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Radiation interaction with DNA

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We developed a model to describe the radiation-DNA interaction in water solution. The model is based on some important aspects of the Bethe Theory for the ionizing process, and on the assumption that the direct interaction between the incident particle and the DNA molecule is negligible in comparison with the indirect effect. This assumption can always be true under controlled conditions. The results show that the number of damages induced by radiation depends on the accumulated dose, on parameters related only to the medium properties, and on the DNA structure, but not on the incident particle. A few applications of the model are discussed, and results are successfully compared with experimental data. New experiments are proposed.

1 Introduction

For many years the studies related to the effect of radiation on living organisms were performed by irradiating living cells or tissues\cite{1, 2, 3}. These experiments are very difficult to undertake and analyze, since many biochemical processes are taking place at the same time, competing with the radiation effects. More recent studies are performed with purified DNA molecules diluted on water solution, with or without the addition of radical-scavengers.

We developed a model to describe, qualitatively and quantitatively, the interaction of different kinds of radiations with organic molecules, in particular the DNA. The model uses, as a starting point, a well established physical theory for describing the ionization process which takes place whenever a charged particle travels across matter - the Bethe Theory\cite{4}. There is one aspect of this theory that is more important here, namely, the fact that the mean-energy transferred to an atom of the medium during its ionization process.

An incident particle with LET $\varepsilon$, creates a number $dn_i$ of radical-pairs while crossing a distance $dl$ in the medium, namely,

$$dn_i = k \varepsilon dl,$$

where $k = 1/\varepsilon_a$, and $\varepsilon_a$ is the average energy transferred to an atom of the medium during its ionization process.

The ions drift away by diffusion and the number of damages in molecules, $n_d$, at a distance between $r$ and $r + dr$ from the incident particle track, is

$$dn_d = dn_i \frac{dn_m \sigma d}{ds},$$

with $dn_m$ being the number of molecules in the volume crossed by the ions,

$$dn_m = \rho_m ds dr,$$
where $ds = 2\pi rd\ell$, $\rho_m$ is the number of molecules per volume unit, and $\sigma_d$ is the cross-section for the damage $d$ induction by the incident radical. Since the ion-pair energy is independent of the characteristics of the incident particle, $\sigma_d$ does not depend on the deposited energy $\varepsilon\ell$. Substituting 3 and 1 in 2, we get

$$dn_d = \rho_m k \varepsilon \sigma_d d\ell dr$$  \hspace{1cm} (4)

If the radical average range is $r_i$, we calculate the approximate average number of damages induced while these ions travels away from the ionization track as

$$dn_d = \rho_m k \varepsilon \sigma_d \int_0^{r_i} dr = \rho_m k \varepsilon \sigma_d r_i d\ell$$  \hspace{1cm} (5)

This expression gives the number of damages in target molecules induced by one incident particle with LET $\varepsilon$ while crossing a distance $d\ell$.

The quantity $\sigma_d$ that we have introduced is related to the structure of the DNA molecule and to its chemical interactions with the radical produced in the medium. However, it is convenient to define the cross section, $\sigma$, for the damage induced by the incident particle, because it can be more easily measured. In fact, if $n_\text{p}$ particles cross an area, $da$, of the DNA sample, the number of damages induced in the molecules is given by

$$dN_d = n_\text{p} \frac{\sigma}{da} d\eta_m,$$  \hspace{1cm} (6)

where

$$d\eta_m = \rho_m d\ell da$$  \hspace{1cm} (7)

is the number of target-molecules inside the irradiated region, then,

$$\sigma = \frac{dN_d}{n_\text{p} \rho_m d\ell da}.$$  \hspace{1cm} (8)

But $dN_d = n_\text{p} d\eta_d$, and $n_d$ can be calculated by equation 5. Then, equation 8 turns into

$$\sigma = \alpha \varepsilon,$$  \hspace{1cm} (9)

where $\alpha = k \sigma_d r_i$.

This expression shows that the cross section is proportional to the incident particle LET, independently of its type or initial energy. Also, the constant $\alpha$ depends only on the medium characteristics and on the target molecule studied. The constant $k$ is related to the minimum energy necessary for the radical production and $r_i$ depends on the distance the produced radical will reach away from the ionizing track; both $k$ and $r_i$ depends on the medium properties. The cross section $\sigma_d$ depends on the properties of the target molecule.

For high density of radical, that could be produced by highly ionizing particles, there is a probability that the ions produced along the track interact with other ions produced by the same ionizing particle. The probability that one ion recombines with another is proportional to the linear radical density along the track, $\lambda = \varepsilon k$. Thus, the number of recombinations may be written as

$$dn_{re} = \xi d\eta_d k \varepsilon = \xi k^2 \varepsilon^2 d\ell,$$  \hspace{1cm} (10)

where $\xi$ is a proportionality factor dependent on chemical properties of the ions and on the solution’s physical characteristics.

