COMPOUND POISSON PROCESSES AND CLUSTERED DAMAGE OF RADIATION INDUCED DNA DOUBLE STRAND BREAKS*

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(Received December 8, 1999)

Recent experimental data have demonstrated that DNA damage induced by densely ionizing radiation in mammalian cells is distributed along the DNA molecule in the form of clusters. The principal constituent of DNA damage are double-strand breaks (DSB) which are formed when the breaks occur in both DNA strands and are directly opposite or separated by only a few base pairs. DSBs are believed to be most important lesions produced in chromosomes by radiation; interaction between DSBs can lead to cell killing, mutation or carcinogenesis. The paper discusses a model of clustered DSB formation viewed in terms of compound Poisson process along with the predictive essay of the formalism in application to experimental data.

PACS numbers: 87.10.+e, 87.50.Gi, 05.40.+j

1. Introduction

Exposure of living cells to ionizing radiation produces various biological effects such as mutations, cell lethality or neoplastic transformation [1]. It is generally accepted that the primary target for radiation action is DNA distributed within the cell's nucleus. Nuclear DNA is organized in a hierarchy of structures which comprise the cell's complement of chromatin. The latter is composed of DNA, histone proteins, other structural and enzymatic proteins and some associated molecules such as RNA. Organization of DNA

* Presented at the XII Marian Smoluchowski Symposium on Statistical Physics, Zakopane, Poland, September 6–12, 1999.

within the chromatin varies with the cell type and changes as the cell progresses through the cell cycle. Ionizing radiation produces variety of damage to DNA including base alterations, single and double strand breaks (DSB) in the sugar-phosphate backbone of the molecule and chromatin breaks [1, 2] The purpose of theoretical modeling of radiation action [3] is to describe qualitatively and quantitatively the results of radiobiological effects at the molecular, chromosomal and cellular level. The basic consideration in such an approach must be then descriptive analysis of breaks in DNA caused by charged particle tracks and by the chemical species produced.

Among various experimental methods used to detect DSBs production in intracellular DNA [4], one of the most popular is the pulse field gel electrophoresis (PFGE) in which the gel electrophoresis is applied to elute high molecular DNA fragments from whole cellular DNA embedded in agarose. The separation of DNA molecules is then based on how quickly the molecules reorient in a switching (pulsed) electrical field. Techniques applying PFGE have been proven to be very sensitive, allowing reproducible measurements with radiation at relatively low doses. The major goal of the experiment is to quantify number of induced DSBs based on relation between fractions of DNA separated on the gel and the average number of DSBs. To analyze the data, the formalism describing random depolarization of polymers of finite size is usually adopted [5,6] giving very well fits to experimental results with X-ray induced DNA fragmentation. In contrast to the findings for sparsely ionizing irradiation (X and γ rays) characterized by low average energy deposition per unit track length (linear energy transfer, LET$\approx$ 1 keV/μm), densely ionizing (high LET) particle track is spatially localized [7]. In effect, multiplicity of ionizations within the track of heavy ions can produced clusters of DSBs on crossed chromosomes [8, 9]. The formation of clusters depends on chromatin geometry in the cell and radiation track structure. DSBs multiplicity and location on chromosomes determine distribution of DNA fragments detected in PFGE experiments. Modeling DNA fragment-size-distributions provides then a tool which allows to elucidate experimentally observed frequencies of fragments. Even without detailed information on the geometry of chromatin, models of radiation action on DNA can serve with some predictive information concerning measured DNA fragment-size-distribution. The purpose of the present paper is to discuss a mathematical model which can be used in analysis of DNA fragment-size- distribution after heavy ion irradiation. The background of the model is the Poisson statistics of radiation events which lead to formation of clusters of DNA damage. The formation of breaks to DNA can be then described as generalized or compound Poisson process for which the overall statistics of damage is an outcome of the random sum of random variables. In the next section we briefly discuss known statistical properties of random sums. Some

biologically relevant distributions are derived and further used (Section 3) in description of fragment size distribution in DNA after irradiation with heavy ions. Model analysis is then applied to predict dose-response curves of experimental data displaying potential practical use of the formalism.

