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BAYESIAN DOSIMETRY: RADIATION DOSE VERSUS FREQUENCIES OF CELLS WITH ABERRATIONS

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SUMMARY

This paper presents a Bayesian analysis of a dose-response experiment in cytogenetic dosimetry. We suggest an inverse linear model for the log-odds transformation of the frequency of aberration. The regression considered is between dose and Bayes estimates. The adjustment obtained seems to produce a very small error thus suggesting that the simple linear and quadratic linear functions usually considered in the literature are not the ideal models.

KEY WORDS *A priori* and *A posteriori* distributions Bayes estimates Binucleated cells Calibration Cytogenetic aberrations Dirichlet distribution Dose–response model Likelihood Logistic-normal model Log-ratio transformation Micronuclei frequency

1. INTRODUCTION

The fundamental statistical problem in toxicology is to obtain a functional relationship between dose and response, where dose refers to the concentration of a damaging agent to which an individual is exposed and response is the observed phenomenon in the individual following the exposure. A purpose of determining such a relationship is to evaluate the dose of exposure once the individual's response has been measured.

In this paper radiation is the agent under consideration and the response is the frequency of cells with cytogenetic aberrations. Experimental data from Balasem and Ali[1] for binucleated cells will be used.

The functional relationship usually prescribed in the literature is a linear model, either simple[2] or quadratic.[3] Some reservations, nevertheless, are naturally raised. Some authors[1,4] recommend these simplistic models only for low doses where a Poisson distribution fits the data. As the response is a frequency, its domain is limited. Thus, when applying linear models to high doses, the values of the response fall off the domain of frequency. Such models, however, may be useful for dose values within the range used in the experiment.

The model introduced here has no such domain restriction. In lieu of a Poisson approximation

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for the raw frequency, we use a normal approximation for a transformation of it – namely the log-odds – with unlimited domain. Letting π be a proportion of cells with aberrations, the log-odds transformation (log-ratio in Aitchison and Shen[5]) is defined by $\theta = \log(\pi/(1-\pi))$.

The statistical viewpoint of this paper is Bayesian as, for example, in Bender *et al.*[6] and Groër and Pereira.[7] In these papers Poisson distributions and linear models were considered, since the interest was on low dose values (and low responses). Here, we deal with both low and high values of dose response, where the solutions presented in the afore-mentioned papers are not suitable.

2. CYTOGENETIC BACKGROUND

The classical cytogenetic end-points used for radiation dosimetry are dicentric and centric rings observed in metaphases obtained from short-term lymphocyte cultures.

The frequency of micronuclei (MN) obtained with the cytokinesis-block assay has been proposed for measuring *in vitro* and *in vivo* exposure.[2] A linear quadratic model has been used to fit such data.[3,8] Micronuclei arise from acentric fragments or whole chromosomes not enclosed in daughter nuclei during cell division. The assay allows observation of MN in binucleated cells, which were prevented from separating as a result of the action of cytochalasin-B, a drug that blocks the division of the cytoplasm but not of the nucleus. The presence and frequencies of MN can be ascertained in mono-, bi- and multinucleated cells.

Since one micronucleus may contain more than one fragment or chromosome, and originate both from a simple break or from an exchange type of aberrations, we propose instead the use of frequency of cells with MN – zero, one and two or more – as the response in our model.

3. BAYESIAN STATISTICS BACKGROUND

A unique feature of the Bayesian viewpoint is that the information about an unknown parameter of interest (here π) is represented by a probability distribution. For instance, when the value of π is known, this total information is represented by probability 1 at the true (known) value of the parameter and zero at all remaining points of the domain. On the other hand, total lack of information – ignorance about the value of π – is represented by a uniform distribution over the range of the parameter, the parameter space. The application of Bayesian statistics consists in using the information (about π) contained in the experimental data (represented by the likelihood function) to calibrate the *a priori* distribution, in order to obtain the *a posteriori* distribution, the main entity of Bayesian analysis.

Bayesian methods for biological experiments have been widely used, e.g. Groër and Pereira[7] and Groër *et al.*[9] For more detailed information on the subject see Bender *et al.*[6] The data analysed in this paper, from Balasem and Ali,[1] consist of frequencies of binucleated cells partitioned in three categories, namely cells with zero MN, one MN and two or more MN. Ten experiments of this kind, corresponding to ten different dose levels of radiation – 5, 10, 25, 50, 100, 200, 300, 400, 500, 600 cGy (centigray) – were considered.

