A NEW BAYESIAN MODEL APPLIED TO CYTOGENETIC PARTIAL BODY IRRADIATION ESTIMATION

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A new zero-inflated Poisson model is introduced for the estimation of partial body irradiation dose and fraction of body irradiated. The Bayes factors are introduced as tools to help determine whether a data set of chromosomal aberrations obtained from a blood sample reflects partial or whole body irradiation. Two examples of simulated cytogenetic radiation exposure data are presented to demonstrate the usefulness of this methodology in cytogenetic biological dosimetry.

INTRODUCTION

The main goal of biological dosimetry is the estimation of the radiation dose received by an exposed individual, in scenarios such as radiation accidents or in radiotherapy settings. Radiation exposure produces breaks in the chromosomal DNA, and the resulting fragments can be repaired in different patterns from their original arrangement. Consequently, frequencies of chromosome aberrations including dicentric and centric rings increase with the amount of absorbed radiation and are a reliable and very well-established biomarker of radiation exposure. The estimation of the dose received by an individual requires dose–effect calibration curves, which are produced by exposing peripheral blood lymphocytes to a range of doses, simulating whole body irradiation. The manual of the International Atomic Energy Agency (IAEA)⁽¹⁾ describes the standards for these calibration experiments.

The construction of a calibration curve starts with the irradiation of blood samples from a healthy donor with different doses. Next, the counts of observed chromosomal aberrations are recorded. It is typically assumed that after exposure to X- or gamma-rays, the number of chromosomal aberrations per cell follows a Poisson distribution with a population mean which is a linear-quadratic function of the dose. The set of parameters of this regression model is usually estimated by maximum likelihood (ML), recording the estimator, called maximum likelihood estimator (MLE) and its variance–covariance matrix, which measures the uncertainty of the estimated parameters. Thus, for an irradiated patient, a blood sample is taken and several tens to thousands of lymphocytes are scored for chromosomal aberrations. The established approach

for calculating the absorbed dose and its confidence limits is to use the classical inverse regression method described as a standard procedure in ref. (1).

The mathematical distribution of chromosomal aberrations in partial body irradiation (PBI) scenarios is different from Poisson. The non-irradiated cells contribute an extra amount of zeros in comparison with the distribution of chromosomal aberrations following whole body irradiation. This proportion of extra zeros can be described by the so-called zero-inflated models. The zero counts of aberrations in this zero-inflated process result from a mixture of cells with zero aberrations from the irradiated population and extra zeros that represent the non-irradiated cells. Zero-inflated count models provide one method to account for the excess zeros in the data by modelling the data as a mixture of two distributions: a distribution taking a single value at zero and a count distribution, in this case Poisson.

The probability mass function (pmf) of a zero-inflated Poisson (ZIP) random variable $\mathcal{Y}$ taking k counts is defined as

$$P(\mathcal{Y} = k; \mu, \omega) = \begin{cases} \omega + (1 - \omega)e^{-\mu} & \text{if } k = 0 \\ (1 - \omega) \frac{\mu^k e^{-\mu}}{k!} & \text{otherwise} \end{cases}$$

where $0 \leq \omega \leq 1$ is the proportion of extra zeros. Note that this pmf is expressed in terms of the Poisson pmf with population mean μ .

The standard procedure to detect PBI is to calculate the sample dispersion index, the ratio of the sample variance to the sample mean, of the counts obtained from the blood sample and then to use the u -test to

reject or not the Poisson assumption⁽²⁾, because of the overdispersion caused by the excess of zeros⁽¹⁾. If the Poisson hypothesis is not rejected, the recommendation is to perform a whole body cytogenetic dose estimation. Otherwise, if the Poisson hypothesis is rejected, the yield of chromosomal aberrations in the irradiated fraction and the fraction of cells irradiated can both be estimated by the MLE of the parameters of a ZIP distribution. Then, the absorbed dose is estimated by performing the whole body cytogenetic dose estimation method for the estimated yield of chromosomal aberrations in the irradiated fraction. Finally, the fraction of the body irradiated (FBI) is estimated by a formula described in ref. (1).