2. Sums of random number of random variables

Consider a sum S_N of N independent random variables X

$$S_N = \sum_{i=1}^{N} X_i \,, \tag{1}$$

where N is a random variable with a probability generating function $g(s)$

$$g(s) = \sum_{i=0}^{\infty} g_i s^i \,. \tag{2}$$

Let us assume that each X_i has the same probability generating function $f(s)$ (that means that $X_i's$ are sampled with the same probability distribution function):

$$f(s) = \sum_{j=1}^{\infty} f_j s^j \,. \tag{3}$$

By use of the *Bayes rule* of conditional probabilities the probability that S_N takes value j can be then written as

$$P(S_N = j) \equiv h_j = \sum_{n=0}^{\infty} P(S_N = j | N = n) P(N = n) \,. \tag{4}$$

For fixed value of n and by using the statistical independence of X_i's, the sum S_N has a probability generating function being a direct product of $f(s)$:

$$F(s) = f(s)^n = \sum_{j=0}^{\infty} F_j s^j \tag{5}$$

from which it follows that $P(S_N = j | N = n) = F_j$. The formula (4) can be then rewritten as

$$h_j = \sum_{n=0}^{\infty} F_j g_n \,. \tag{6}$$

So that the **compound** probability generating function of S_N is then

$$\begin{aligned} h(s) &= \sum_{j=0}^{\infty} h_j s^j \\ &= \sum_{j=0}^{\infty}\sum_{n=0}^{\infty} F_j g_n s^j \\ &= \sum_{n=0}^{\infty} g_n f(s)^n \equiv g\{f(s)\}\,. \end{aligned} \tag{7}$$

In a similar way conditional expectations rules can be used to determine moments of a random sum. Given $E[N]=\nu$, $E[X_i]=\mu$, $\mathrm{Var}\,[N]=\tau^2$ and $\mathrm{Var}\,[X_i]=\sigma^2$, the first and the second moment of the random sum S_N are

$$E[S_N]=\mu\nu, \qquad \mathrm{Var}\,[S_N]=\nu\sigma^2+\mu^2\tau^2\,. \tag{8}$$

Example 1
A **compound Poisson process** is defined as time dependent random sum:

$$S_N(t)=\sum_{j=0}^{N(t)} X_j\,, \tag{9}$$

where the counting process $N(t)$ is assumed to be Poissonian with a rate λ. If $N(t)$ is independent of X_j which are random variables with the same density function $p(X)$ and characteristic function $\Phi(\omega)=E[\exp(i\omega X_1)]$, the compound Poisson process $S_N(t)$ has a characteristic function given by

$$\begin{aligned} \Phi_S(\omega) &\equiv E[\mathrm{e}^{i\omega S_N(t)}] = \sum_{m=0}^{\infty} \Phi^m(\omega)\mathrm{Prob}\,[N(t)=m] = \mathrm{e}^{\lambda t[\Phi(\omega)-1]} \\ &= \exp\left[\lambda t \int_{-\infty}^{\infty} p(X)\left(\mathrm{e}^{i\omega X}-1\right)dx\right] \end{aligned} \tag{10}$$

with moments

$$E[S_N(t)]=\lambda t E[X_1], \qquad \mathrm{Var}\,[S_N(t)]=\lambda t(\mathrm{Var}\,[X_1]+E[X_1]^2)\,. \tag{11}$$

The above compound distribution is an example describing "clustered statistics" of events grouped in a number N of clusters which itself has a distribution. As such, it is sometimes described in literature [10] as "mixture of distributions". In particular, the broad class of Poisson processes $\{S(t)\}$

with the rate constant λ being also a random variable (or constituting the stochastic process of itself) are referred to as *Cox processes* [11, 12]. The marginal distribution for such a process is constructed by using the Bayes rule:

$$\text{Prob}\{S(t)=k\} = \int_0^\infty \frac{(\lambda t)^k \mathrm{e}^{-\lambda t}}{k!} f(\lambda) d\lambda \,, \tag{12}$$

where λ has been assumed to be a continuous random variable with probability density function $f(\lambda)$. One of the most popular working examples is a mixing of Poisson distribution with the Gamma distribution of λ of mean arrival times between subsequent events:

$$f(\lambda) = \mathrm{e}^{-c\lambda}\lambda^{r-1}\frac{c^r}{\Gamma(r)} \,. \tag{13}$$

