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# Bayesian spatial mixture of experts for a flexible dose-response assessment after brain radiotherapy

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## Context and motivation

- High-grade glioma:** The most frequent high-grade brain tumor in adults.
- Radiotherapy (RT):** One of the most important treatments, generally combined with surgery and/or chemotherapy:
  - increased patient survival,
  - but also an increase in side effects like cognitive impairments [Bompaire et al., 2018].
- Clinical question:** Potential neurotoxicity of brain RT on the central nervous system?
- Aim:** To estimate the potential association between the occurrence of white-matter hyperintensities (WMH) and the absorbed dose after brain RT.
- Background:** Mass univariate analysis (voxel-based t-tests, voxel-based logistic regression).
- Our idea:** Model-based approach at the voxel level  $\implies$  Extensions of GLiM models [Deleforge et al., 2015] to the context of binary outcomes and zero-inflated mixture components.

## Data

- There are three types:
- Segmentation map (binary data) of WMHs observed from one 3D brain MRI, observed at multiple time.
  - Dosimetric CT-scan, giving the absorbed dose to each voxel of the brain during RT.
  - Clinical variables (sex, age, etc).
- Aim:** use our model on the EpiBrain-Rad cohort [Durand et al., 2015].

## Modelling

For an individual  $i$  and a voxel  $v$  and a time  $t$ , let  $Y_{ivt}$  be the outcome variable describing the presence/absence of a WMH,  $D_{ivt}$  the absorbed dose,  $W_i^{1:P}$  some individual-specific covariates and  $C_v$  the unknown class label of the voxel. Pour  $k \in \{1, \dots, K\}$ :

$$Y_{ivt} | D_{ivt}, W_i^{1:P}, C_v = k \sim \text{Bern}(p_{ivt})$$

$$\text{logit } p_{ivt} = \eta_{ivt} = \beta_0^k + \beta_1^k d_{ivt} + \beta_{2:P+1} W_i^{1:P}$$

$$D_{ivt} | C_v = k \sim \begin{cases} \delta_0 & \text{si } k = 0 \\ \text{Log-}\mathcal{N}(\mu_k, \tau_k^{-1}) & \text{si } k \neq 0 \end{cases}$$

$$C_v \sim \text{Multinomial}(1, \{\pi_1, \dots, \pi_K\})$$

## Data modelling

For all  $k \in \{1, \dots, K\}$ :

$$\beta^k \sim \mathcal{N}_2(m_0 = 0, \sigma_0 = 10^3)$$

$$\mu_k \sim \mathcal{N}(\mu_0 = 0, \lambda_0 = 10^3)$$

$$\tau_k \sim \mathcal{G}(a_0 = 10^{-3}, b_0 = 10^{-3})$$

$$\pi_k \sim \text{sym-Dirichlet}(\alpha/K)$$

## Prior distributions

## Bayesian inference

- Variational Bayes [Durante and Rigon, 2019]
- Gibbs Sampler [Polson et al., 2013]

## Difficulties

- Large amount of data:  $512 \times 512 \times 121 \sim 10^7$  voxels per MRI, 250 individuals with multiple times.
- Registration of MRI longitudinally and inter-individuals when brains deal with deformations.

## Further modelling

- Add a temporal interaction with the dose in the regressor :

$$\eta_{ivt} = \beta_0^k + (\beta_{1_0}^k + \beta_{1_1}^k t) d_{ivt} + \beta_{2:P+1} W_i^{1:P}$$

- Add spatiality

- through a residual  $\xi_v$ :
 
$$\eta_{ivt} = \beta_0^k + \beta_{1_0}^k d_{ivt} + \dots + \xi_v$$

with  $\xi_v | \xi_{-v} \sim \mathcal{N}(\frac{\sum_{u \in \partial v} \xi_u}{n(\partial v)}, \frac{\sigma^2}{n(\partial v)})$

- through a centred autologistic model using the pseudo-likelihood:

$$\eta_{ivt} = \beta_0^k + \beta_{1_0}^k d_{ivt} + \dots + \gamma \sum_{u \in \partial v} (Y_{iut} - \mu_{iut})$$

with  $\mu_{iut} = \mathbb{E}[Y_{iut} | \gamma = 0]$ .