The alternative to the classic methodology described above is Bayesian analysis, which lends itself to retrospective dosimetry, because it presents the probability of an event in terms of prior knowledge about its expectation and uncertainty. There is a recent publication⁽³⁾ with Bayesian models that allow the reconsideration of most of the published examples of radiation exposures that were analysed using the classical methods for dose estimation following homogeneous exposure. A review of Bayesian methods in biodosimetry can be found in ref. (4), containing one appendix dedicated to the description and derivation of a Bayesian model for cytogenetic dose estimation. There are also two recent programs, CytoBayesJ⁽⁵⁾, which provides some basic software tools for Bayesian analysis of cytogenetic radiation dosimetry data, and radir⁽⁶⁾, which is an R⁽⁷⁾ package for applying the models in ref. (3).

However, in the field of cytogenetic biodosimetry, there are currently no Bayesian methodologies in use

for the detection of PBI. In this article, a new cytogenetic method is presented for the estimation of the absorbed dose and the FBI in PBI scenarios, based on prior determination of whether a partial or whole body exposure had been received.

CALIBRATION AND TEST DATA

Table 1 displays *in vitro* dose–response data for dicentric plus centric rings (Dic + CR) obtained in a recent calibration experiment within a high dose range⁽⁸⁾ that was performed in accordance with the IAEA requirements⁽¹⁾. The detailed protocols and conditions of blood irradiation, lymphocyte culturing, cell fixing, metaphase staining, aberration scoring and QA/QC procedures were fully presented in⁽⁸⁾. The dose rate was 0.5 Gy min^{−1} for 2, 4 and 6 Gy and 1.2 Gy min^{−1} for 8, 10, 16 and 20 Gy.

The test data sets representing the Dic + CR scored after the simulated PBI (Table 2) were generated within a separate experiment, which was carried out in the framework of the IAEA Coordinated Research Project E.3.50.08. They have not yet been published elsewhere. Peripheral blood was taken from one healthy male volunteer, corresponding to Donor I in calibration experiment⁽⁸⁾, to minimise the potential impact of intrinsic individual variations in this study. The donor participation was with written informed consent and in accordance with the institutional ethics protocol.

Blood sampling and irradiation conditions, cell culturing details and aberration scoring criteria in the PBI simulation experiment were identical to those used in the calibration experiment⁽⁸⁾. Briefly, the donor's blood samples were collected into VacutainerTM tubes with lithium heparin anticoagulant and exposed to 1.98 and 11.88 Gy ⁶⁰Co acute gamma rays in accordance with the IAEA requirements⁽¹⁾. The dose rate was 0.5 Gy min^{−1} for 2 Gy and 1.2 Gy min^{−1} for 12 Gy. The irradiated samples were accompanied by a sham-treated zero-dose control sample.

To simulate PBI, the unirradiated and irradiated blood at each dose was mixed, so that the exposed blood fraction comprised 90 % for 12 Gy and 10 % for 2 Gy; thus, the equivalent whole body doses were 10.8 and 0.2 Gy, respectively. Lymphocyte cultures

Table 1. Calibration data.

Dose (Gy)	Cells	Dic + CR
0.00	5389	5
1.96	924	279
3.96	475	504
5.88	331	675
7.84	300	1028
9.59	157	735
16.36	34	295
20.30	60	927

Table 2. Frequency distributions of the number of Dic + CR of the test data samples.

Sample	Dose (Gy)	Number of Dic + CR											$\bar{y}$	d	u	2 log BF
		FBI (%)	0	1	2	3	4	5	6	7	8	≥9				
1	2	10	1043	16	3								0.021	1.253	5.967	9.410
2	12	90	148		4	4	11	10	9	7	3	3 ^a	1.357	4.667	36.551	505.480

^aTwo cells with 9 Dic + CR, and 1 with 11.

were set up according to the standard technique⁽¹⁾ with cell cycle control using BrdU. After 52 h of culturing, cells were fixed and conventional chromosomal analysis was carried out on metaphase preparations stained with the fluorescence-plus-Giemsa method. The microscopy of all preparations was performed on coded slides by the same cytogeneticist, to avoid an observer bias and possible inter-operator variability. The scorer has over 20 y of experience in microscopy of aberrations and participated actively in generating the calibration data, and scored essential number of cells and aberrations at each dose-response point, with all QA/QC procedures described in ref. (8). Chromosomal damage was scored only in the first *in vitro* division, diploid metaphases and registered using the stringent aberration scoring criteria⁽¹⁾. All unstable chromosome-type aberrations were recorded; polycentrics were converted into the equivalent number of dicentrics. For the present work, the yields of dicentrics and centric rings accompanied by a fragment were selected.