In effect, Eq. (12) reads

$$\begin{aligned} \text{Prob}\{S(t)=k\} &= \frac{t^k c^r}{k!\Gamma(r)} \int_0^\infty \lambda^{k+r-1}\mathrm{e}^{-\lambda(c+t)} d\lambda \\ &= \frac{\Gamma(k+r)}{\Gamma(r)k!}\left(\frac{c}{c+t}\right)^r \left(\frac{t}{c+t}\right)^k \end{aligned} \tag{14}$$

and the resulting distribution is a negative binomial with parameters r and $p = c(c+t)^{-1}$. Alternatively, negative binomial distribution can be produced as a compound distribution with a logarithmic distribution of objects in a "cluster" [10]. It can be shown that a mixture of Poisson distributions resulting from using any unimodal continuous function $f(\lambda)$ is a unimodal discrete distribution. It is not so, however, in case of unimodal discrete mixing as shown in the example below.

Example 2

The mixture of Poisson distributions can be easily analyzed in terms of random sums. By virtue of the above formalism and by using the formulae (7), (10), the generating function of the compound Poisson–Poisson distribution is $W = \sum_{i=1}^N W_i$ is given by:

$$g = \exp\left(-\lambda(1-f(s))\right), \tag{15}$$

where the random variables X_i are distributed according to a Poisson law

$$f(s) = \exp(-\mu + \mu s) \tag{16}$$

and the total S_N is a random variable with a compound Poisson–Poisson (*Neyman type A*) distribution:

$$P(S_N = x) \equiv P(x; \mu, \lambda) = \sum_{N=0}^{\infty} \frac{(N\mu)^x \mathrm{e}^{-N\mu}}{x!} \frac{\lambda^N \mathrm{e}^{-\lambda}}{N!} \,. \tag{17}$$

Figures 1, 2 presents function (17) for two various sets of parameters λ, μ. The **compound Poisson distribution** (CPD) has a wide application in

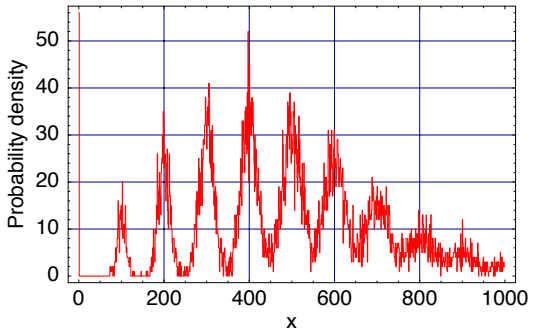

Fig. 1. Simulated probability density function for the Neyman-type A distribution (17) with $\lambda = 5, \mu = 100$ for $N = 10000$ points

ecology, nuclear chain reactions and queuing theory. It is sometimes known as the distribution of a "branching process" [11] and as such has been also commonly used to describe radiobiological effects in cells (*see* below).

Example 3

In their cluster theory of the effects of ionizing radiation, Tobias *et al.* [13] have used so called Neyman [14] distribution (see above, **Example 2**) which is nothing but a compound Poisson-binomial (or in a limiting case Poisson–Poisson) distribution. In the derivation the following reasoning has been used:

- When a single heavy ion crosses a cell nucleus, it may produce DNA strand breaks and chromatin scissions wherever the ionizing track structure overlaps chromatin structure.
- The multiple yield of such lesions depends on the radial distribution of deposited energy and on the microdistribution of DNA in the cell nucleus.
- The number of crossings strongly depends on the geometry of DNA coiling in the cell nucleus (in a human cell nucleus, the total length of doubled-stranded DNA is more than one meter and in the nucleus

the DNA is packed in coiled strands). For a given cell line, a "typical" average number n of possible crossings per a particle is assumed.

- If p is a probability that a chromatin break occurs at each particle crossing (and q is the probability that it does not), the distribution of the number of chromatin breaks in the cluster per one-particle traversal is binomial

$$P(i|n) = \binom{n}{i} p^i q^{(n-i)} \tag{18}$$

with the probability generating function

$$g_s = [sp + (1-p)]^n \,. \tag{19}$$

- The probability that j particles cross the nucleus is given by a Poisson distribution

$$\mathcal{P} = \frac{(\sigma F)^j}{j!} \mathrm{e}^{-\sigma F} \tag{20}$$

with an expectation value σF which is proportional to absorbed dose and represents product of particle fluence F and nuclear cross section σ.