The observed data, for a particular dose i ($i = 0, 1, \ldots, 9$), consist of a vector of three components $\mathbf{y}_i = (y_{i0}, y_{i1}, y_{i2})$, where y_{i0} is the number of cells with zero MN, y_{i1} is the number of cells with one MN, and y_{i2} is the number of cells with two or more MN. Hence, the statistical model for any particular dose i is assumed to be a trinomial distribution with parameters $(n_i; \pi_{i0}, \pi_{i1}, \pi_{i2})$ where $n_i = y_{i0} + y_{i1} + y_{i2}$, $\pi_{i0} + \pi_{i1} + \pi_{i2} = 1$ and $0 \leq \pi_{ij} \leq 1$, $j = 0, 1, 2$. That

is, the sampling probability function (the likelihood) is given by

$$p_i(\mathbf{y}_i \mid \boldsymbol{\pi}_i) = \frac{n_i!}{y_{i0}!y_{i1}!y_{i2}!}\, \pi_{i0}^{y_{i0}}\, \pi_{i1}^{y_{i1}}\, \pi_{i2}^{y_{i2}},$$

where $\boldsymbol{\pi}_i = (\pi_{i0}, \pi_{i1}, \pi_{i2})$ is the unknown parameter of interest for dose i. π_{i0}, π_{i1} and π_{i2} are, respectively, the populational frequencies of cells with zero MN, one MN and two or more MN.

The statistical model for the whole data set, since we have independent experiments among doses, is the product of the corresponding sampling probability functions of the ten doses. That is,

$$f(\mathbf{y} \mid \boldsymbol{\pi}) = \prod_{i=0}^{9} p_i(\mathbf{y}_i \mid \boldsymbol{\pi}_i),$$

where $\mathbf{y} = (\mathbf{y}_0, \ldots, \mathbf{y}_9)$, and $\boldsymbol{\pi} = (\boldsymbol{\pi}_0, \ldots, \boldsymbol{\pi}_9)$.

The class of prior distributions usually considered for multinomial models is the Dirichlet family (for its interesting properties see Basu and Pereira[10]). This class, besides being rich in shapes, is also a conjugate class of distributions for multinomial likelihoods. This allows representation of most prior opinions by members of the class. Conjugate means that the *a posteriori* distribution is also a member of the class. For more on these topics, see Irony.[11]

Suppose now that the *a priori* distribution for $\boldsymbol{\pi}_i$ is chosen in this class. That is, $\boldsymbol{\pi}_i \sim D_3(a_{i0}, a_{i1}, a_{i2})$, which means that $\boldsymbol{\pi}_i$ is distributed as a Dirichlet of order 3 with parameter $\mathbf{a}_i = (a_{i0}, a_{i1}, a_{i2})$ where $a_{i0} \geq 0$, $a_{i1} \geq 0$ and $a_{i2} \geq 0$. After having observed $\mathbf{y}_i$, the *a posteriori* distribution of $\boldsymbol{\pi}_i$ is $D_3(\mathbf{A}_i)$, where $\mathbf{A}_i = \mathbf{a}_i + \mathbf{y}_i = (A_{i0}, A_{i1}, A_{i2})$. Also for simplicity we will denote $a_{i.} = a_{i0} + a_{i1} + a_{i2}$ and $A_{i.} = A_{i0} + A_{i1} + A_{i2}$. Hence, if $\boldsymbol{\pi}_i \sim D_3(\mathbf{a}_i)$ *a priori*, then $\boldsymbol{\pi}_i|\mathbf{y}_i \sim D_3(\mathbf{A}_i)$ *a posteriori*. Representing the gamma function by $\Gamma(.)$, we write the *a posteriori* Dirichlet density as

$$f(\boldsymbol{\pi}_i \mid \mathbf{y}_i) = \frac{\Gamma(A_{i.})}{\Gamma(A_{i0})\Gamma(A_{i1})\Gamma(A_{i2})}\, \pi_{i0}^{A_{i0}}\, \pi_{i1}^{A_{i1}}\, \pi_{i2}^{A_{i2}}.$$

