Krajowa Konferencja Zastosowań Matematyki w Biologii i Medycynie

Sandomierz, 5th–9th September 2016

THE USE OF BAYESIAN ANALYSIS FOR BIOLOGICAL DOSE ASSESSMENT BY THE DICENTRIC ASSAY AFTER OVEREXPOSURES OF PEOPLE TO FISSION NEUTRONS

Maria Kowalska[1], Iwona Słonecka[2], Krzysztof W. Fornalski[3]

[1,2]Central Laboratory for Radiological Protection
ul. Konwaliowa 7, 03-194 Warszawa
[3]PGE EJ 1 Sp. z o. o.
ul. Mysia 2, 00-496 Warszawa
[1]kowalska@clor.waw.pl

ABSTRACT

The objective of this paper is to present methods currently used in biological dosimetry by cytogenetics for estimation of individual doses after accidental exposures to fission neutrons from the uncontrolled chain reaction in a nuclear reactor, in an assembly of fissile material or in fissile materials in a chemical process. These are a classical (frequentist) method recommended by the International Atomic Energy Agency and a new method based on modern Bayesian statistics. The key elements of both methods are indicated as well. The results of estimation of neutron and gamma doses from in vitro exposure of a blood sample in radiation field of the experimental nuclear reactor MARIA in NCBJ provide an illustration of the issue discussed.

INTRODUCTION

Biological dosimetry refers to the use of radiation-induced changes in human body to estimate the radiation dose to which an individual has been exposed in the case of radiation accident or cancer radiotherapy. Cytogenetic effects of ionising radiation are thought to result principally from incompletely or incorrectly repaired double strand breaks (DSBs) in DNA of unduplicated chromosomes [1]. Consequently, the frequency of structural chromosome aberrations is closely related to the linear energy transfer (LET) of radiation and the absorbed dose, and is reliable and well-established biological marker of radiation exposure. The chromosome aberration to be used is a dicentric. This is an aberrant chromosome with two centromeres instead of the one normally present in each chromosome. In order to produce the dicentric, two DNA DSBs must be induced in the two chromosomes involved such that the free ends of the lesions located on those chromosomes may rejoin incorrectly [1]. The dicentric assay is highly specific and sensitive for radiation. Moreover, general dose-response models for dicentrics induced by low- and high-LET radiation are well known. Therefore, the frequency of dicentrics in cultured human peripheral blood lymphocytes (PBL) is the recommended method for biological dose assessment up to a few months after the exposure to radiation [1]. Th frequency of dicentrics observed in a sample of PBL taken from the potentially exposed person is converted into an estimate of absorbed dose by reference to an appropriate *in vitro* calibration curve. In order to produce this curve, PBL from various blood donors are exposed to a range of doses, simulating whole body irradiation.

Such biological dosimetry is complementary to physical dosimetry based on the characteristics of a radiation source involved in an accidental overexposure, and is especially important in these cases, where no physical dosimetry is present.

The main exposures to neutrons released from the nuclear fission reactions are related to occupation or medical irradiation of patients (Boron Neutron Capture Therapy, BNCT). Occupational exposures to fission spectrum neutrons occur mainly in the nuclear industry and research. Accidental overexposures of people are rare events but more complex in evaluation than those where a dose is deposited by a single type of radiation. This is because the body is irradiated not only by neutrons but also by gamma rays generated as a result of the neutron interaction with matter. These two radiation types have significantly different effectiveness at inducing specified health effects in exposed people [1]. Therefore, in the case of an accident, it is important to estimate the total dose as well as its neutron and gamma components. In order to differentiate between dicentrics induced by neutrons and those induced by gamma rays, an ancillary information regarding the contribution of each radiation type to the total dose must be provided. In practise this information is expressed in form of a neutron to gamma dose ratio, denoted ρ below, and may be available from physical measurements [1]

$$\rho = \frac{D_n}{D_g} \,. \tag{1}$$

The objective of this paper is to present methods currently used for estimation of separate neutron and gamma doses with the dicentric assay. These are an iterative method recommended in the IAEA manual [1] and new methods based on modern Bayesian statistics [2, 3]. The key elements of these methods are indicated as well. The results of estimates of neutron and gamma doses from *in vitro* exposure of a blood sample at the H8 horizontal channel of the nuclear reactor MARIA in NCBJ in Poland provide an illustration of the issue discussed [4].

