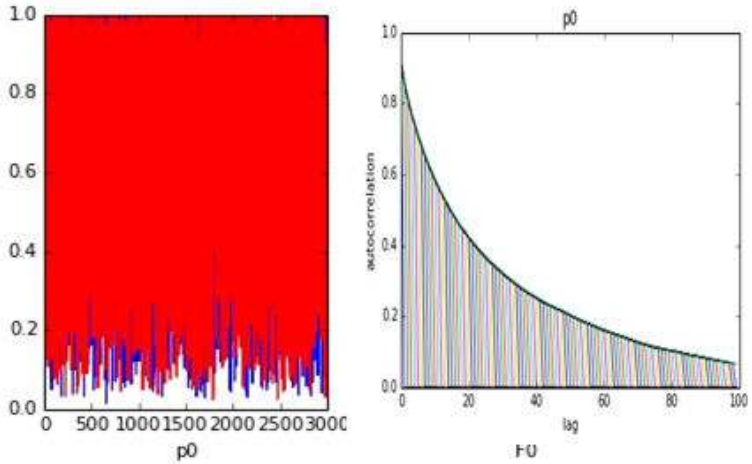








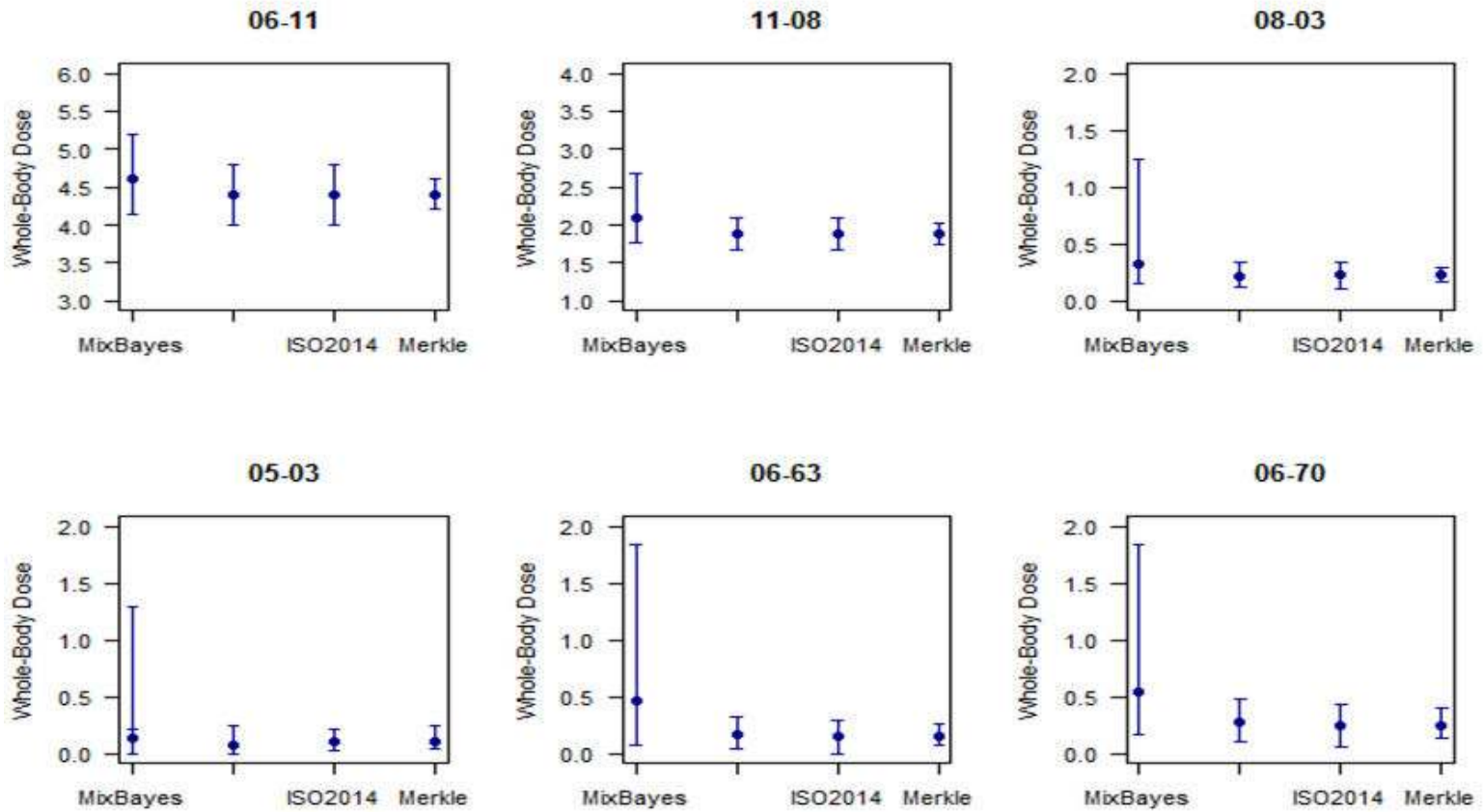




Posterior statistics, Bayes factor and posterior probability of $\mathcal{M}_1$

	Bayesian Mixture approach Informative prior on D_0 Non-informative prior on p_0					Bayes Factor M_1 vs M_0 (Kass & Raftery (1995))	$P(M_1 \mid y)$
	D_0 posterior median 95%CI	*p_0 posterior median 95%CI*	*F_0 posterior median 95%CI*	*$P(p_0>0.8)$*	*$P(p_0<0.2)$*		
06-11	4.61 [4.14; 5.19]	0.91 [0.76,1.00]	0.97 [0.90; 1.00]	0.93	0.0	+∞ (very strong)	1 [1.0; 1.0]
11-08	2.09 [1.76; 2.69]	0.84 [0.56; 1.00]	0.90 [0.69; 1.00]	0.60	0.0	1.75e+185 (very strong)	1 [1.0; 1.0]
