National Cancer Institute

Kazakhstan Study: Approaches/Methods to Incorporate Dose Uncertainty into Risk Assessment

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National

The Main Issue

- Instead of single point estimate of dose for each individual, we have uncertainty in each person's does.

- Specifically, we have *M* sets of doses for the entire cohort. The variability of dose for individuals with similar attributes is represented within each set; and the uncertainty of dose-related model parameters is represented across all the sets.

- **Issue: "How to incorporate dose uncertainty to obtain a point estimate of risk along with a confidence interval?"**

Three Different Approaches

(1) Multiple imputation approach (MI) : naïve & likelihood-weighted

(2) Monte Carlo Maximum Likelihood approach (MCML)

(3) Bayesian approach

The Dose-Response Model

Odds=baseline× (1+dose response× dose-response modifiers)

$$=\exp\{\Sigma_i \alpha_i X_i\}[1+(\beta_1 \text{External Dose} + \beta_2 \text{Internal Dose})(\exp\{\Sigma_k \gamma_k Z_k\})]$$

where outcome variable is a binary variable for presence of thyroid nodule, X_i=potential risk factors and Z_k=effect modifiers from Land, C., et al. (Radiation Research, 2008)

Note: We are trying to estimate β_1 and β_2. These are excess odds ratios (EOR/Gy).

Multiple Imputation Approach (naïve)

Begin with *M* dose realizations (e.g., *M*=100). So we have 100 'imputed' data sets.

Fit the dose-response model to obtain 100 estimates for β_1 and β_2 together with their standard errors.

For simplicity we focus on β_1.

$$\bar{\beta}_1 = \frac{1}{100}\sum_{j=1}^{100}\hat{\beta}_{1,j}$$ (average of β_1 estimates)

$$\bar{U} = \frac{1}{100}\sum_{j=1}^{100}\hat{U}_j$$ (average of variances for β_1 estimates)

Multiple Imputation Approach (naïve)
(cont'd)

Now, define the 'between imputation' variance as:

$$B = \frac{1}{100-1}\sum_{j=1}^{100}(\hat{\beta}_{1,j} - \bar{\beta}_1)^2$$

Then the total variance estimate for $\bar{\beta}_1$, is given by:

$$\text{var}(\bar{\beta}_1) = \bar{U} + \left(1 + \frac{1}{100}\right)B$$

Using this variance we can get a confidence interval for $\bar{\beta}_1$.

Multiple Imputation (likelihood-weighted)

This is essentially the same approach as naïve approach.

Only difference is likelihood-weights.

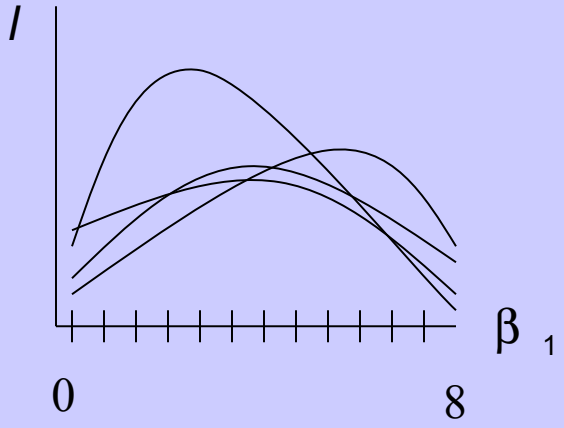
Define weights as: $$w_i = \frac{l_i}{\sum_{j=1}^{100} l_j}, \; i = 1, \ldots, 100$$

,where l_i are likelihoods

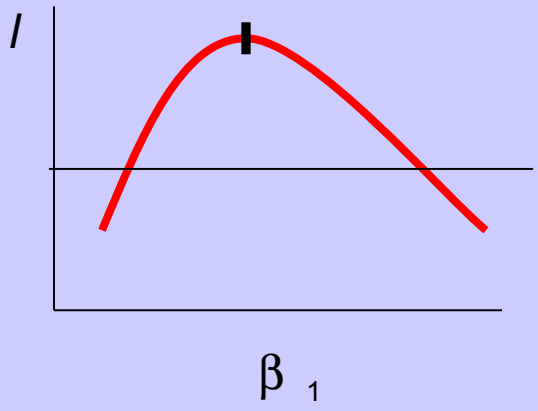
Monte Carlo Maximum Likelihood (MCML) Approach