To obtain a point estimation of $\boldsymbol{\pi}_i$, we consider here the quadratic loss function as usual. Hence, the Bayes estimator of $\boldsymbol{\pi}_i$, the posterior mean, is given by

$$\hat{\boldsymbol{\pi}}_i = (\hat{\pi}_{i0}, \hat{\pi}_{i1}, \hat{\pi}_{i2}) = \frac{1}{A_{i.}}(A_{i0}, A_{i1}, A_{i2})$$

and the posterior variance-covariance matrix is

$$\frac{1}{A_{i.}+1}\begin{pmatrix} \hat{\pi}_{i0}(1-\hat{\pi}_{i0}) & -\hat{\pi}_{i0}\hat{\pi}_{i1} & -\hat{\pi}_{i0}\hat{\pi}_{i2} \\ -\hat{\pi}_{i0}\hat{\pi}_{i1} & \hat{\pi}_{i1}(1-\hat{\pi}_{i1}) & -\hat{\pi}_{i1}\hat{\pi}_{i2} \\ -\hat{\pi}_{i0}\hat{\pi}_{i2} & -\hat{\pi}_{i1}\hat{\pi}_{i2} & \hat{\pi}_{i2}(1-\hat{\pi}_{i2}) \end{pmatrix}.$$

Since the prior parameters $\mathbf{a}_i$ can be chosen in order to describe a natural stochastic ordering of the $\boldsymbol{\pi}_i$, we consider the $\boldsymbol{\pi}_i$ as mutually independent *a priori*. Consequently, owing to the statistical independence of the $\mathbf{y}_i$, the $\boldsymbol{\pi}_i$ are also independent *a posteriori*. The *a posteriori* joint density of the $\boldsymbol{\pi}_i$ is therefore given by

$$\prod_{i=0}^{9} f(\boldsymbol{\pi}_i \mid \mathbf{y}_i).$$

Table I presents data of Balasem and Ali[1] and the parameters of the *a priori* (*a posteriori*)

Table I. Data and parameters of the *a priori* (*a posteriori*) distribution

i	Dose (cGy)	Data				Prior (posterior) parameters			
		y_{i0}	y_{i1}	y_{i2}	n_i	$a_{i0}(A_{i0})$	$a_{i1}(A_{i1})$	$a_{i2}(A_{i2})$	$a_{i.}(A_{i.})$
0	5	481	17	2	500	12 (493)	2 (19)	1 (3)	15 (515)
1	10	477	19	4	500	11 (488)	2 (21)	1 (5)	14 (514)
2	25	471	24	5	500	10 (481)	2 (26)	1 (6)	13 (513)
3	50	450	44	6	500	9 (459)	2 (46)	1 (7)	12 (512)
4	100	431	59	10	500	8 (439)	2 (61)	1 (11)	11 (511)
5	200	339	140	21	500	7 (346)	2 (142)	1 (22)	10 (510)
6	300	304	132	64	500	6 (310)	2 (134)	1 (65)	9 (509)
7	400	240	189	72	501	5 (245)	2 (191)	1 (73)	8 (509)
8	500	174	197	129	500	4 (178)	2 (199)	1 (130)	7 (507)
9	600	122	173	211	506	3 (125)	2 (175)	1 (212)	6 (512)

Dirichlet distributions. Table II presents the Bayes estimates and the posterior variances of the π_i. Table III presents the posterior covariances multiplied by 1000. Recall that, between doses, the covariances are null.

With the figures of Tables II and III, usual inferences about the parameters of interest π_i, can be obtained. Note also that as the posterior distribution is completely described, credible sets may be numerically computed. The prior parameters, chosen in Table I, reflect the biologist's belief