## Data illustration

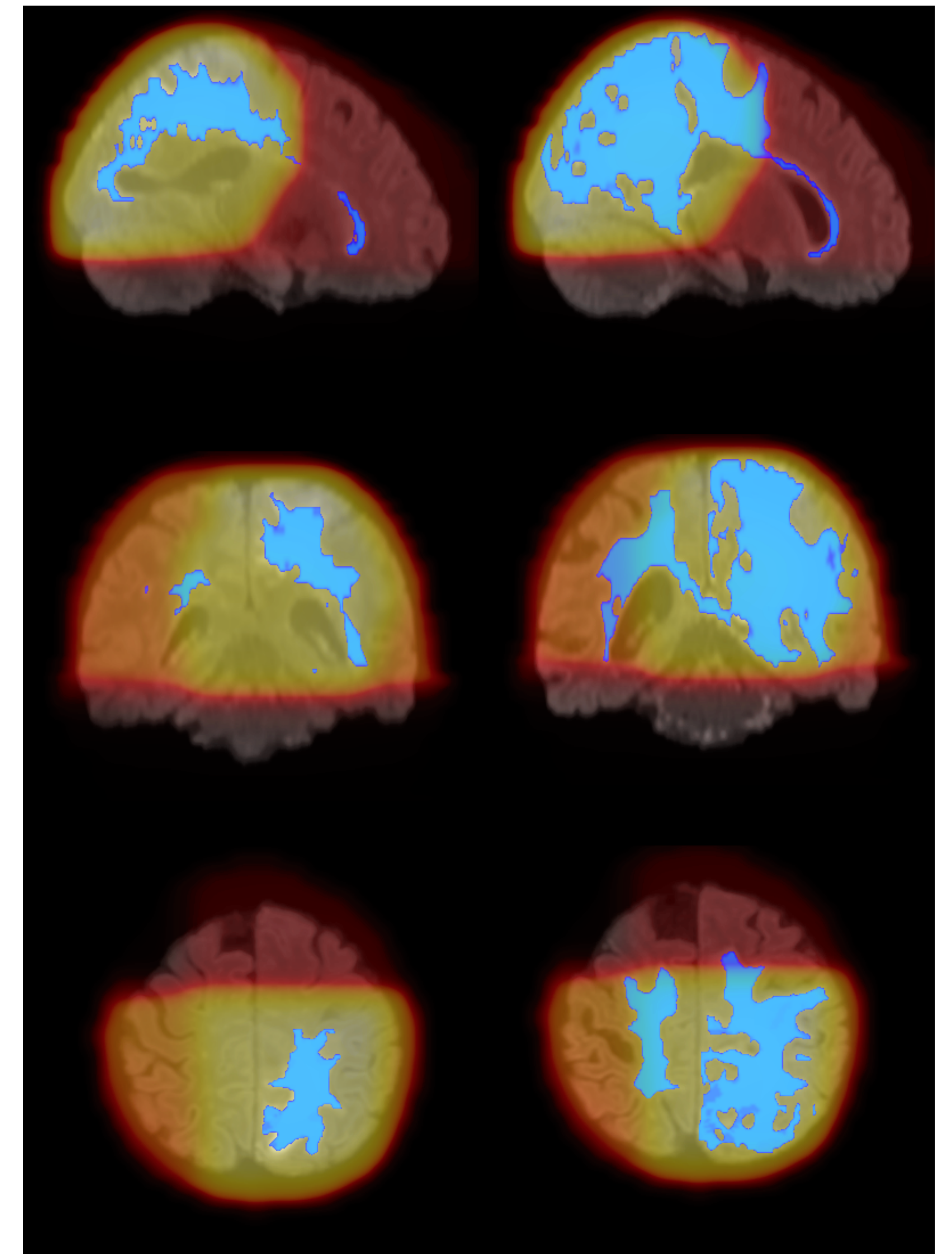


Figure 1: Example of a patient FLAIR, WMH in blue and dose from black=0 through a red to yellow gradient finishing with white~ 60 Gy. On the left 6 months after RT and on the right 47 months after RT.

## Preliminary results on one patient from simulated data ...

Our model is fitted on 100 simulated datasets. Coverage rate (CR) of the true regression parameters are displayed on the right, estimated mixture parameters are not shown:

- Markov chains obtained using MH sampler are strongly auto-correlated, effective sample size is almost 0 and assessing the convergence is not possible.

- Gibbs sampler with Pólya-Gamma latent random variables yields much better Markov chains,

- VBEM: much more faster but a far worse coverage rate compared to the Gibbs sampler.