THE ZERO-INFLATED POISSON MODEL

Assuming the test (patient) data $y = \{y_1, y_2, \dots, y_n\}$ formed by n count data observations, representing the number of chromosomal aberrations in n blood cells, to be ZIP(μ, ω) (μ the population mean and ω the proportion of extra zeros) distributed, the likelihood of this sample, following⁽⁹⁾, is proportional to

$$L(y|\mu, \omega) = \prod_{i=1}^n P(y_i) \propto \mu^s \sum_{j=1}^{n_0} \binom{n_0}{j} \frac{\omega^j (1-\omega)^{n-j}}{e^{(n-j)\mu}}, \quad (1)$$

where n_0 and s are the sample frequency of zeros and the sum of the total number of chromosomal aberrations, respectively. Multiplying and dividing by $(n-j)^s$ inside the summatory of (1), the likelihood leads to

$$L(y|\mu, \omega) \propto \sum_{j=1}^{n_0} \binom{n_0}{j} \times \frac{\omega^j (1-\omega)^{n-j} [(n-j)\mu]^s}{(n-j)^s e^{(n-j)\mu}}. \quad (2)$$

Note that the last fraction of (2) is proportional to the probability of a Poisson distribution with population mean $(n-j)\mu$ taking s counts.

THE BAYES FACTOR

The Bayes factor is the main Bayesian model comparison tool. Given a data set y , the probabilities of two different models, in this case ZIP and Poisson, on

y are compared. Following⁽¹⁰⁾ this, the Bayes factor remains

$$BF = \frac{n_0!}{(n+1)!} \sum_{j=0}^{n_0} \frac{(n-j)!}{(n_0-j)!} (1-j/n)^{-(s+1/2)}, \quad (3)$$

and in accordance with ref. (11), $2 \log BF > 0, 2, 6$ and 10 gives ‘weak positive’, ‘positive’, ‘strong’ and ‘very strong’ evidence in support of the ZIP model, respectively.

DOSE AND BODY FRACTION ESTIMATION

Here, the probability of extra zeros ω represents the proportion of non-irradiated cells and D the absorbed dose in the blood sample y . Following ref. (1), the FBI, F , is calculated as

$$F = \frac{(1-\omega)e^{D/d_0}}{\omega + (1-\omega)e^{D/d_0}}, \quad (4)$$

where d_0 is the 37 % cell survival dose, with experimental evidence to be between 2.7 and 3.5 Gy⁽¹⁾. Following Equation (4), the proportion of non-irradiated cells ω as a function of D , F and d_0 results

$$\omega = \frac{1-F}{Fe^{-D/d_0} - F + 1}, \quad (5)$$

thus substituting ω by Equation (5), the likelihood in (2) results

$$\begin{aligned} \mathcal{L}(y|\mu, F, d_0) &= L\left(y \middle| \mu, \frac{1-F}{Fe^{-D/d_0} - F + 1}\right) \\ &\propto (Fe^{-D/d_0} - F + 1)^{-n} \sum_{j=1}^{n_0} \binom{n_0}{j} \frac{F^{n-j} (1-F)^j}{(n-j)^s} \\ &\quad \times \frac{[(n-j)\mu]^s}{e^{(n-j)\mu}}. \end{aligned} \quad (6)$$

Let $\mu = f(D, \beta)$ be the calibration curve, and $v(D, \beta) = \nabla \times \hat{\Sigma}_{\hat{\beta}} \times \nabla^T$, where $\hat{\Sigma}_{\hat{\beta}}$ is the variance matrix of β and ∇ denotes the gradient of $f(D, \beta)$ respect β , the *mean prior* is defined for the purposes of inverse regression as in ref. (3), i.e.

$$\mu|D \sim \text{Gamma}\left(\frac{f(D, \hat{\beta})^2}{v(D, \hat{\beta})}, \frac{f(D, \hat{\beta})}{v(D, \hat{\beta})}\right). \quad (7)$$