Table II. Estimates and posterior variances ($\times 1000$) of the π_{ij}

i	$\hat{\pi}_{i0}$	$\hat{\pi}_{i1}$	$\hat{\pi}_{i2}$	$V(\pi_{i0})$	$V(\pi_{i1})$	$V(\pi_{i2})$
0	0.9573	0.0369	0.0058	0.0792	0.0689	0.0112
1	0.9494	0.0409	0.0097	0.0933	0.0762	0.0186
2	0.9376	0.0507	0.0117	0.1138	0.0936	0.0225
3	0.8965	0.0898	0.0137	0.1809	0.1593	0.0263
4	0.8591	0.1194	0.0215	0.2364	0.2053	0.0411
5	0.6784	0.2784	0.0431	0.4269	0.3931	0.0807
6	0.6090	0.2633	0.1277	0.4669	0.3803	0.2184
7	0.4813	0.3752	0.1434	0.4895	0.4596	0.2408
8	0.3511	0.3925	0.2564	0.4485	0.4694	0.3753
9	0.2441	0.3418	0.4141	0.3597	0.4385	0.4729

Table III. Posterior covariances ($\times 1000$)

i	(π_{i0}, π_{i1})	(π_{i0}, π_{i2})	(π_{i1}, π_{i2})
0	−0.0684	−0.0108	−0.0004
1	−0.0754	−0.0179	−0.0008
2	−0.0925	−0.0213	−0.0011
3	−0.1569	−0.0239	−0.0024
4	−0.2003	−0.0361	−0.0050
5	−0.3696	−0.0572	−0.0235
6	−0.3144	−0.1525	−0.0659
7	−0.3541	−0.1353	−0.1055
8	−0.2713	−0.1772	−0.1981
9	−0.1626	−0.1970	−0.2759

that the π_{i0} decrease with dose levels, while the π_{i1} and π_{i2} increase. Also, as low doses are more natural than high doses, the $a_{i.}$ decrease with dose values in order to reflect the fact that information is more precise for low doses. Note that prior variances decrease whenever the $a_{i.}$'s increase. The next section introduces the transformation model.

4. LOGISTIC-NORMAL MODEL

Up to this point, the dose value has been controlled, the responses, y_i, have been observed and, based on the response, the parameters of interest, π_i, were estimated. In practice, however, one may have an opposite question: having observed a response y_∂, the scientist is asked to 'estimate' which unknown dose level ∂ has produced that response. To answer this question the scientist must consider a functional relationship between dose and the parameter π_∂ that is involved in the distribution of y_∂. Note that y_∂ is conditionally (on π_∂) distributed as a trinomial with parameter π_∂ and sample size n.

The difficulty in relating the parameter π to the dose ∂ is that ∂ is a positive real number (with unknown upper limit) and π_∂ is a vector with components in the unit interval. That is, $\partial \geq 0$ and $0 \leq \pi_j \leq 1$, where π_j is any component of π_∂. In order to solve this problem, we consider a transformation of π_∂ suggested by Aitchison and Shen,[5] known as the log-ratio transformation:

$$\theta_j = \log \frac{\pi_j}{\pi_0},$$

where π_0 is the proportion of cells with no MN. The inverse transformation, for $j = 1, 2$,

$$\pi_j = \frac{\exp\{\theta_j\}}{1 + \exp\{\theta_1\} + \exp\{\theta_2\}}, \tag{1}$$

is known as the logistic transformation.

The very interesting property of the log-ratio transformation is that $\theta = (\theta_1, \theta_2)$ is bivariate normal whenever π is Dirichlet.[5] To obtain the mean and the variance-covariance matrix of θ we follow the same steps as Pereira and Pericchi.[12] We introduce the subscript i to indicate that the posterior parameters of the normal distribution are related to the doses used in Table I. Hence, $\theta_i = (\theta_{i1}, \theta_{i2})$ is the new parameter corresponding to the ith dose. Its *a posteriori* distribution is bivariate normal with the following parameters:

$$m_{ij} = E\{\theta_{ij}\} = \psi(A_{ij}) - \psi(A_{i0})$$

$$s_{ij}^2 = \text{var}\{\theta_{ij}\} = \psi'(A_{ij}) + \psi'(A_{i0})$$

$$c_i = \text{cov}\{\theta_{i1}, \theta_{i2}\} = \psi'(A_{i0})$$

where $\psi(.)$ and $\psi'(.)$ are the digamma and trigamma functions, respectively. Table IV presents the values of these posterior parameters. Section 5 is devoted to the dose–response model adjustment.