- The overall probability that i lesions will be observed after m particles traversed the nucleus is given by a *Neyman distribution*

$$\boldsymbol{P}(i|\sigma, F, n) = \sum_{m=1}^{\infty} \frac{(nm)! p^i q^{(nm-i)} (\sigma F)^m \mathrm{e}^{-\sigma F}}{i!(nm-i)!m!} \tag{21}$$

with a compound probability generating function

$$G(s) = \exp(-\lambda + \lambda[sp + 1 - p]^{nm}) \,, \tag{22}$$

where $\lambda = \sigma F$.

From the latter, by direct differentiation one gets expected (mean) value and variance

$$\begin{aligned} \langle i \rangle &= n\lambda p \,, \\ \langle i^2 \rangle - \langle i \rangle^2 &= n(n-1)\lambda p^2 + n\lambda p \,. \end{aligned} \tag{23}$$

Aggregation of observed cellular damage potentially leads to the phenomenon of "overdispersion" — that is, the variance of the aggregate may be larger than Poisson variance yielding "relative variance" $\mathrm{Var}_{\mathrm{rel}} = (\langle i^2\rangle - \langle i\rangle^2)/\langle i\rangle$ larger than 1. Assuming thus the Poisson statistics of radiative events, for any distribution of lesions per a particle traversal, the condition for overdispersion can be easily rephrased in terms of (11)

$$\frac{\mathrm{Var}\,[X_1]}{E[X_1]+E[X_1]} > 1\,. \tag{24}$$

By assuming a repairless cell line (*i.e.* no repair process is involved in diminishing number of initially produced lesions), one is able to derive the surviving fraction as a zero class of the initial distribution, *i.e.* the proportion of cells with no breaks:

$$\begin{aligned} \boldsymbol{P}(0|\sigma,F,n) &= \sum_{m=1}^{\infty} \frac{(nm)!q^{nm}(\sigma F)^m \mathrm{e}^{-\sigma F}}{(nm)!m!} \\ &= \exp[-\sigma F(1-q^n)]\,. \end{aligned} \tag{25}$$

Note the difference between Neyman and Poisson distribution, for which

$$\boldsymbol{P}(0|\sigma,F,n) = \exp[-\sigma F] = \exp[-\langle i\rangle]\,. \tag{26}$$

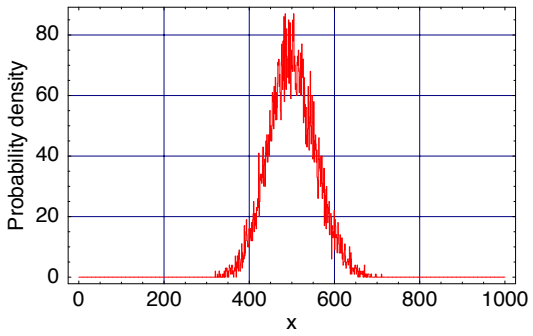

Fig. 2. Simulated probability density function for the Neyman-type A distribution (17) with $\lambda = 100, \mu = 5$ for $N = 10000$ points

The production of clusters of radiolesions can be quantitated in the experiments aiming to determine yield of chromatin breaks in cells exposed to particle beams. One of techniques employed is the premature chromosome condensation [1,15] which allows to visualize radiation induced damage produced in interphase chromosomes, *i.e.* before the mitotic division of the cell takes place. The fusion of mitotic and interphase cells results in the

premature condensation of interphase chromosomes. Such an induction enables one to measure the breakage and rejoining of chromosomes without the perturbing influence of processes associated with cell-cycle progression to mitosis and interphase death of cells which may modify their expression. Distribution of PCC fragments among cells exposed to sparsely ionizing radiation (X- and γ-rays) have been reported to be consistent with Poisson statistics of "randomly" produced breakage. In contrast, overdispersion of the distribution appears [16, 17] as a general feature of particle induced fragmentation (*cf.* figure 3). The phenomenon is explainable under the assumption that single particle traversals are capable of producing multiple