BACKGROUND INFORMATION FOR DOSE ESTIMATION WITH DICENTRIC ASSAY AFTER EXPOSURE TO MIXED FISSION NEUTRONS AND GAMMA RAYS

Iterative dose estimation

It is assumed that after exposure to high doses of neutrons or gamma rays, the number of dicentrics per cell follows a Poisson distribution with a population mean (Y), which is a linear function of the absorbed dose (D) for neutrons and a linear-quadratic for gamma rays [1]

$$Y = \alpha D + c \,, \tag{2}$$

$$Y = \beta D + \gamma D^2 + c \,, \tag{3}$$

The mean of dicentrics per cell is called the expected frequency of dicentrics per cell. The α, β and γ parameters of the dose-response models are estimated with the data from controlled calibration experiments, and c is a spontaneous frequency of dicentrics observed at zero dose in control samples [1].

If the ratio of neutron to gamma doses (ρ) is know from physical measurements, it is possible to divide the dicentric frequency observed after the exposure to a combination of neutrons and gamma rays between this induced by gamma rays and that induced by neutrons using the iterative method [1]. It is done by assuming that both radiation qualities are additive (*i.e.* independent) in inducing chromosome aberrations, and by referring the separate dicentric frequencies to dose-response calibration curves for acute exposures to fission neutrons and ^{60}Co gamma rays. The iterative estimation of doses proceeds as follow [1]:

(1) All observed dicentrics are assumed to be due to neutrons, and from the observed dicentric frequency a neutron dose is estimated from Eq. (2).
(2) The ρ given in Eq. (1) is then used to estimate the dose due to gamma rays.

(3) From the estimate of gamma dose a frequency of dicentrics due to gamma rays is obtained using Eq. (3).
(4) The dicentric frequency due to neutrons is now obtained by subtraction the calculated dicentric frequency due to gamma rays from the observed dicentric frequency.
(5) A new estimate of the neutron dose is made and steps 2 to 5 are repeated until self-consistent estimates are obtained.

The advantage of this method is that each iteration allows obtaining more consistent estimates of the neutron and gamma doses as well as the dicentric frequencies induced by those doses. However, in these cases, where a true value of the neutron to gamma dose ratio is not known precisely, as for example after a criticality accident, the use of this method is not possible. Therefore, an attractive alternative to the iterative dose estimation is a Bayesian approach, which allows to simply include the results of any previous measurement. Groer and Pereira [2] were the first who introduced the Bayesian concept for dose estimation with the dicentric assay when a single radiation type deposits a dose, and since then several researchers have used Bayesian methods in cytogenetic dosimetry. This paper presents a new Bayesian approach of Brame and Groer [3] for dose estimation after exposure to a combination of neutrons and gamma rays, which has been successfully validated in a simulated criticality accident at the experimental reactor SILLENE in Valduc in France [5].

Key elements of bayesian statistics

The fundamental difference between classical and Bayesian statistics lies in a quite different approach to the concept of probability, representing unknown parameters. Probability in classical statistics is considered as a relative frequency observed in a number of repetitions of the experiment. In contrast, probability in Bayesian statistics reflects the state of our incomplete knowledge about the value of an unknown parameter. This state is a result of information obtained from measurements as well as that information, which was available prior to such measurements. Therefore, in the frequentist statistics, parameters are fixed quantities, whereas in Bayesian statistics the true value of a parameter can be thought of as being a random variable to which one can assign a probability distribution, known specifically as *prior information*. A Bayesian analysis synthesises two sources of information about the unknown parameters of interest trough Eq (4).

$$Posterior \propto LF \times PD \; . \tag{4}$$

The first source of this information is the sample data, expressed formally by the *likelihood function* (LF). The second is the *prior distribution* (PD), which represent additional information that is available to the investigator. The product of the likelihood function and the prior distribution, called the *posterior distribution*, expresses what is known about the unknown parameter based on both the sample data and prior information.