		$\beta_1^1 = 0.02$			$\beta_0^1 = -3.90$		
Method	CR 95%	Relative bias	Var	CR 95%	Relative bias	Var	
VBEM	50	2.20e01	1.39e00	54	2.80e-03	2.32e-02	
Gibbs	93	2.81e01	8.92e00	93	3.80e-03	1.49e-01	

		$\beta_1^2 = 0.10$			$\beta_0^2 = -4.30$		
Method	CR 95%	Relative bias	Var	CR 95%	Relative bias	Var	
VBEM	82	1.36e-01	1.90e-04	75	5.12e-02	4.03e-02	
Gibbs	99	1.39e-01	4.80e-04	96	5.25e-02	1.32e-01	

		$\beta_1^3 = 0.15$			$\beta_0^3 = -5.45$		
Method	CR 95%	Relative bias	Var	CR 95%	Relative bias	Var	
VBEM	88	4.78e-02	8.00e-05	88	4.34e-02	1.08e-01	
Gibbs	92	4.86e-02	1.40e-04	94	4.42e-02	1.77e-01	

		$\beta_1^4 = 0.20$			$\beta_0^4 = -7.70$		
Method	CR 95%	Relative bias	Var	CR 95%	Relative bias	Var	
VBEM	82	4.66e-02	9.00e-04	83	7.51e-02	3.24e-00	
Gibbs	98	4.45e-02	3.90e-03	98	7.26e-02	1.29e-01	

Table 2: Statistics computed on 100 simulated datasets

	$\mu$	$\tau$	$\pi$	Mode (Gray)
Class 1	-1.21	1.00	0.57	0.11
Class 2	2.63	0.48	0.18	11
Class 3	3.72	0.17	0.11	40
Class 4	4.17	0.15	0.14	63

Table 1: True mixture parameters

## ... and from real data

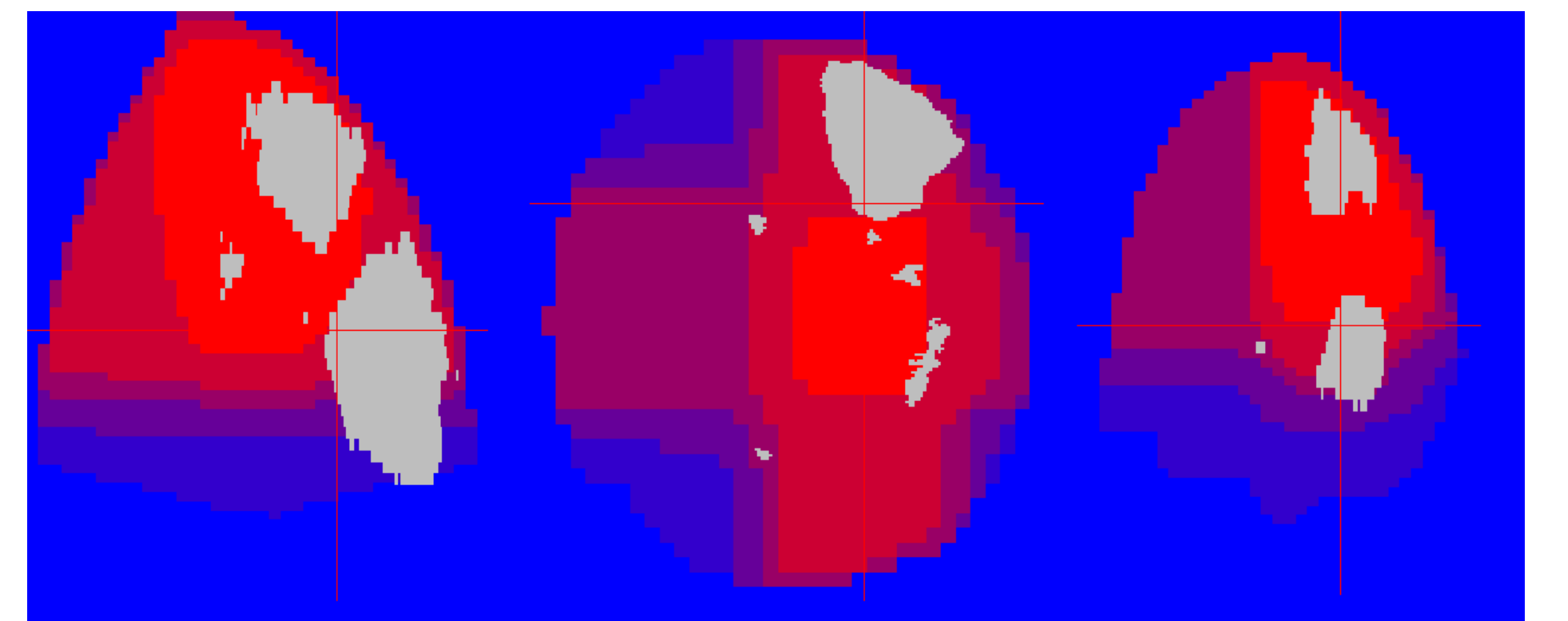


Figure 2: Six classes obtained with the model. Grey voxels indicate a WMH.