5. DOSE–RESPONSE MODEL

In this section we propose a functional relationship between doses and θ. Recall that $\theta_{ij} = m_{ij} + \varepsilon_{ij}$, where the ε_{ij} are the normal errors associated with the ith dose. Letting D_i

Table IV. Parameters of the *a posterior* distribution of $(\theta_{i1}, \theta_{i2})$

i	m_{i1}	m_{i2}	s_{i1}^2	s_{i2}^2	c_i
0	−3.28	−5.28	0.06	0.40	0.0020
1	−3.17	−4.68	0.05	0.22	0.0020
2	−2.93	−4.46	0.04	0.18	0.0021
3	−2.31	−4.26	0.02	0.16	0.0022
4	−1.98	−3.73	0.02	0.10	0.0023
5	−0.89	−2.77	0.01	0.05	0.0029
6	−0.84	−1.56	0.01	0.02	0.0032
7	−0.25	−1.22	0.01	0.02	0.0041
8	0.11	−0.32	0.01	0.01	0.0056
9	0.34	0.53	0.01	0.01	0.0080

denote the ith dose level, the dose–response model proposed here is

$$-m_{ij} = \alpha_j + \frac{\beta_j}{\gamma_j + D_i}, \tag{2}$$

where α_j, β_j and γ_j are real numbers.

With the data presented in Table IV and using the non-linear regression procedure, NLR, of the SPSS package, we obtain

$$\alpha_1 = -1.79, \quad \alpha_2 = -12.01 \tag{3}$$

$$\beta_1 = 1303.35, \quad \beta_2 = 22033.86 \tag{4}$$

$$\gamma_1 = 254.15, \quad \gamma_2 = 1298.50. \tag{5}$$

Table V presents the adjusted values $\hat{m}_{ij}$ and the corresponding observed errors.

To obtain a function which relates dose values to π, we use relation (1) taking m_{ij} for θ_{ij}. Hence, by replacing m_{ij} by its adjusted function (2), we obtain the estimated functional relationship between doses and frequencies π_{ij}. That is,

$$\pi_{ij} = \frac{\exp\{-(\alpha_j + \frac{\beta_j}{\gamma_j + D_i})\}}{1 + \exp\{-(\alpha_1 + \frac{\beta_1}{\gamma_1 + D_i})\} + \exp\{-(\alpha_2 + \frac{\beta_2}{\gamma_2 + D_i})\}}.$$

Table VI presents the adjusted values $\tilde{\pi}_{ij}$ and the corresponding observed errors $\tilde{\varepsilon}_{ij}$. Note that

Table V. The adjusted log-ratios and their respective errors

i	$\hat{m}_{i1}$	ϵ_{i1}	$\hat{m}_{i2}$	ϵ_{i2}
0	−3.24	0.04	−4.89	−0.39
1	−3.14	−0.03	−4.83	0.15
2	−2.88	−0.05	−4.64	0.18
3	−2.49	0.18	−4.33	0.07
4	−1.89	−0.09	−3.74	0.01
5	−1.08	0.19	−2.69	−0.08
6	−0.56	−0.28	−1.77	0.21
7	−0.20	−0.05	−0.96	−0.26
8	0.06	0.05	−0.24	−0.08
9	0.26	0.08	0.40	0.13

Table VI. The adjusted frequencies and their respective errors

i	$\tilde{\pi}_{i0}$	$\tilde{\epsilon}_{i0}$	$\tilde{\pi}_{i1}$	$\tilde{\epsilon}_{i1}$	$\tilde{\pi}_{i2}$	$\tilde{\epsilon}_{i2}$
0	0.95	0.01	0.04	−0.01	0.01	0.00
1	0.95	0.00	0.04	0.00	0.01	0.00
2	0.94	0.00	0.05	0.00	0.01	0.00
3	0.91	−0.01	0.08	0.01	0.01	0.00
4	0.85	0.01	0.13	−0.01	0.02	0.00
5	0.71	−0.03	0.24	0.04	0.05	−0.01
6	0.57	0.04	0.33	−0.07	0.10	0.03
7	0.45	0.03	0.37	0.01	0.17	−0.03
8	0.35	0.00	0.37	0.02	0.28	−0.02
9	0.26	−0.02	0.34	0.00	0.39	0.03