Bayesian approach to dose estimation of Brame and Groer

If the neutron to gamma dose ratio (ρ) is uncertain, the total dose as well as the neutron and gamma doses are estimated in a fashion presented below.

- The ρ is treated as an unknown parameter and its prior distribution, $p(\rho)$, is established by applying the Gausian distribution for $\rho \pm \sigma_p$ and its expected value $\hat{\rho}$

$$p(\rho) = \frac{1}{\sqrt{2\pi}\sigma_p} \exp\left[\frac{-\left(\rho - \hat{\rho}\right)^2}{2\sigma_p^2}\right] \; . \tag{5}$$

- Then ρ is transformed to a new variable θ, which corresponds to the fractional contribution of a gamma dose to the total dose and is given by

$$\theta = \frac{D_g}{D_g + D_n} = \frac{1}{\rho + 1} \; . \tag{6}$$

- If ρ is expressed in terms of θ, the Gaussian prior distributions for θ can be rewritten as

$$p(\theta) = \frac{1}{\sqrt{2\pi}\sigma_p\theta^2}\exp\left\{\frac{-1}{2\sigma_p^2}\left[\left(\frac{1}{\theta}-1\right)-\hat{\rho}\right]^2\right\}, \tag{7}$$

  where $\hat{\rho}$ is the expected value for ρ and σ_p is its standard deviation. Note that $0 \leq \theta \geq 1$. Therefore, $p(\theta)$ is the Gaussian prior distribution scaled in the range of $0 \div 1$.
- The likelihood function expresses what is known about the expected frequency of dicentrics induced by unknown total dose as well as the neutron and gamma doses. It is approximated by the Poisson distribution represented by

$$L(D_x|\theta) = \frac{(m_f y_f)^n e^{-m} f^y f}{n!}, \tag{8}$$

  where n is the number of dicentrics observed in a sample of m_f lymphocytes after irradiation with mixed $(n+\gamma)$ radiation, and y_f is the expected frequency of dicentrics per cell.
- The dose-response model parameters (α, β and γ) are estimated with data sets from controlled calibration experiments using the Bayesian parameter estimation procedure [2].
- Based on the assumption that the number of dicentrics observed in a sample of m_f irradiated lymphocytes is Poissonisn distributed with the mean of $m_f(\alpha N_f + \beta G_f + \gamma G_f^2)$, the posterior distribution of the unknown total dose is given by

$$p(t_f|D_A) \propto p(t_f)\int_P\int_\Gamma\int_B\int_A L(t_f|\alpha,\beta,\gamma,\rho,y_f,m_f)p(\alpha)p(\beta)p(\gamma)p(\rho)d\alpha d\beta d\gamma d\rho\ . \tag{9}$$

  In Eq. (9) the subscript f refers to a future individual exposure after the accident. The variables N_f and G_f denote the neutron and gamma doses. The D_A consists the future calibration data sets D_n and D_g used to obtain $p(\alpha)$, $p(\beta)$ and $p(\gamma)$ that are the gamma priors of estimate parameters of fission neutron and gamma calibration curves. The $p(t_f)$ is the prior distribution for the unknown total dose, $p(\rho)$ is the prior distribution for the neutron to gamma dose ratio and $L(t_f|\alpha,\beta,\gamma,\sigma,y_f,m_f)$ is the likelihood function for the unknown total dose.

For information how to calculate posterior distributions for the neutron dose and gamma dose readers are referred to the article of Brame and Groer [3].

Clor's Bayesian procedure for neutron and gamma dose estimation

The methodology presented above was successfully implemented in the CLOR [4, 6]. However, some changes have been made by Fornalski [6] in order to simplify mathematical calculations. For calculations of posterior distributions for both components of the total dose, numerical values of the fitted parameters of α, β and γ were used instead of the calibration data sets for fission neutrons and ^{60}Co gamma rays. Moreover, the information regarding the contribution of each radiation type to the total dose was expressed in the form of a fractional contribution of gamma dose to the total dose (θ).

