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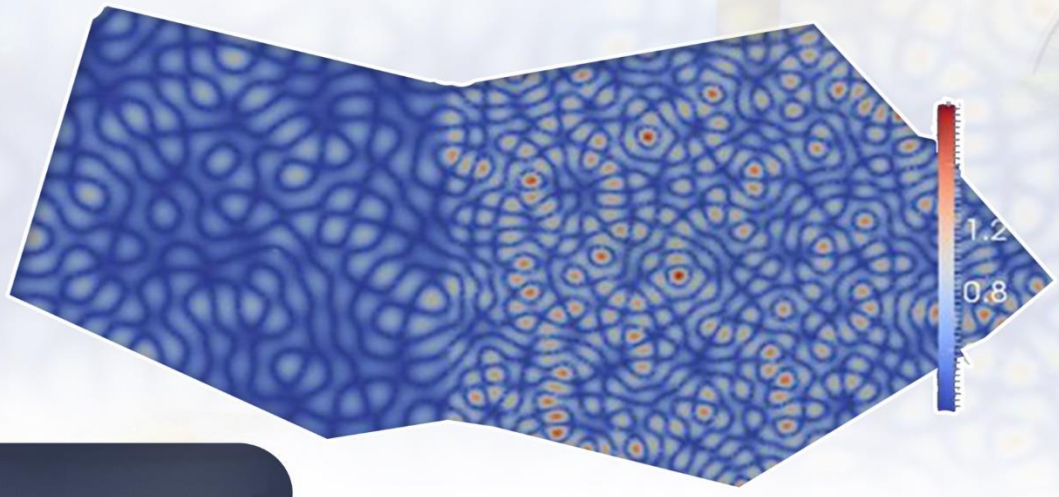

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The Unified Approach of Ionizing Radiation on Biological Matter: Action of Heavy Charged Particles on Mammalian Cells

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A B S T R A C T

Damaging effects to mammalian cells by heavy charged particles have been realized in terms of the mean free path for linear primary ionization (the spacing of ionizing events along the charged particle tracks) using *in vitro* radiobiological experimentation data. Damage is found to be optimum when the mean free path for linear primary ionization along the tracks in the cell nucleus matches the mean chord length of approximately 1.8 nm through a DNA segment. A simple semi-theoretical model is proposed to define absolute biological effectiveness based on effect inactivation cross section σ (μm^2) which is interrelated to the mean free path for linear primary ionization λ. For heavy charged particles, the model shows a saturation region for the effect cross section, $\sigma_s = 60\ \mu m^2$ for $\lambda \leq 1.8$ nm. The model explains the mechanisms leading to cell death via DNA strand scissions. In the saturation region, double strand breaks of the DNA are predominant, unrepaired or mismatched repair processes lead to maximum damage. At higher mean free path; $\lambda > 1.8$ nm, single strand breaks of the DNA is the main basic mechanism and thus repairable processes are possible.

1 Introduction

Even though that DNA is accepted as a critical target responsible for cell killing by ionizing radiation, the exact nature of cell death remains unknown (Ward, 1994; Pouget et al., 2004). Biophysical modelling could provide answers to how DNA strand breaks are related to cell killing (Chadwick and Leenhouts, 1981). Damage to mammalian cells is usually quantified with what is known as the Relative Biological Effectiveness (RBE), in terms of track average Linear Energy Transfer (LET) (ICRU-16, 1970; Barendsen, 1993; 1994). Problems associated with dose energy dependent quantities as seen by the former relation, RBE vs. LET, were subjects to debates (Kellerer, 1975; Watt et al. 1994; Simmons and Watt, 1994). The correlation between biological effects and a number of physical quality parameters led to propositions of several biophysical models (Katz, Ackerson et al., 1971; Kiefer, 1982; Kampf, 1982). The main objective of these models is to investigate the damage mechanisms, at molecular level, leading to cell death (Kramer and Kraft, 1991; Harder et al., 1992; Kellerer and Rossi, 1972). The conceptual foundations of many of the existing models were criticized by many researchers (Kraft et al., 1992).

In the last few decades, researchers have provided evidences that the double breaks of DNA opposite strands; dsb's, is responsible for cell death (Ward, 1990; Iliakis, 1991). Watt and his group suggested that the spacing of ionizing events along charged particle tracks can explain the details of the different mechanisms at nanometric scales. It is thus far better to define ionizing events at macro-molecular level with the mean free path for linear primary ionization (Watt et al, 1985).

Radiobiological experiments involving *in vitro* exposure of mammalian cells to different types of heavy charged

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particles (HCP's) would provide useful information to quantify damaging effects. The damaging effect which is also known as "reproductive cell death" characterizes an end-point effect by survival curves against dose, where survival fraction presented in logarithmic scale against radiation dose in linear scale. The shape of the curve depends on radiation type and to a certain extent on cells type. For sparsely ionizing radiations (SIR's), such as x-rays, and fast electrons, the curves have shoulder shapes, while HCP's such as slow protons, alpha particles have linear response type. It is continuously useful to use linear-quadratic fitting formula $F(S) = \ln(S/S_o) = -\alpha D-\beta D^2$, where α (Gy^{-1}), β(Gy^{-2}) are constant parameters for any specific curve. The first term represents the slope of survival curve at zero dose, which is also known as the radio sensitivity parameter. For linear survival curve, $\beta = 0$, and the equations becomes simply as $F(S) = \ln(S/S_o) = -\alpha D$.