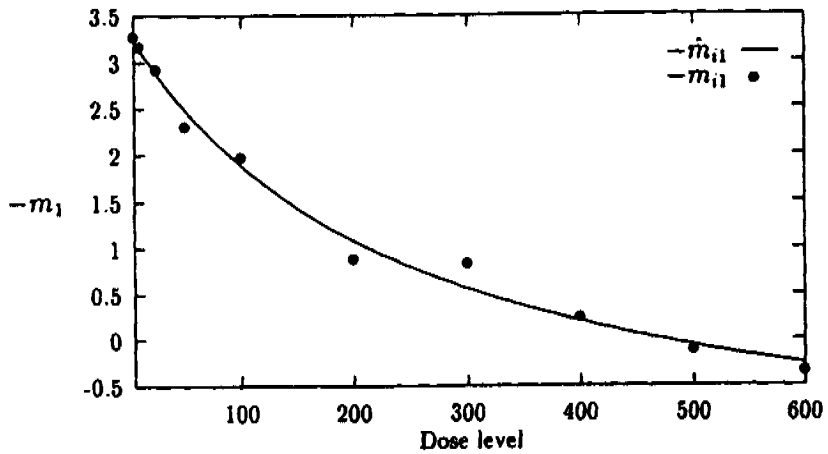

Figure 1. One MN log-ratio

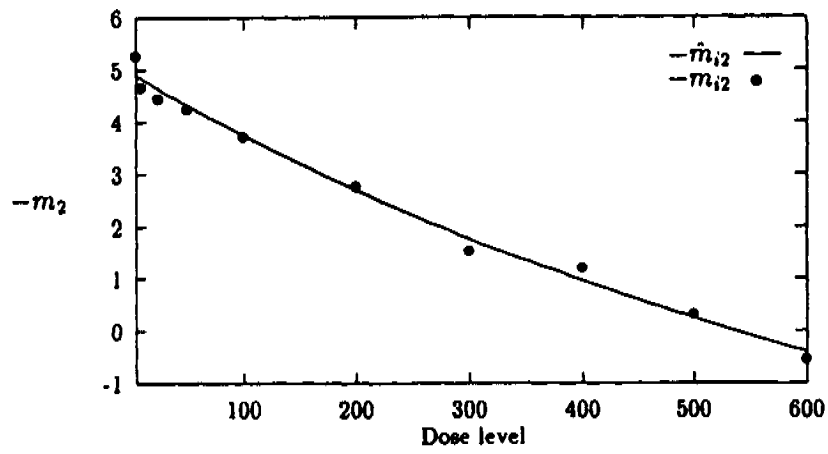

Figure 2. Two MN log-ratio

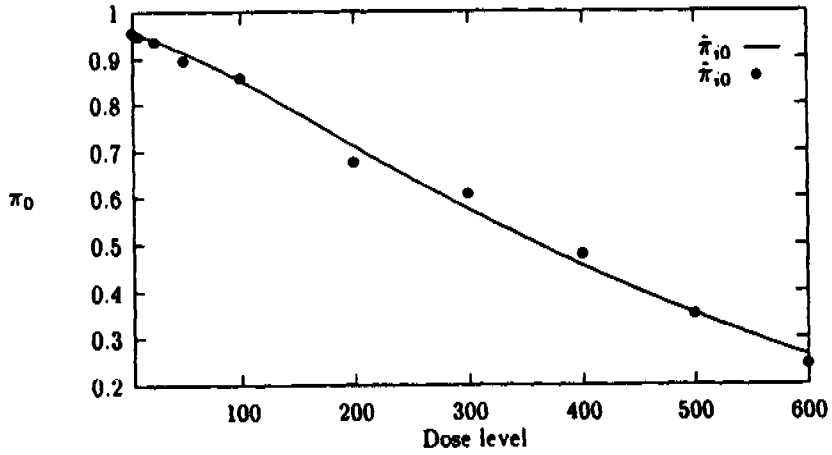

Figure 3. Zero MN frequency

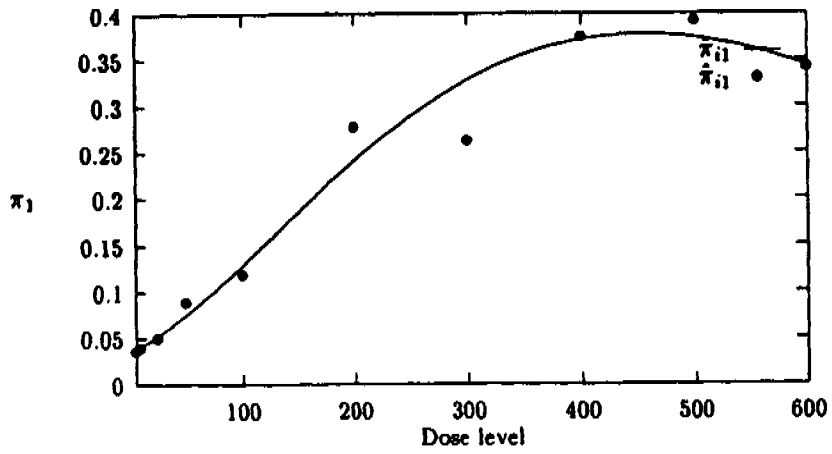

Figure 4. One MN frequency

$\tilde{\pi}_{i0} = 1 - \tilde{\pi}_{i1} - \tilde{\pi}_{i2}$. Figures 1 and 2 illustrate how well the model is adjusted. Figures 3, 4 and 5 illustrate the adjustment for the original proportions π. Note that there is a drop at the end of Figure 4. This is expected since, for high dose levels, the number of cells with more than one MN increases (Figure 5). Consequently, the number of cells with only one MN decreases.

6. FINAL REMARKS

The scoring of cells with or without MN is made in preparations obtained from blood cultures exposed to different levels of radiation. The presence of MN in a cell depends on the cell division, in culture. When the nucleus divides, cytochalasin-B prevents the division of the cytoplasm and the two daughter nuclei are enclosed in the same cytoplasm forming a binucleated cell. Fragments or dicentrics induced by radiation also remain in the cytoplasm, originating one or more MN. Some cells, however, escape the process and mononucleated cells with MN may occur.

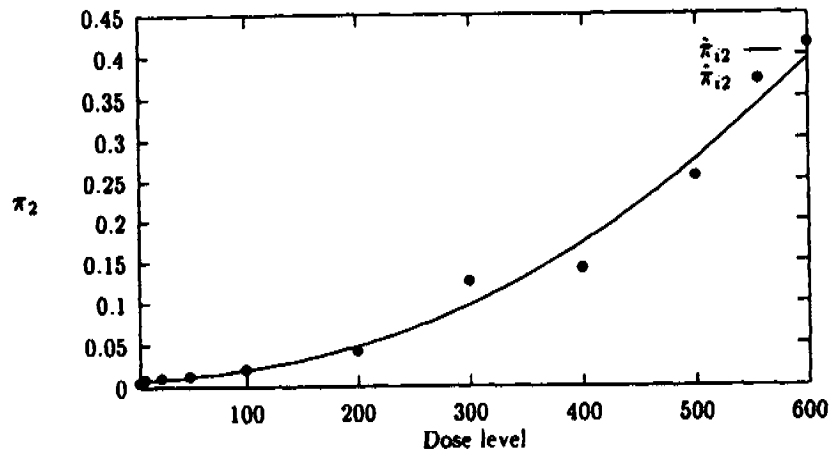

Figure 5. Two MN frequency

In a pilot experiment where samples of mononucleated cells were considered, we have applied the procedure introduced in this paper, also with a good fit of the model to the data. We could, however, discard the independent parameter α_j; that is, in this case $\alpha_j = 0$.

To exemplify a potential practical situation where our method could be adequate, consider a fictitious nuclear accident where a worker suffered an exposure to an unknown radiation dose ∂. In order to estimate the dose to which this individual was exposed, a calibration experiment is designed. Blood cultures from other workers from the same occupational environment, but who did not suffer the same accident, are exposed to different levels of radiation and the values of the respective responses y are obtained. Assume that the values observed for the exposed individual were $\mathbf{y}_\partial = (230, 190, 80)$ and that the data from the calibration experiment are those in Table I. The estimated constants of the dose–response model are those in (3), (4) and (5). Suppose that the posterior parameter of the Dirichlet distribution for the frequency of cells with zero MN, one MN and two or more MN is $\mathbf{A}_\partial = (236, 193, 81)$. With these figures applied to function (2) using the adjusted constants (3), (4) and (5), we conclude that the dose ∂ is a number in the interval (385, 401).

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