Analogously to ref. (3), because the knowledge of μ implies the knowledge of D , then $\mathcal{L}(y|\mu, F, d_0) = \mathcal{L}(y|\mu, D, F, d_0)$, (6). Therefore, an application of the Bayes theorem shows the expression of the likelihood of the absorbed dose D and the FBI F for the given the

test data y ,

$$\begin{aligned} \mathcal{L}(y|D, F, d_0) & \\ \propto \int_0^{+\infty} \mathcal{L}(y|\mu, F, d_0) P(\mu|D) d\mu & \\ = (Fe^{-D/d_0} - F + 1)^{-n} & \\ \times \sum_{j=1}^{n_0} \binom{n_0}{j} \frac{F^{n-j}(1-F)^j}{(n-j)^s} P(\mathcal{X}_j = s|D), & \end{aligned} \quad (8)$$

where $\mathcal{X}_j$ is a random variable negative binomial distribution with mean $(n-j)f(x, \beta)$ and variance $(n-j)f(D, \beta) + (n-j)^2 v(D, \beta)$. Different fonts to indicate the likelihood as function of different variables have been used in Equations (1), (6) and (8).

Considering D , F and d_0 as independent random variables, consequently their joint probability density remains $P(D, F, d_0) = P(D)P(F)P(d_0)$. For the FBI, F , a beta prior is applied. For the cell survival dose, d_0 , a uniform prior $\mathcal{U}(c, d)$ is applied, where $c \geq 2.7$ and $d \leq 3.5$. These least informative choices are applied in case there is no information about F and $F \sim \text{Beta}(1, 1) \equiv \mathcal{U}(0, 1)$ and $d_0 \sim \mathcal{U}(2.7, 3.5)$.

A prior gamma distribution is applied for the absorbed dose D , as in ref. (12). This prior information can be defined through expert judgement or by an empirical Bayes method. The empirical Bayes method is applied using the MLE of D and its standard error from (8), i.e. a gamma distribution with mean $\hat{D}$ and variance $\hat{\sigma}_D^2$:

$$D \sim \text{Gamma} \left(a = \frac{\hat{D}^2}{\hat{\sigma}_D^2}, b = \frac{\hat{D}}{\hat{\sigma}_D^2} \right). \quad (9)$$

Therefore, the joint posterior density remains

$$P(D, F, d_0|y) = \frac{\mathcal{L}(y|D, F, d_0) P(D, F, d_0)}{\int \mathcal{L}(y|D, F, d_0) P(D, F, d_0) dD dF dd_0}. \quad (10)$$

To calculate this joint posterior density (10), with a non-tractable form, and its marginal densities, the acceptance–rejection method is used to simulate the posterior distribution. This approach generates a random vector (D, F) of size m following $P(D, F, d_0|y)$:

- S1 Generate u from $\mathcal{U}(0, 1)$.
- S2 Generate a random variate D^* from $\text{Gamma}(a, b)$, a random variate F^* from $\text{Beta}(\alpha, \beta)$ and a random variate d_0^* from $\mathcal{U}(c, d)$, all them independent of u .
- S3 If $u \leq \mathcal{L}(y|D^*, F^*, d_0^*) / \mathcal{L}(y|\hat{D}, \hat{F}, \hat{d}_0)$, then set $(D, F) \leftarrow (D^*, F^*) \cup (D^*, F^*)$. While the size of $(D, F) < m$, go to S1.

Here, $\hat{D}$, $\hat{F}$ and $\hat{d}_0$ represent the MLE from (8) of the absorbed dose, the FBI and the cell survival dose, respectively. Thus, $\mathcal{L}(y|\hat{D}, \hat{F}, \hat{d}_0)$ is the maximum of (8). The efficiency is $\text{eff} = m/M$, where M is the total number of times that this process is repeated until m simulations are achieved. An approximation of C , the normalising constant of the joint posterior density, is $C \approx \text{eff} \times \mathcal{L}(y|\hat{D}, \hat{F}, \hat{d}_0)$.

RESULTS AND DISCUSSION

The values in the last column of Table 2 show that the Bayes factors, Equation (3), give ‘strong’ and ‘very strong’ evidence in support to the ZIP assumption, respectively, for Samples 1 and 2.

Following the notation in Expression (1), in Sample 1 $n_0 = 1043$, $s = 22$ and $n = 1062$, i.e. 1043 cells free of Dic + CR and 22 scored Dic + CR in 1062 blood cells, and in Sample 2 $n_0 = 148$, $s = 270$ and $n = 199$.