- The model assigns a class to each voxel (figure 2).
- To each class is assigned a dose response-relationship, which leads to a piece-wise logistic association (graph 3).
- Thus, it becomes possible to have a relation at the scale of an organ, the white-matter or the whole brain.

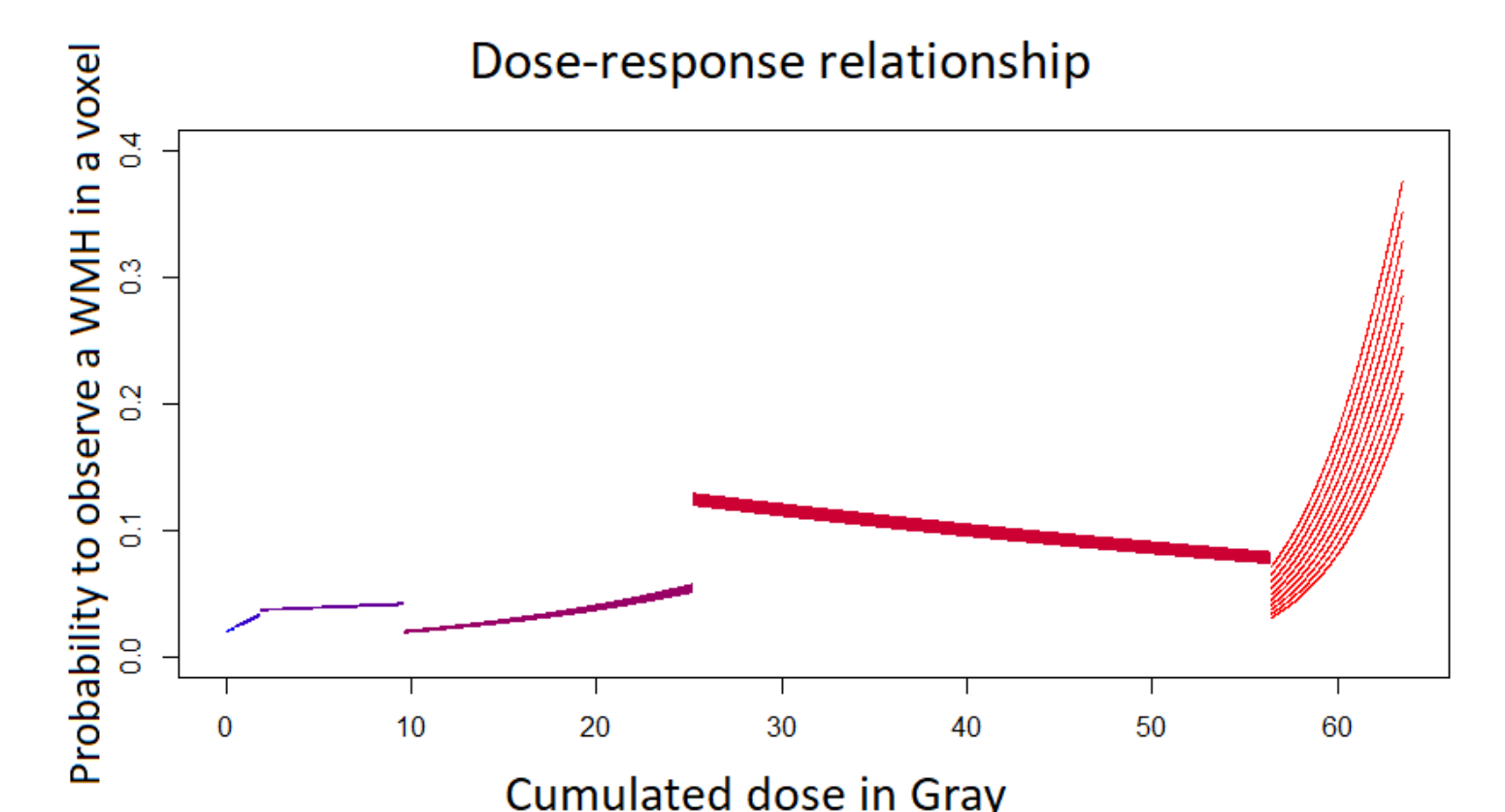


Figure 3: Dose-response relationship estimated (with the associated uncertainty), depending on classes.