08-03	0.32 [0.15; 1.25]	0.67 [0.10; 1.00]	0.69 [0.11; 1.00]	0.39	0.11	>10^7 (very strong)	1 [1.0; 1.0]
05-03	0.13 [0.0002; 1.29]	0.54 [0.011; 1.0]	0;55 [0.01; 1.0]	0.31	0.25	4 (Positive)	0.67 [0.63; 0.70]
06-63	0.47 [0.08; 1.84]	0.23 [0.02; 0.99]	0.26 [0.02; 0.99]	0.16	0.46	8.3 (Positive)	0.86 [0.83; 0.88]
06-70	0.55 [0.16; 1.84]	0.36 [0.04; 1.00]	0.40 [0.06; 1.00]	0.21	0.33	303.03 (Very Strong)	1.00 [1.0; 1.0]

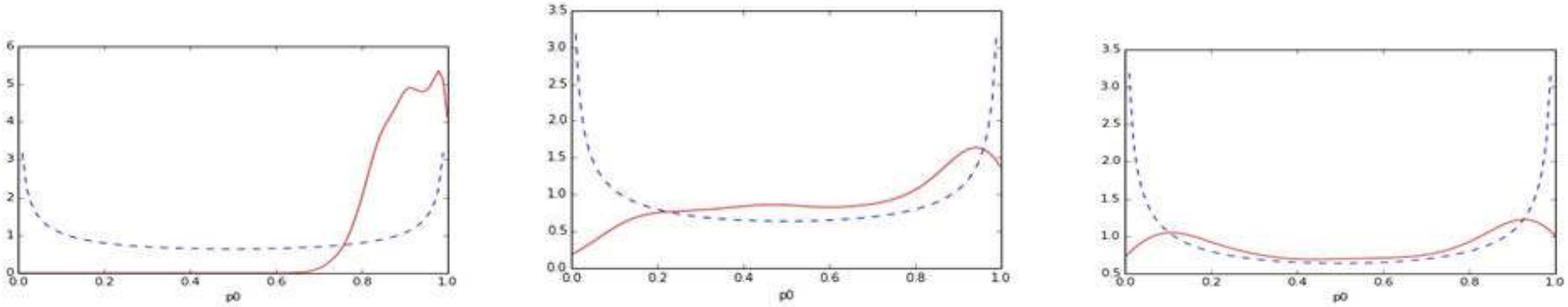
Comparison of dose estimations



Posterior medians + 95% credible intervals
ISO2014 = Multivariate Delta Method

Comparing prior and posterior probability distributions on p_0

Prior probability distribution on p_0 : Beta(0.5,0.5)

