

Biological Dosimetry, Statistical Challenges: Biological Dosimetry After High-Dose Exposures to Ionizing Radiation

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Abstract A statistical model to deal with low and high-dose exposures is presented. The model is based on a weighted Poisson distribution which allows to explain the underdispersion observed in the empirical data. A Gompertz type calibration curve is also introduced.

When a radiological accident occurs, it is very important to estimate the dose of ionizing radiation (IR) received to guide medical care. If physical measurements are not available or it is suspected that dosimeters have not been used correctly, biological dosimetry methods are necessary for a precise dose-assessment. Within the different methodologies, the most widely used is to score dicentric chromosomes in metaphases of peripheral blood lymphocytes. This method accurately estimates doses in cases of acute and recent exposures; see [1]. Currently, the majority of dose-effect curves for dicentric chromosomes include doses from 0 to 5 Gy. For this dose range and for low LET radiation types, such as X and gamma rays, the dose-effect relationship fits well to a linear-quadratic model. Additionally after whole body exposure from 0 to 5 Gy the distribution of dicentrics among cells agrees with the Poisson distribution, allowing the detection of partial body exposures when deviations of the Poisson are detected; see [3, 10].

Some accidents have demonstrated the need to evaluate exposures to high doses and if they are whole or partial body exposures; see [4, 11, 12]. Not only because they occur but also for the improvements reached in medical care after IR over-exposures [2], and the development of acute radiation syndrome mitigators [6, 9]. However, the dicentric based biodosimetry is not suitable for doses of IR higher than 5 Gy, because the number of cells able to reach metaphase decreases dramatically when the dose increases. After a high dose exposure heavily damaged cells,

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show a delay or even the impossibility of progressing through the G2/M cell cycle checkpoint to reach mitosis; see [1]. A way to overcome this problem is inhibiting this checkpoint using a caffeine treatment; see [7, 9]. Here, we show the analysis of dicentric chromosomes after irradiating at doses from 0 to 25 Gy.

As expected, a clear increase in the frequency of dicentrics was observed as the dose increased (Table 1). The agreement of dicentrics cell distribution with Poisson, tested by the normalized unit U of the dispersion index, was not rejected for six of the ten doses evaluated. However, in all cases U values were negative and, for 3, 5, 7 and 10 Gy, U values were significantly underdispersed.

Another observed result was that the frequency of dicentrics tend to saturate at highest doses. At higher doses, fewer cells with an elevated number of dicentrics were observed. This is mainly due by the limited number of chromosomes, which in human lymphocytes is 46. The theoretical maximum of possible dicentrics are 23. In addition, from 5 G to 25 Gy, the number of cells without dicentrics was lower than expected from the Poisson distribution, this last phenomena probably due to a major misrejoining probability at higher doses. The saturation and the low number of cells without dicentrics would contribute to the observed underdispersion.

A new count probability function has been considered to model our underdispersed count data, having the form

$$P(k; b, \lambda) = \frac{1 + bk^2}{1 + b(\lambda + \lambda^2)} \frac{\lambda^k e^{-\lambda}}{k!}, \quad k = 0, 1, 2, \dots \quad (1)$$

This is a specific weighted Poisson distribution with a weight equal to $w(k) = 1 + bk^2$, representing the sighting mechanism. The domain of the parameters is $b \geq 0$, $\lambda > 0$, and for $b = 0$ this is just the Poisson probability function. It is immediate to verify that changing the values of the parameters b , λ , the dispersion index can take values slightly greater than 1 or values lower than 1. Therefore, the probability distribution described in (1) is useful to model count data presenting underdispersion, like that observed in our empirical distributions.

Taken into account that in biological dosimetry dose-effect calibration curves for dicentric chromosomes are linear or linear-quadratic models, the challenge was to consider parameter λ in (1) to be dependent of the dose d , using a Gompertz type curve of the form, $\lambda(d) = \beta_0 e^{-\beta_1 e^{-\beta_2 d}}$, where $\beta_0, \beta_1, \beta_2$ are suitable parameters to be estimated from the data. Moreover, parameter b in (1) must also be considered depending of the dose, and following a simple linear relationship, $b(d) = \beta_3 d$, where β_3 is another parameter. Our Gompertz type curve is very flexible, having a sigmoid profile very suitable to fit our empirical data.

The maximum likelihood method has been used to estimate the four parameters of the model. The details and an R program to fit he data can be found in [8]. This model can be also applied to partial body irradiation problems, as it is described in [8]. Gompertz type model can be also used under the Poisson assumption (in (1)), leading to a three parameter model. To fit the data in this situation, the RADIR package is a Bayesian-based suitable tool that can be downloaded from CRAN repository; see [5].

Table 1 Dicentric chromosomes observed after γ -irradiation at doses from 0 to 25 Gy (dose rate of 5.25 Gy/min). For each dose, the number of cells scored and the distribution of dicentric chromosomes among cells is indicated. Gy = Gray; Total dic = total number of dicentric chromosomes; Y = frequency of dicentric chromosomes; U = values of the u-test; u values lower than -1.96 are indicative of a significant underdispersion

Dose (Gy)	Cells	Dicentric distribution among cells																		Total Dic	Y	U	
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17				18
0	2000	1999	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.00	-
0.1	2000	1989	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	0.01	-0.17
0.5	2000	1922	78	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	78	0.04	-1.23
1	1000	886	108	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	120	0.12	-0.43
3	500	213	192	85	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	393	0.79	-2.91
5	150	3	23	58	38	15	10	2	1	0	0	0	0	0	0	0	0	0	0	0	382	2.55	-3.29
7	150	0	4	23	35	35	29	10	9	4	1	0	0	0	0	0	0	0	0	0	604	4.03	-2.85
10	150	0	0	0	3	18	40	35	25	16	9	4	0	0	0	0	0	0	0	0	915	6.10	-5.11
15	100	0	0	0	0	3	10	12	21	10	16	7	7	3	1	3	0	0	0	0	834	8.34	-1.31
20	100	0	0	0	0	0	6	9	10	12	17	13	9	6	8	1	1	2	0	0	967	9.57	-1.17
25	100	0	0	0	0	0	4	5	5	8	18	16	12	7	3	9	4	3	3	0	1065	10.65	-0.42

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