Calculations of posterior distributions for neutrons and gamma doses are conducted as follow

- The θ is treated as an unknown parameter and its prior distribution, $p(\theta)$, is established by applying the Gaussian distribution for $\theta \pm \sigma_\theta$ and an expected value $\hat{\theta}$

$$p(\theta) = \frac{1}{\sqrt{2\pi}\sigma_\theta}\exp\left[\frac{-(\theta-\hat{\theta})^2}{2\sigma_\theta^2}\right]\ . \tag{10}$$

- For mixed neutron and gamma radiation the expected frequency of dicentrics per cell is a combination of Eqs. (2) and (3), and for gamma rays can written as

$$y_f = c + \alpha\frac{1-\theta}{\theta}D_g + \beta D_g + \gamma D_g^2\ , \tag{11}$$

where $D_n = \frac{1-\theta}{\theta} D_n$.

- For neutrons Eq. (11) can be rewritten as

$$y_f = c + \alpha D_n + \beta \frac{\theta}{1-\theta} D_n + \gamma \left(\frac{\theta}{1-\theta} D_g \right)^2 , \tag{12}$$

where $D_g = \frac{\theta}{1-\theta} D_n$.

- The likelihood function has the Poisson distribution given by Eq. (8), and using Eqs. (11) and (12) can be written as

$$L(D_g|\theta) = \frac{\left[m \left(c + \alpha \frac{1-\theta}{\theta} D_g + \beta D_g + \gamma D_g^2 \right) \right]^n}{n!} \mathrm{e}^{-m\left(c + \alpha \frac{1-\theta}{\theta} D_g + \beta D_g + \gamma D_g^2 \right)} , \tag{13}$$

$$\begin{aligned} L(D_n|\theta) &= \frac{\left\{ m \left[c + \alpha D_n + \beta \frac{\theta}{1-\theta} D_n + \gamma \left(\frac{\theta}{1-\theta} D_g \right)^2 \right] \right\}^n}{n!} \\ &\quad \times \mathrm{e}^{-m\left[c + \alpha D_n + \beta \frac{\theta}{1-\theta} D_n + \gamma \left(\frac{\theta}{1-\theta} D_n \right)^2 \right]} , \end{aligned} \tag{14}$$

where n is number of dicentrics observed in a sample of m irradiated lymphocytes.

- The posterior distribution of the unknown neutron or gamma dose is expressed as

$$P(D_x|\theta) = \int_0^1 L(D_x|\theta) p(\theta) d\theta . \tag{15}$$

- Finally, the posterior Gaussian distribution of the unknown gamma dose has the form

$$\begin{aligned} P(D_g) &= \int_0^1 \frac{\left[m \left(c + \alpha \frac{1-\theta}{\theta} D_g + \beta D_g + \gamma D_g^2 \right) \right]^n}{n!} \mathrm{e}^{-m\left(c + \alpha \frac{1-\theta}{\theta} D_g + \beta D_g + \gamma D_g^2 \right)} \\ &\quad \times \frac{1}{\sqrt{2\pi}\sigma_\theta} \mathrm{e}^{-\frac{-(\theta-\hat{\theta})^2}{2\sigma_\theta^2}} d\theta . \end{aligned} \tag{16}$$

- The posterior Gaussian distribution of the unknown neutron dose can be obtained in a similar way.
- A value of the unknown dose can be found from the maximum of the posterior distribution curve, which is equivalent to the first derivative equation

$$\frac{dP(D_x)}{dD_x} = 0 . \tag{17}$$

- The uncertainties of dose estimations, σ_{D_x}, can be assessed from the shape of distributions or calculated using the Cramér-Rao theorem

$$\sigma_{D_x} \geq \frac{1}{\sqrt{\left| \frac{d^2 \ln P(D_x|\theta)}{dD_x^2} \right|}} , \tag{18}$$

where $\ln(P)$ is a natural logarithm of $P(D_x)$ due to the maximal likelihood method.

In practice all presented calculations need numerical solutions, because analytical ones are too complicated in some cases.