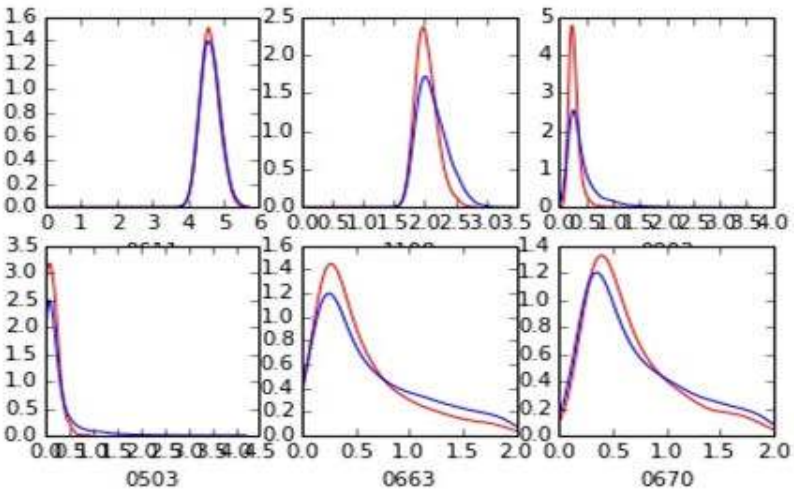


From left to right : Victims 06-11 (Estimated dose: 4.61 Gy), 08-03 (Estimated dose: 0.32Gy), 05-03 (Estimated dose: 0.13Gy)

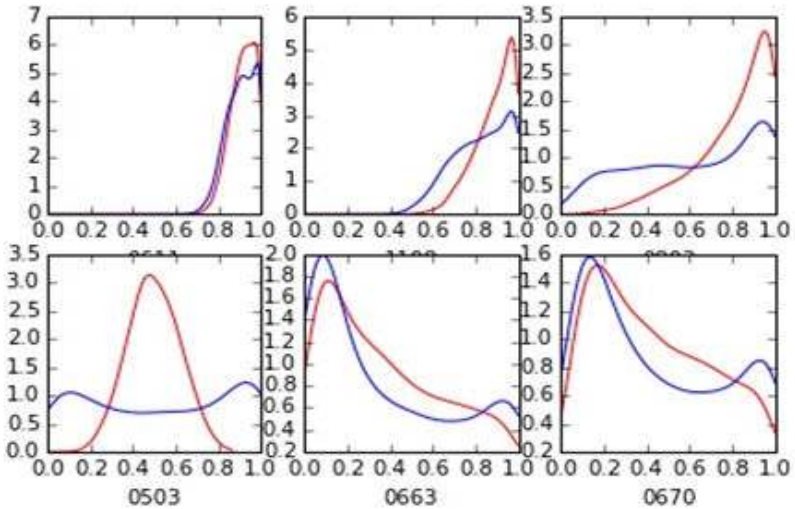
- Weak influence of the prior choice on D_0 (results not shown)
- Lack of information in the data to infer p_0 especially when dose is small
  $\Rightarrow$ **More data needed to infer p_0 (and then answer Q_1)?**

Sensitivity to the prior choice on p_0

- Informative Beta priors defined from expert knowledge
- Jeffrey's prior Beta(0.5,0.5)



Posterior distribution on the dose D_0



Posterior distribution on the weight p_0

$\Rightarrow$ **Sensitivity is clearly present but should naturally vanish as the number of analyzed blood lymphocytes increases**

Conclusions

- **First fully Bayesian approach** proposed to simultaneously answer to two main questions of interest in biological retrospective dosimetry
  - $\Rightarrow$ New insights to the **European Radiation Dosimetry (EURADOS)** Working Group 10, task 10.6
- Using the proposed mixture model $\mathcal{M}_{mix}$ allows to get **rich probabilistic answers** to questions Q_1 and Q_2
  - $\Rightarrow$ Relevant input data for **decision-making** in the contexts of clinical management of patients, rapid triage after large-scale radiation incident, reassuring the 'worried-well'...
- In case of low suspected dose, the number of analyzed blood lymphocytes **should be higher** to obtain more precise answers to question Q_1

Perspectives

- **Simulation studies** to validate the whole methodology and calibrate the decision thresholds (c_1, c_2, U)
- Validate the whole methodology from new experimental data for which D_0 and p_0 are known
- Bayesian optimal design to define the number of analyzed cells n_0 required to optimally answer to question Q_1 and Q_2 under budget constraint
- **Extend** the proposed approach to other chromosome aberrations
- Provide **operational tools** to dosimetrists

Bibliography

[1] IAEA 2011 report (2011) Cytogenetic dosimetry: applications in preparedness anfor and response to radiation emergencies. International Atomic Energy Agency: Vienna.
[2] Merkle W. (1983) Statistical Methods in Regression and Calibration Analysis of Chromosome Aberration Data. Radiat Environ Biophys. 1:217-233
[3] Ainsbury et al. (2014) Review of Bayesian statistical analysis methods for cytogenetic radiation biodosimetry with a practical example. Radiation Protection Dosimetry. 162(3):185-96
[4] Higueras et al. (2016) A new Bayesian model applied to cytogenetic partial body irradiation estimation. Radiation Protection Dosimetry. 168(3):330-6
[5] Kamary K., Mengersen K., Robert CP., Rousseau J. (2014) Testing hypotheses via a mixture estimation model. ArXiv:1412.2044v2