In this example, the appropriate dose–response curve is linear quadratic, $f(D, \beta) = \beta_2 D^2 + \beta_1 D + \beta_0$ (Figure 1). For high doses, Gompertz-type dose–response curves are also suitable, as shown in a recent publication⁽¹³⁾. Note that the saturation effect is often quoted as leading to incorrect dose estimates at doses $> \approx 5$ Gy; however, for low linear energy transfer (LET) irradiation, doses of up to 20 Gy have been demonstrated to induce approximately linear-quadratic responses in terms of chromosome aberrations (e.g. ref. (14)).

Following ref. (8), it is assumed that the distributions of Dic + CR are Poisson, and thus, the ML parameter estimates and their estimated covariance matrix are the following:

Figure 1. Observed means (dots), plus/minus twice their standard errors (error bars) and predicted means (solid line) of the number of Dic + CR.

- Fitted coefficients:

$$\begin{aligned}\hat{\beta}_0 &= 9.073 \times 10^{-4}, \quad \hat{\beta}_1 = 1.291 \times 10^{-1}, \\ \hat{\beta}_2 &= 3.357 \times 10^{-2}.\end{aligned}$$

- Estimated covariance matrix:

$$\hat{\Sigma}_{\hat{\beta}} = \begin{pmatrix} 168.354 & -73.146 & 4.933 \\ -73.146 & 85611.557 & -9365.947 \\ 4.933 & -9365.947 & 1560.911 \end{pmatrix} \times 10^{-9}.$$

According to (7), $\mu|D$ will follow a Gamma distribution with mean $f(D, \hat{\beta}) = \hat{\beta}_2 D^2 + \hat{\beta}_1 D + \hat{\beta}_0$ and variance $v(x, \hat{\beta}) = \nabla \times \hat{\Sigma}_{\hat{\beta}} \times \nabla^T$, where

$$\nabla = \left(\frac{\partial f}{\partial \beta_0}, \frac{\partial f}{\partial \beta_1}, \frac{\partial f}{\partial \beta_2} \right) = (1, D, D^2),$$

and therefore, $v(D, \hat{\beta}) = \hat{\Sigma}_{33} D^4 + 2\hat{\Sigma}_{23} D^3 + 2\hat{\Sigma}_{13} D^2 + \hat{\Sigma}_{22} D^2 + 2\hat{\Sigma}_{12} D + \hat{\Sigma}_{11}$.

According to Expression (8), $P(\mathcal{X}_j = s|D)$ represents the probability of a negative binomial random variable taking a value of 74 counts for Sample 1, 270 for Sample 2, with mean $(n-j)(3.357 \times 10^{-2} D^2 + 1.291 \times 10^{-1} D + 9.073 \times 10^{-4})$ and variance $(n-j)(3.357 \times 10^{-2} D^2 +$

$$1.291 \times 10^{-1} D + 9.073 \times 10^{-4}) + (n-j)^2 (15.609 D^4 - 187.319 D^3 + 856.214 D^2 - 1.463 D + 1.683) \times 10^{-7}.$$

To define the prior of D , the empirical Bayes method is applied. The MLE of Sample 1 for D is $\hat{D} = 1.636$ and $\hat{\sigma}_D^2 = 0.508$, then according to (9), the prior of the absorbed dose is $D \sim \text{Gamma}(5.271, 3.221)$. For Sample 2, $\hat{D} = 10.746$, $\hat{\sigma}_D^2 = 0.156$ and $x \sim \text{Gamma}(739.362, 68.800)$.

For both the samples $F \sim \mathcal{U}(0, 1)$ and $d_0 \sim \mathcal{U}(2.7, 3.5)$, the less informative priors.

Table 3 and Figures 2–4, show the results of the posterior densities. These results are sensible compared with the real doses and FBIs, only the real absorbed dose in Sample 2 is not covered by the 95 % credible interval (CI). It is remarkable that the marginal densities of the FBI in both the samples have narrow shapes, localising the FBI most likely values in a small range.