Then, the number of ions drifting out of the track has to be correct as

$$dn_i = k \varepsilon d\ell \left(1 - \gamma \varepsilon\right),$$  \hspace{1cm} (11)

which can be rewritten more appropriately as

$$dn_i = \frac{k \varepsilon d\ell}{1 + \beta \varepsilon},$$  \hspace{1cm} (12)

where $\beta = \xi k$. With this correction the cross section obtained in eq. 9 is modified into

$$\sigma = \frac{\alpha \varepsilon}{1 + \beta \varepsilon}.$$  \hspace{1cm} (13)

The radiation-induced damage has, therefore, a cross section which is approximately linear at low LET, and deviates from linearity as the LET increases. Equations 9 and 13 allow us to access the radical-DNA cross section ($\sigma_d$), which may be defined for each damage $d$.

Equations 9 and 13 are the main findings of our model. We now discuss how these results can be applied to different studies related to radiation-DNA interaction.

One of the most studied radiation-induced damage in DNA is the single strand break, because it can be easily observed and quantified by using the electrophoresis technique. In this case, from equation 13 we obtain the radiation-induced SSB (single strand break) cross section,

$$\sigma_{ssb} = \frac{\alpha \varepsilon}{1 + \beta \varepsilon}.$$  \hspace{1cm} (14)

This result is compared in Fig. 1 with data from literature obtained with different incident particles for LET values ranging from $\sim 1\text{kev/\mu m}$ to $\sim 10^3\text{kev/\mu m}$. We fitted the parameter $\alpha$ and $\beta$ in equation 14, obtaining $\alpha = (1.6 \pm 0.2) \times 10^{-3} \mu \text{m}^3/\text{keV}$ and $\beta = (1.2 \pm 0.2) \times 10^{-2} \mu \text{m}/\text{keV}$. The nice fitting obtained is an indication of the reliability of the model developed in this work.
Figure 1. The cross section for SSB as a function of the LET. Data points are from ref. [3] for x-ray, $^4$He, $^{12}$C, $^{16}$O and $^{20}$Ne, and the full line represents the results of our calculation.

Another application of our model is the calculation of the number of induced damages ($N_d$) as a function of the delivered dose. Let us consider that $dn_p(\varepsilon) d\varepsilon$ is the number of incident particles with LET between $\varepsilon$ and $\varepsilon + d\varepsilon$ in an area $dv$ of the volume $dV$. From equation 6 we get

$$\frac{dn_d}{d\varepsilon} = n \sigma \rho_m.$$  

Equation 19 shows that the exponential reduction of undamaged molecules, characterized by the parameter $\gamma$, depends on the medium density and on its parameter $k$, defined in equation 1. It also depends on the radical mean-free-path in the medium, $\lambda$, which is related to diffusion characteristics that may depend on the solution’s chemical properties, temperature, and other physical conditions. In particular, the parameter $\lambda$ depends on scavengers concentrations in the solution.

3 Experimental verification

In order to verify at least some of the results and implications of our model, we started the development of an experimental program which has as one of its objectives the realization of measurements of relevant quantities in the radiation-DNA interaction under controlled conditions, so that the experiments performed with different kinds of radiation can be compared among themselves.

We choose to measure, at a first step, the number of single strand breaks induced by gamma, protons and neutrons, as a function of dose, using as target a plasmid produced by Stratagene, the pBSKS + purified through a standard purification process[5]. At present we have the first results with gamma and proton irradiations. A comprehensive description of these experiments will be published elsewhere, but here we will show some features of the experiments with protons, since a new experimental setup was constructed to study the effects of this radiation on DNA in water solution.

Since protons have high LET, their range inside the DNA solution is very small, resulting in additional difficulties to carry out this experiments which are not present in those with gamma and neutrons. In fact, some problems we had to face are

- the small range of protons in water, which limit the thickness of the target solution;
- the strong heating process of the target, induced by the proton beam, which prevent us of using the direct proton beam;
- the problem of quantifying the number of molecules with gel electrophoresis; which led us to the development of a software specially designed for carefully analyzing the gel image.
in agreement with the prediction of our model, according to equation 19. Also, as discussed in the text below that equation, the exponent parameter $\gamma$ which characterizes the exponential decreasing of the surviving fraction should be independent of the radiation type. It is not simple to compare the different sets because since all the relevant experimental conditions determining this parameter were not the same in each experiment. But from a preliminary analysis, according to the fitting process for the experimental results shown in Fig. 2, the exponential constants which best describe neutron and gamma results (Fig. 2a), or the protons results(Fig. 2b) and gamma results may be considered the same, inside the experimental errors. Although for neutron this parameter is slightly different from the others, due to the relatively large experimental errors we can not say they are not compatible. Therefore two of the main results of the model developed by us were proved to be in accordance with the experimental results.

4 Conclusions

In this work we developed a model to describe the radiation-DNA interaction. This model addresses the problem of quantifying the damages induced in DNA molecules in water solution samples, when irradiated with different particles and at different energies. We have shown that the cross section for damages induced by radiation does not depend on the kind of incident particle and on its energy.

In order to verify if the predictions of this model are correct, we gave start to the development of an experimental program which have among its main purposes to test the results of this model. Here we show the first results obtained with protons and gamma irradiations. The analysis of the experimental data show that they are in agreement with the theoretical results. A more comprehensive description of the experiments and detailed analysis of the results will be presented in a forthcoming paper.

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