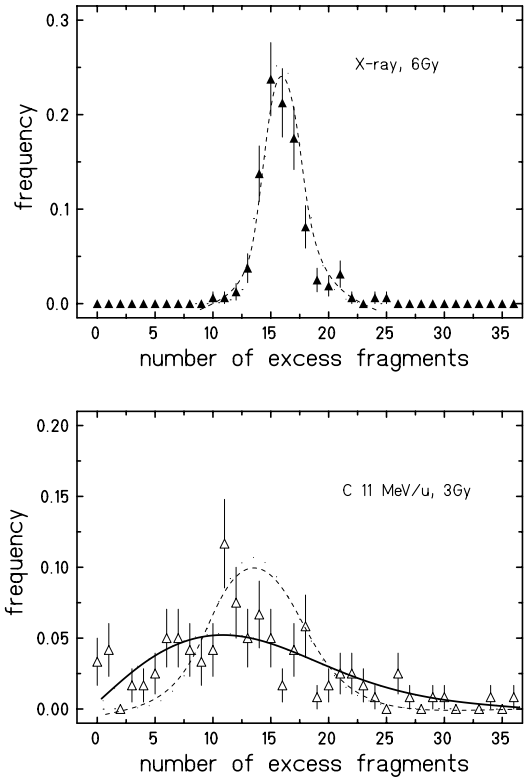

Fig. 3. Frequency distribution of PCC fragments after exposure to X-rays and carbon ions at doses leading to similar biological effect measured in number of "excess fragments" being produced (*cf.* text). Dotted line represents theoretical Poisson curves fitted to experimental data; solid line represents Neyman distribution fitted with $\mu = 3.43 \pm 0.59$ and $\lambda = 3.90 \pm 0.65$. 75% probability of fit has been estimated based on "goodness-of-fit" χ^2 test. As can be clearly seen, comparable biological effect of carbon ions is registered at twice lower dose than for X-rays.

PCC fragments ("clusters" of damage, as discussed in **Example 3** above). Similar conclusions can be drawn from other PCC studies [18] with heavy ions: with increasing linear energy transfer of the ion, the number of breaks per particle traversing the cell nucleus rises and breaks become increasingly "clustered".

3. A model of DNA fragments distribution generated by irradiation with heavy ions

Lesions observed in PCC experiments are known to be the $10 \pm 15\%$ subset of breaks produced at the DNA level. DNA double strands in a size range from a few hundred kilobase pairs to several megabase pairs can be observed by PFGE technique. Randomly distributed DSBs are detected as smears of DNA fragments. To interpret the experimental material one needs to relate percentage of fragments in defined size ranges to number of induced DSBs. For that purpose several models have been derived, mainly based on the description of random depolarization of polymers of finite size [5,6,19]. Although the models give satisfactory prediction of size-frequency distribution of fragments after sparsely ionizing radiation (*i.e* for X-rays and γ), they generally fail to describe the data after densely ionizing radiation [3,9,19]. The experiments with heavy ions [7,20] demonstrate that exposure to densely ionizing particles gives rise to substantially overdispersed distribution of DNA fragments which indicates the occurrence of clusters of damage. The following analysis presents a model which takes into account formation of aggregates of lesions after heavy ion irradiation.

Fragment distribution in PFGE studies is measured with fluorescence technique or radioactive labeling with the result being the intensity distribution. Generated signal is proportional to the relative intensity distribution of DNA fragments and can be expressed as

$$I(x) = xD(x) \tag{27}$$

with

$$D(x) = \sum_{j=0}^{\infty} D(x|j) P(j; \mu, \lambda)\,, \tag{28}$$

where $D(x|j)$ stands for the density of fragments of length x provided j DSBs occur on the chromosome of size S. Frequency distribution of the number of DSBs is assumed here in the form of CPD (17) with parameters μ and λ representing average number of breaks produced by a single particle traversal and average number of particle traversals, respectively (*cf.* **Example 3**

above). The "broken-stick" distribution [19,21] for j breaks on a chromosome of size S yields a frequency of fragments of size x:

$$D(x|j) = \delta(x-S) + 2j\frac{1}{S}\left(1-\frac{x}{S}\right)^{j-1} + j(j-1)\frac{1}{S}\left(1-\frac{x}{S}\right)^{j-1}, \quad (29)$$

where the first two terms describe contributions from the edge fragments of the chromosome and the third term describes contribution from the internal fragments of length $x < S$. The first term applies to the situation when $j = 0$; the edge contribution can be understood by observing that the first and the $j+1$ fragment have the same probability of being size x. Direct summation in formula (28) leads to

$$\begin{aligned} D(x) \;=\; & \exp(-\lambda(1-e^{-\mu}))\delta(x-S) \\ & + \frac{2\lambda\mu}{S}\exp(-\mu\frac{x}{S} + \lambda(\mathrm{e}^{-\mu\frac{x}{S}-1})) \\ & + \mathrm{e}^{-\lambda}(1-\frac{x}{S})\frac{\mu^2\lambda}{S}(1+\lambda\mathrm{e}^{-\mu\frac{x}{S}})\exp(-\mu\frac{x}{S}+\lambda\mathrm{e}^{-\mu\frac{x}{S}}). \end{aligned} \quad (30)$$