- Take a realization of dose estimates. Compute a profile likelihood for β_1, at many points from a pre-specified range (0-8). Repeat for all the 100 realizations, and we get 100 profile likelihood curves.
- Average all likelihood curves point-wise to get an average likelihood curve.
- Find maximum value from average likelihood and obtain a confidence interval.

Profile likelihood curves



Average of 100 curves



Bayesian Approach

Posterior $\propto$ likelihood $\times$ prior

Likelihood:

$$l(\alpha,\beta,\gamma)=\prod^{N} p_{y_i}(1-p_i)^{(1-y_i)},$$

Logit(p_i)= {$\alpha_1 X_{1i} + \alpha_2 X_{2i} + \alpha_3 X_{3i} + \alpha_4 X_{4i} + \alpha_5 X_{5i}$}+log[1+ ($\beta_1$ *external dose*$_i$+ β_2 *internal dose*$_i$)(exp{γZ_i})]

Priors:

$\beta_1 \sim$ *exponential dist(10),* $\beta_2 \sim$ *exponential dist(10),*

$\alpha_i \sim Normal(0, 1000)$, $i=1,\ldots,5$, $\gamma \sim Normal(0, 1000)$,

θ (dose set selection) ~ discrete uniform(1/100,…,1/100), ($\theta \in \{1,\ldots,100\}$)

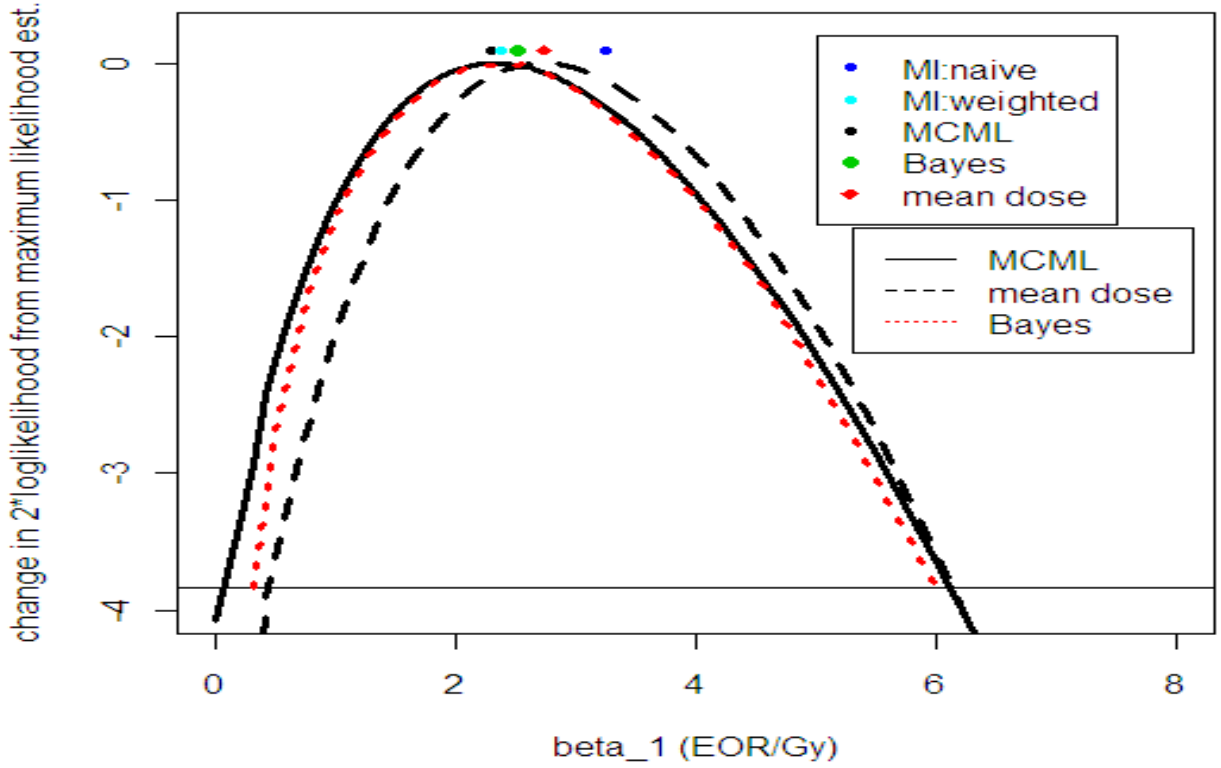
Result of Bayesian approach is based on 10,000 sampling from posteriors after 1,000 burn-in.