RESULTS AND DISCUSSION

Experimental results obtained after *in vitro* irradiation of a whole blood sample at the H8 horizontal channel of the reactor MARIA will be used below to provide an illustration of the issue discussed. The radiation field, composed mainly by gamma radiation and thermal neutrons, has been characterised in terms of tissue kerma using twin detector technique and the recombination method [?poz9]. Therefore, an estimated contribution of gamma dose to the total dose of $\theta = 0.92 \pm 0.02$ was known precisely. Irradiation of a blood sample with a total dose of

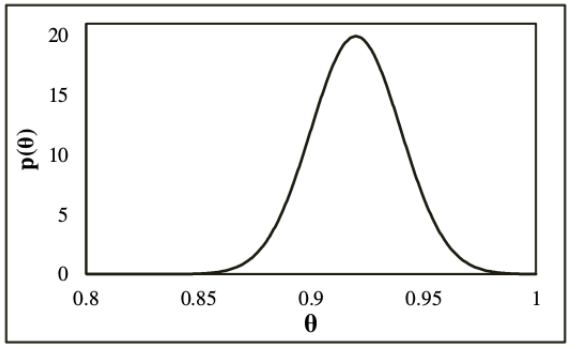

Figure 1. Prior distribution for $\theta = 0.92$.

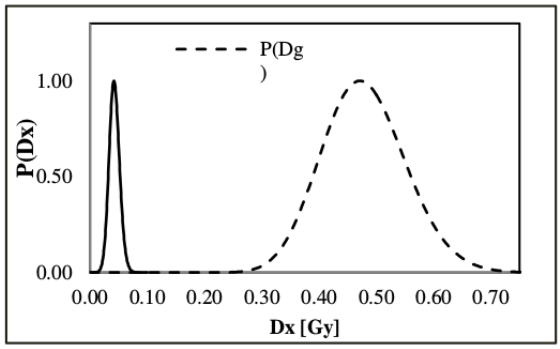

Figure 2. Posterior distributions for D_n and D_g.

0.50 ± 0.03 Gy resulted in 33 dicentrics scored in 1000 lymphocytes. The observed dicentric frequency was then used for estimating the neutron and gamma doses in the blood sample by reference to CLORâĂŹs calibration curves for fission neutrons and ^{60}Co gamma rays. The best-fit coefficients of the linear and linear-quadratic models with respective standard errors have following values: $c = 0.0005 \pm 0.0001$ dic·cell^{-1}, $\alpha = 0.354 \pm 0.003$ dic·cell^{-1}Gy^{-1}, $\beta = 0.012 \pm 0.003$ dic·cell^{-1}Gy^{-1} and $\gamma = 0.056 \pm 0.002$ dic·cell^{-1}Gy^{-2}. The dose-response fitting was done by maximum likelihood method and the goodness-of-fit was tested by a Chi-square (χ^2) test, using the CABAS computer software. In order to estimate the neutron and gamma doses, the iterative method and the Bayesian method were applied. The iterative method was based on a calculated neutron to gamma dose ratio ($\rho = \theta^{-1} - 1$) of 0.087. For Bayesian dose estimation, the contribution of gamma dose to the total dose (θ) was assumed to be uncertain. So, the prior distribution of Îÿ was established, using $\theta = 0.92$ as an expected value of the Gaussian distribution. Additionally, it was assumed that the value of θ obtained in a previous measurement was 0.80 and the prior of that θ was also used for dose estimation.

The results given in Table 1 show that values of doses derived for the precise θ are in good agreement. However a less precise information on the true value of θ leads to distinct uncertainty in the dose estimates. The prior distribution for $\theta = 0.92$ is shown in Fig. 1. Figure 2 shows the posterior distributions of the unknown neutron and gamma doses, respectively.