Integration of $I(x)$ from 0 to some average (marker) size X^* and division by S yields the relative fraction of DNA content. For $\lambda \gg 1$ and $\mu \ll 1$, the Neyman-type A distribution converges to a simple Poisson. In such a case, simplified expression (30) leads to results known in literature as "Blöcher formalism" [5,6] which describes well the DNA content in probes irradiated with X-rays and γ.

Figures 4, 5 present predicted dose-response curves for the model. The amount of DNA content is shown in function of dose and fragment size. In

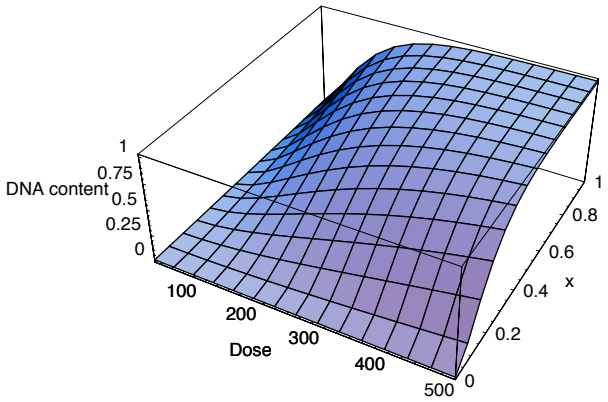

Fig. 4. Distribution of DNA content (integrated Eq. (27)) as a function of the dose and fragment size for $S = 245$Mbp, $\mu = 5$. The fragments length is in Mbp units.

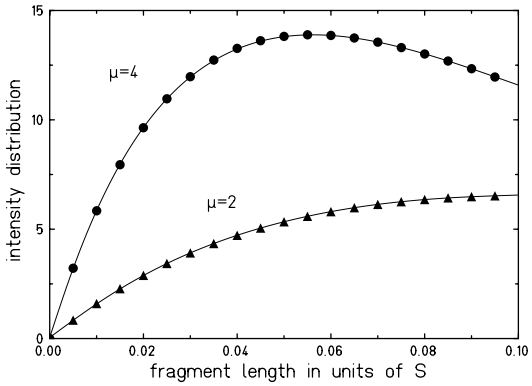

Fig. 5. Predicted intensity $I(x)$ of the signal in function of fragment length for different mean values μ of number of DSBs produced at the same dose (fluence) of particles. In calculations the distribution of inner fragments $D_{in}(x)$, Eq. (30) has been used.

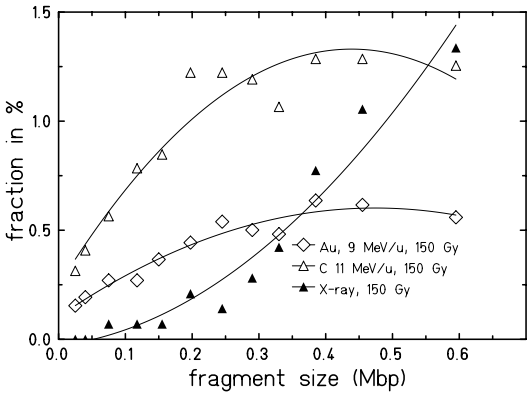

Fig. 6. Fraction of DNA content observed experimentally within the range of sizes 0.1-1.0 Mbp. Data show higher probability of producing short fragments after irradiation with particles than for sparsely ionizing radiation at comparative dose. Lines represent the "best-eye" fit through experimental points.

calculation, the parameter $S = 245$ mega base pairs has been used which is the mean chromosome size for Chinese hamster cells, the cell line for which experimental data are displayed in figures 3 and 6. The increase in multiplicity of DSBs produced per one traversal of a particle leads to pronounced increase in production of shorter fragments which is illustrated in the shift of the peak intensity towards smaller x values.