Results from the Three Approaches

	β_1 (EOR/Gy for external dose)	
	estimate	95% C.I.
MI: naïve	3.25	0.37-6.13
MI: weighted	2.38	0.31-6.2
MCML	2.3	0.08-6.1
Bayes	2.5	0.29-6
Mean dose	2.73	0.42-6.1

Results from the Three Approaches
(cont'd)

Profile likelihoods & point estimates for β_1



Note: For Bayes, curve is reconstructed from equal-tail credible intervals. For mean dose, we use mean of 100 dose realizations.

Summary/Discussion

- Based on the preliminary analysis, Bayes, MI: weighted, and MCML approaches give similar point estimates. The MI naïve approach gives a higher estimate. [Which method is preferable? Why is the MI: naïve estimate higher?]

- MCML approach yields a slightly wider confidence interval than other approaches.

- Posterior of θ is similar to likelihood weights. Two realization have large weights (realization 42 & 17). Their weights are .56 and .36, respectively. Posterior of these are .54 and .37, respectively. This analysis is based on only 100 realizations of dose. Results show that only two realizations dominate (magnitude of likelihood). [Do we need more dose realizations ?]

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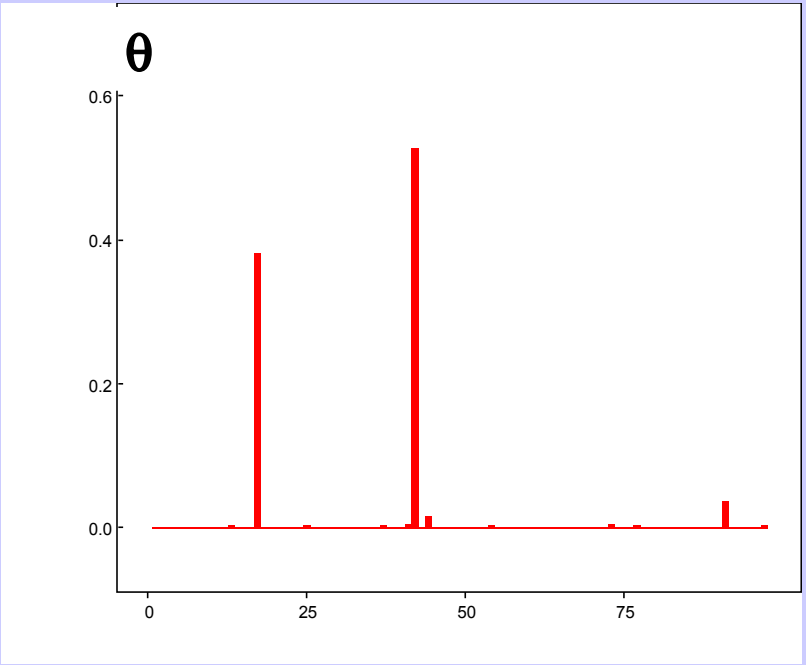
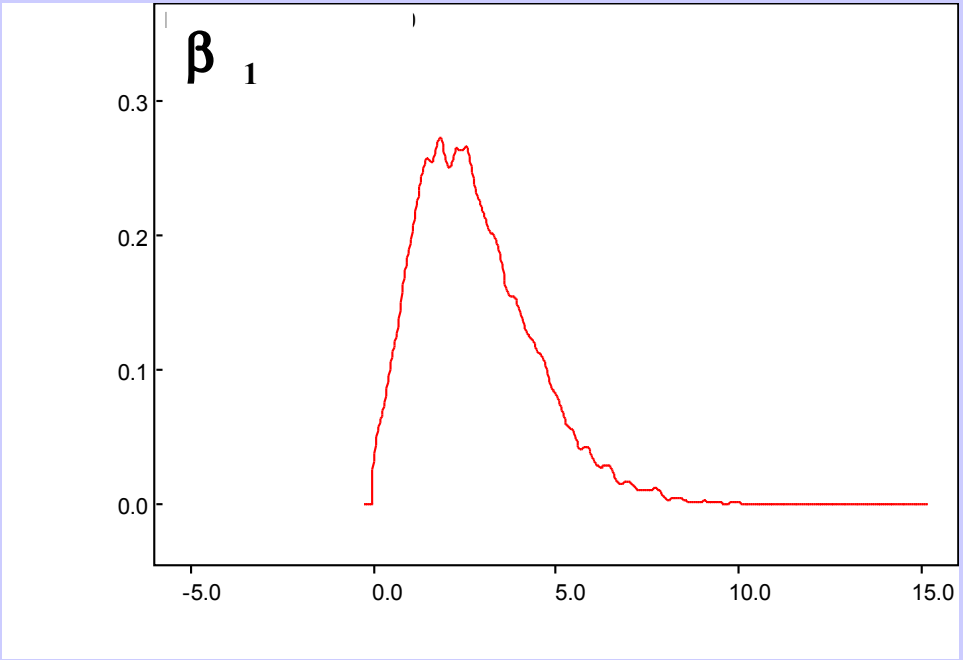
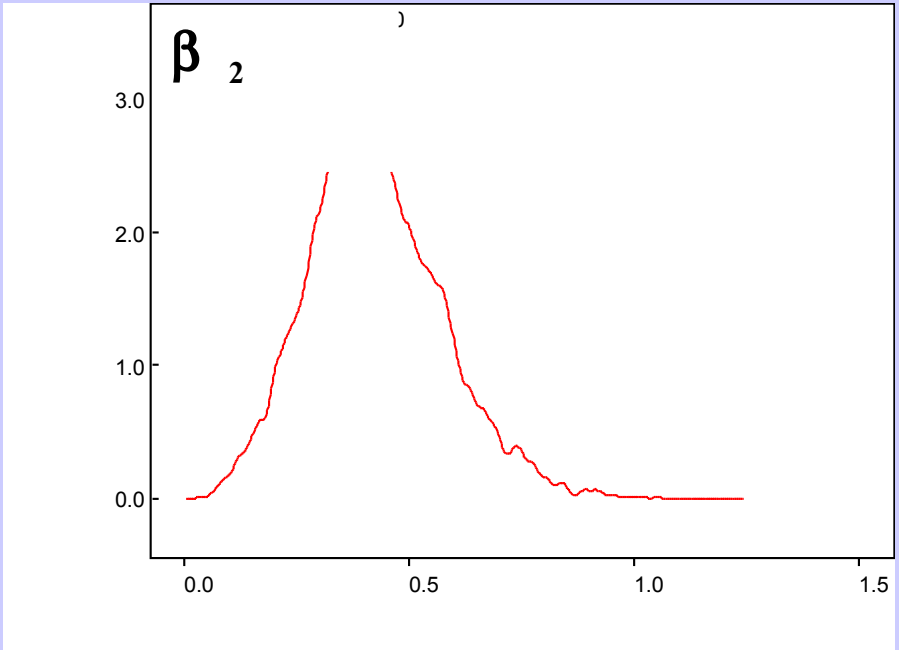
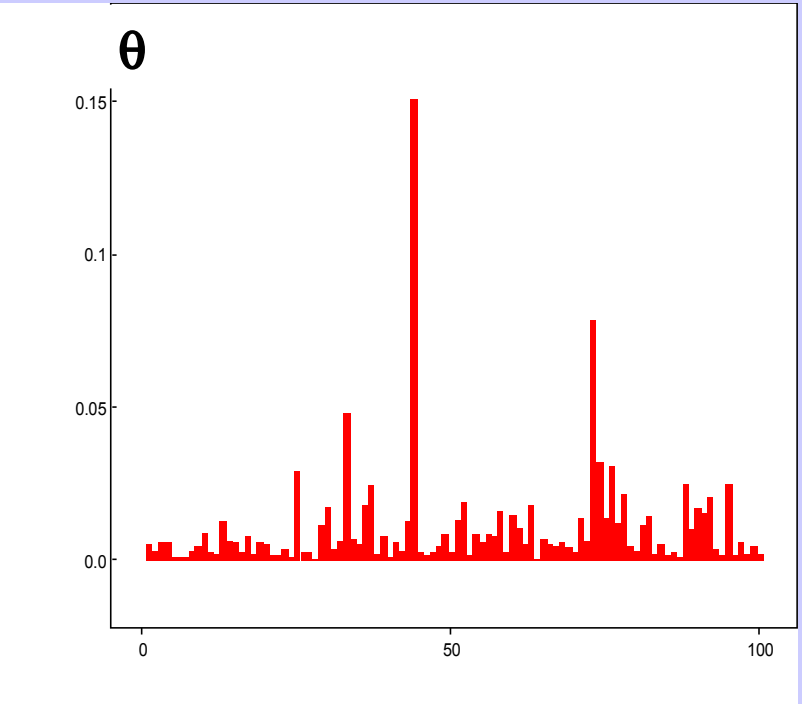
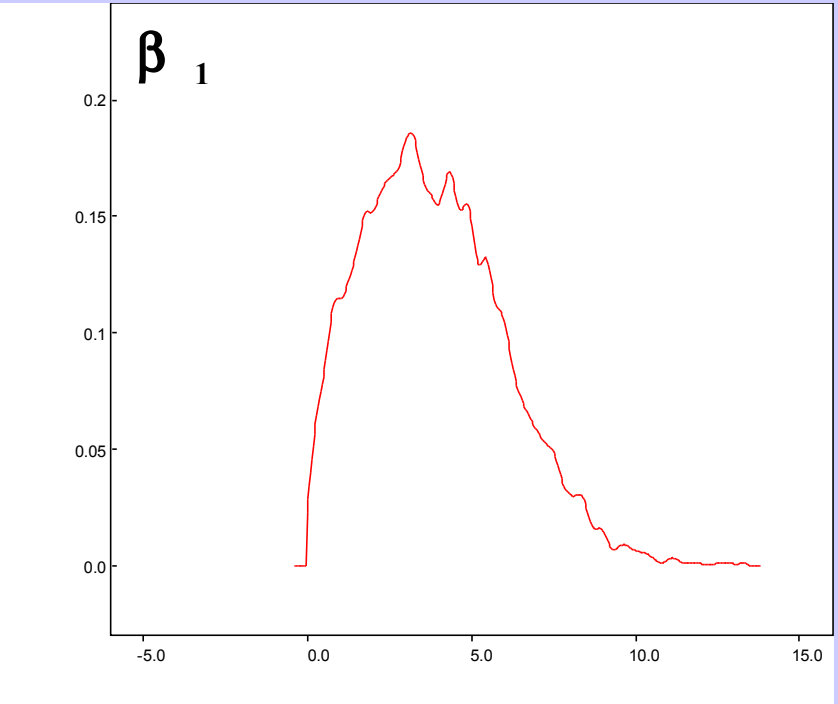

θ
0.6
0.4
0.2
0.0
0
25
50
75


β 1
0.3
0.2
0.1
0.0
-5.0
0.0
5.0
10.0
15.0


β 2
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5


θ
0.15
0.1
0.05
0.0
0
50
100


β 1
0.2
0.15
0.1
0.05
0.0
-5.0
0.0
5.0
10.0
15.0