CONCLUSIONS

In this paper two Bayesian approaches for dicentric chromosome dosimetry of fission neutrons have been presented to demonstrate usefulness of this methodology for dose assessment after an accidental exposure or a medical irradiation. In the case of neutron accidents, knowledge of the

Table 1. Comparison of dose estimates obtained by iterative and Bayesian methods

Status of θ	**Methods**	$\mathbf{D_g \pm U^*}$ **[Gy]**	$\mathbf{D_n \pm U}$ **[Gy]**	$\mathbf{D_{n+g} \pm U}$ **[Gy]**
Precisely know ($\rho = \theta^{-1} - 1 = 0.087$)	Iterative	0.466 ± 0.133	0.041 ± 0.016	0.507 ± 0.149
Considered as uncertain ($\theta = 0.92$)	Bayesian	0.471 ± 0.144	0.041 ± 0.018	0.512 ± 0.162
Considered as uncertain ($\theta = 0.80$)	Bayesian	0.297 ± 0.053	0.070 ± 0.012	0.367 ± 0.065

separate neutron and gamma doses to which an individual has been exposed is needed in order to provide the appropriate medical care and to mitigate the effect of exposure. After Boron Neutron Capture Therapy, it is important to know neutron and gamma doses in blood of patients in order to prevent possible complications or side effects. The BNCT is used to treat cancers of brain, head, neck and liver. The treatment is based on selective concentration of boron isotope (^{10}B) within cancer cells and external irradiation of the cancer region with a flux of thermal or epithermal fission neutrons with energies from 0.2 eV to 30 keV [8]. Due to the neutron captures by the boron nuclei, $^{10}\mathrm{B}(n,\alpha)\ ^{7}\mathrm{Li}$, alpha particles and recoiling lithium nuclei are released. Because the path of alpha particles and lithium ions in biological tissue is comparable to the cell diameter, almost entire energy of these particles is absorbed practically inside cancer cells. Therefore, the radiation dose in cancer tissue is much higher than in the adjacent normal tissue, which absorb organic boron carriers less efficiently than the target tumor tissue. Currently the neutron sources for the BNCT are limited to nuclear reactors. Since 2014 research on the BNCT therapy has been conducted at the reactor MARIA in NCBJ. MARIA is technically well suited to exit a beam of epithermal neutrons outside its core due to the use of uranium converter, and to arrange irradiation of the BNCT patients at the H2 horizontal channel.

ACKNOWLEDGMENTS

Authors wish to thank Professor P. G. Groer and Doctor R. S. Brame for detailed explanation of their method. This research was supported by the Polish National Centre for Research and Development [grant number SP/J/16/143339/8].

REFERENCES

[1] IAEA: *Cytogenetic Dosimetry: Applications in preparedness for and response to radiation emergencies*, International Atomic Energy Agency, Vienna, 2011.

[2] P.G. Groer and C.A. Pereira: *Calibration of radiation detector: chromosome dosimetry for neutrons*, Probability and bayesian statistics (R. Viertl, ed.), Plenum Publishing, New York, 1987, pp. 225–232.

[3] R.S. Brame and P.G. Groer: *Bayesian methods for chromosome dosimetry following a criticality accident*, Radiat. Prot. Dosim. **104** (2003), 61–63.

[4] I. Pacyniak and M. Kowalska: *Zastosowanie statystyki Bayesowskiej w dozymetrii biologicznej promieniowania mieszanego $n + \gamma$*, Metody matematyczne w zastosowaniach **3** (2015), 157–185.

[5] P. Voisin, L. Roy, P.A. Hone, A.A. Edwards, D.C. Lloyd, G. Stephan, H. Romm, P.G. Groer, and R.S. Brame: *Criticality accident dosimetry by chromosomal analysis*, Radiat. Prot. Dosim. **110** (2004), 443–447.

[6] K.W. Fornalski: *Alternative statistical methods for cytogenetic radiation biological dosimetry*, arXiv.org/abs/1412.2048 (2014).

[7] Golnik N., Gryziński M.A., M. Kowalska, K. Meronka, and P. Tulik: *Characterisation of radiation field for irradiation of biological samples at nuclear reactor-comparison of twin-detectors and recombination methods*, Radiat. Prot. Dosim., DOI 10.1093/rpd/nct341.2014.

[8] IAEA: *Current status of neutron captures therapy*, International Atomic Energy Agency, Vienna, 2011.