4. Spatial clustering of breaks and non-Poisson statistics

Clustering of breakage events can be viewed as the process leading to non-exponential "spacing" between subsequent events, similar to the standard analysis of level repulsion in spectra of polyatomic molecules and complex nuclei [22]. For a random sequence, the probability that a DSB will be in the infinitesimal interval

$$(X + x, X + x + dx)\,, \tag{31}$$

proportional to dx is independent of whether or not there is a break at X. This result can be easily changed by using the concept of breaks 'repulsion'. Given a break at X, let $P(x)dx$ be the probability that the next break $(x \geq 0)$ be found in the interval $(X + x, X + x + dx)$. We then have for the nearest-neighbour spacing distribution of breaks the following formula:

$$P(x)dx = \text{Prob}\,(1 \in dx|0 \in x)\text{Prob}\,(0 \in x)\,, \tag{32}$$

where $\text{Prob}\,(n \in dx|m \in x)$ is the conditional probability that the infinitesimal interval of length dx contains n breaks whereas that of length x contains m of those. The first term on the right-hand side of the above equation is dx times a function of x which we denote by $r(x)$, depending explicitly on the choices 1 and 0 of the discrete variables n and m. The second term is given by the probability that the spacing is larger than x:

$$\int_x^\infty P(y)dy\,. \tag{33}$$

Accordingly, one obtains

$$P(x) = r(x)\int_x^\infty P(y)dy\,, \tag{34}$$

whose solution can be easily found to be

$$P(x) = Cr(x)\exp\left(-\int^x r(y)dy\right)\,, \tag{35}$$

where C is a constant. The Poisson law, which reflects lack of correlation between breaks, follows if one takes $r(x) = \lambda$, where λ^{-1} is the mean spacing between DSBs. If choosing on the other hand

$$r(x) = \alpha x \tag{36}$$

i.e. by assuming a linear repulsion, one ends up with the *Wigner's law*. The constants C and α can then be determined from appropriate conditions, *e.g.*

$$\int P(x)dx = 1, \tag{37}$$

and

$$\int xP(x)dx = \lambda^{-1}. \tag{38}$$

One then finds that

$$P(x) = \lambda \mathrm{e}^{-\lambda x} \tag{39}$$

for the Poisson distribution and

$$P(x) = \frac{\pi x \lambda^2}{2} \mathrm{e}^{-\pi(\lambda x)^2/4} \tag{40}$$

for the Wigner's distribution. The latter displays "repulsion", since $P(0) = 0$, in contrast to the Poisson case which gives maximum at $x = 0$. The Wigner distribution is a standard in statistics. It is the distribution for the square root of the sum of the squares of two independent Gaussian random variables of type $N(0, \lambda^{-1}\sqrt{2/\pi})$ and is sometimes called the Rayleigh distribution. The above result Eq. (40) is widely known in literature on random matrices and chaotic systems. The onset of chaos in classical Hamiltonian system is due to the breaking of symmetries. In quantum systems, symmetry breaking manifests itself as a change in the spectral spacing statistics of the energy-level spectrum. Quite similarly, in random walks [23–25] symmetry breaking transition manifests itself as a change in the spectral spacing statistics of decay rates. In all those cases, the statistics of events of interest deviates, as a counting process, from the regularity of Poisson process, for which the subsequent event arrivals are spaced with a constant mean λ^{-1}. The clustered statistics of breakage can be thus viewed as a Cox process (*cf.* Section 1, **Example 1**) for which the process increments over disjoint intervals are, in general, statistically dependent. In this sense, Neyman distribution Eq. (17) is a model example which could be also derived as a marginal one for the Cox process Eq. (12) with Poisson distribution of λ.

5. Conclusions

An existing substantial evidence demonstrates that exposure to densely ionizing charged particles gives rise to overdispersed distribution of chromatin breaks and DNA fragments which is indicative of clustered damage

occurring in irradiated cells. The clustering process can be expressed for any particular class of events such as ionizations or radical species formation and is a consequence of energy localization in the radiation track. Chromosomal aberrations expressed in irradiated cells are formed in process of misrejoining of fragments which result from production of double strand breaks in DNA. The location of double strand breaks along chromosomes determines DNA fragment-size distribution which can be observed experimentally. The task of stochastic modeling is then to relate parameters of such distributions to relevant quantities describing number of induced DSBs. Application of the formalism of clustered breakage offers thus a tool in evaluation of the radiation response of DNA fragment-size distribution and assessment of radiation induced biological damage.

The authors acknowledge many discussions with Drs. Michael Scholz and Michael Kraemer. The project has been partially supported by the KBN grant 2PO3 98 14.

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