Applying Dolphin's method in the classical framework⁽¹⁾ to Sample 1 (2 Gy, 10 % FBI) gives a dose estimate of 1.631 Gy with a confidence interval of (0, 2.994) Gy, and the estimation of the FBI is 0.113; for Sample 2 (12 Gy, 90 % FBI), the dose estimate is 10.658 Gy with a confidence interval of (9.634, 11.717) Gy and an FBI estimate of 0.922.

In trying to demonstrate the practical applicability of the suggested method, two marginal scenarios of

Table 3. Statistics summary of the marginal posterior densities of the absorbed dose and the FBI (D in Gy, F in fraction).

Sample	Variable	Modal	Expected	SD	95 % CI
1	$D _y$	1.392	1.502	0.498	(0.658, 2.577)
	$F _y$	0.111	0.134	0.048	(0.071, 0.250)
2	$D _y$	10.724	10.736	0.281	(10.182, 11.277)
	$F _y$	0.910	0.910	0.025	(0.856, 0.951)

Figure 2. Marginal posterior dose (left) and FBI (right) densities for Sample 1, 2 Gy and 10 % irradiated fraction.

Figure 3. Marginal posterior dose (left) and FBI (right) densities for Sample 2, 12 Gy and 90 % irradiated fraction.

Figure 4. Histograms of the joint posterior density of (D, F) for Sample 1, 2 Gy and 10 % of irradiated fraction, left; and Sample 2, 12 Gy and 90 % of irradiated fraction, right.

PBI were selected in this study, which can be of great interest for clinicians and which are traditionally not easy for conventional biodosimetry. Very localised (10 %) exposure to 2 Gy and subtotal (90 %) exposure to 12 Gy could easily be misinterpreted as total body irradiation, and such a mistake may lead to serious clinical consequences. In the 2 Gy/10 % scenario, the calculations of cancer risk to organs would be based on the underestimated dose, and for 12 Gy/90 %, ignoring the partial nature of exposure might result in an incorrect decision regarding the necessity of bone marrow transplantation. However, the new technique presented here should help to avoid such mistakes. In Figures 2 and 3, the shapes of the curves clearly

indicate the partial nature of exposure, and the maximum probable values of both D and F are in acceptable agreement with the true values. It is important to highlight the histograms in Figure 4, because to the best of the authors' knowledge, this is the first time that the correlation between the estimates of the dose and irradiated fraction in cytogenetic dosimetry has been highlighted and visualised. From this, the end user of the information (e.g. a clinician dealing with an irradiated patient) can make a judgement by analysing the most probable dose/volume estimates to the clinical symptoms.

In contrast to the classical estimation method for PBI, the Bayesian methods return results in the form

of probability densities that intrinsically contain both modal dose and uncertainty information, and more information such as the skewness can be observed. In addition, the cell survival dose is considered a random variable, while in the classical method, it is a point value, fixed before the estimation. The posterior joint density for (D, F) allows the correlation to be studied between the absorbed dose and the FBI. However, the prior distribution choices influence the final results. Potential future work includes to study the application of informative priors for d_0 .

The number of simulations for both samples is $m = 100\,000$. This is a huge number of simulations, and consequently the joint posterior density calculation takes time (≈ 40 min). It is necessary to use such a large number of simulations to plot accurate bivariate histograms for (D, F) of both the samples, Figure 4. In case there is only interest in plotting the marginal posteriors, a lower number of simulations are recommended, and this calculation will be quicker (e.g. for $m = 10\,000$ it takes ≈ 3 min).

The R codes that reproduce these examples are provided upon request to the corresponding author.

CONCLUSIONS

This article presents a new ZIP Bayesian method for PBI estimation. The ZIP distribution is introduced, and its application in cytogenetic biodosimetry is described.

The method to estimate the absorbed dose and the FBI is also derived. To use this methodology, only the estimates of the parameters and covariance matrix of the dose–response curve are required, which are available from the classical analysis⁽¹⁾ and many examples of which are published. Acceptance–rejection sampling is applied to simulate the joint posterior density.

Finally, the illustrative examples show the application of this methodology in biological dosimetry. This methodology has other potential uses; it could be applied for other types of chromosomal aberration assays, biomarkers and agents (e.g. chemicals).

Further evolution of the methodology presented here will focus on the development of zero-inflated compound Poisson models for estimating dose and FBI in partial body exposure scenarios where the chromosomal aberration yield in the irradiated fraction is overdispersed, e.g. high LET sources like alpha particles.

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