The present study will focus on physical parameterization of the biological damage caused by HCP's. Hence presenting a model that unifies the action of HCP's on mammalian cells.

2 Materials and Methods

The cellular damage induced by ionizing radiation can be defined as the probability to produce cellular damage in units of area, which also known as inactivation cross section; σ_s. Inactivation cross sections, σ_s (in μm^2) of a variety of mammalian cells were calculated using the relation (Watt, 1996):

$$\sigma_s = \frac{L_T}{6.25\ \rho\ D_o}$$

where L_T is the track average linear energy transfer; LET (in keV/μm) for the equilibrium spectrum of charged particles involved, *do* is the initial dose (in Gy) and ρ is the density of biological matter (in g/cm^3).

Cross sections were determined for the initial slope of survival curves to avoid any problems associated with cell recovery. The initial slope for cell survival curve is simply the slope of curve at zero dose. For survival curves, whether the relationship is shouldered or linear type the slope is equivalent to α. Hence the inactivation cross section is evaluated at $D_o = 1/\alpha$. For wet cells, the density of medium is assumed of water.

The cell survival parameters were extracted by the author from published data in previous work (Watt and Alkharam, 1994). The corresponding cross sections were plotted as a function of the mean free path for primary ionization λ (in nm). The track average structure parameters; LET and λ, are estimated using Watt's group foundations (Watt, 1994; 1995a; 1995b).

The search for model imply trying a function F= F(λ), provided that the semi-empirical formula fits the curve observed by the σ–λ in terms of justifiable physical parameters.

3 Results and Discussion

Cross sections for the various mammalian cells including human cells are shown as a function of λ for HCP's. Visual inspection clarifies the grouping of σ and λ data within the spread of the physical and biological errors.

On examining the σ–λ concurrent relationship, there exist a clear inflection point around λ_o = 1.8 nm. In the saturation region, where λ < 1.8 nm, the maximum damaging effect is attributed to the mean chord of the strands in the DNA segment which can only identify that the double strand break (dsb) of the DNA are the critical lesions for inactivation for all HCP's. The spikes shown over this region are due to delta rays effect (δ-ray). These fast electrons produced in this region by HCP's would have their own tracks and thus multiply damaging effects. The damage mechanism for neutrons, shows an identical behaviour as HCP's for λ >1.8 nm but could never reach saturation damage as clearly seen in Figure-1. That is because of the limited range of protons at optimum λ. For λ > 1.8, the σ-λ relation shows a linear correlation on log-log scale graph. This part of the curve is attributed to the repairable single strand breaks of the DNA (ssb's) whether induced by the directly ionizing radiation or the water radicals along the track of DNA strands.

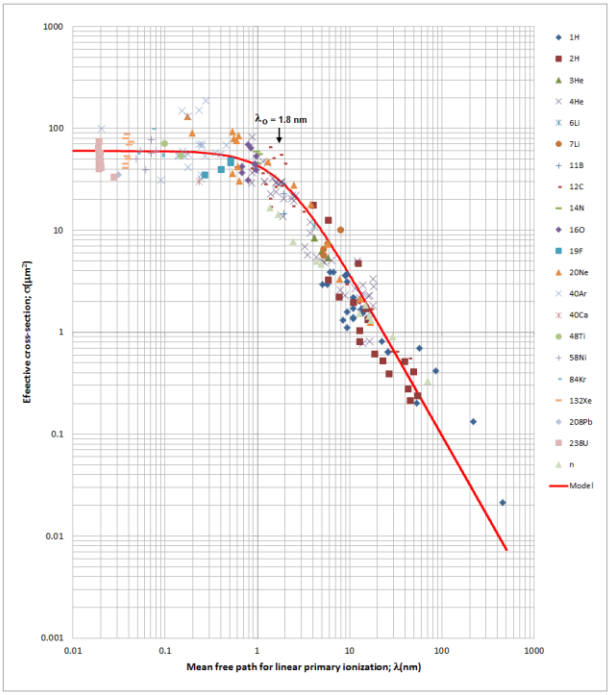

Figure (1). The effective cross section σ (μm^2) for mammalian cells vs. mean free path for linear primary ionization λ(nm) for HCP's.

Earlier investigation by the author shows similar behaviour of SIR's (Alkharam, 2022). The study concluded that SIR's like x-rays, γ–rays and fast electrons have smaller cross sections as compared to what would be expected by HCP's, as clearly shown in Figure 2. The study showed that only C_k ultra-soft x-rays with photons of energy around 0.278 keV can induce highest biological damage near the inflection point where λ_o = 1.8 nm. Higher energy photons, i.e., x-rays and γ-rays have much lower cross sections. The dominant interactions produced by SIR's are ssb's of the DNA.

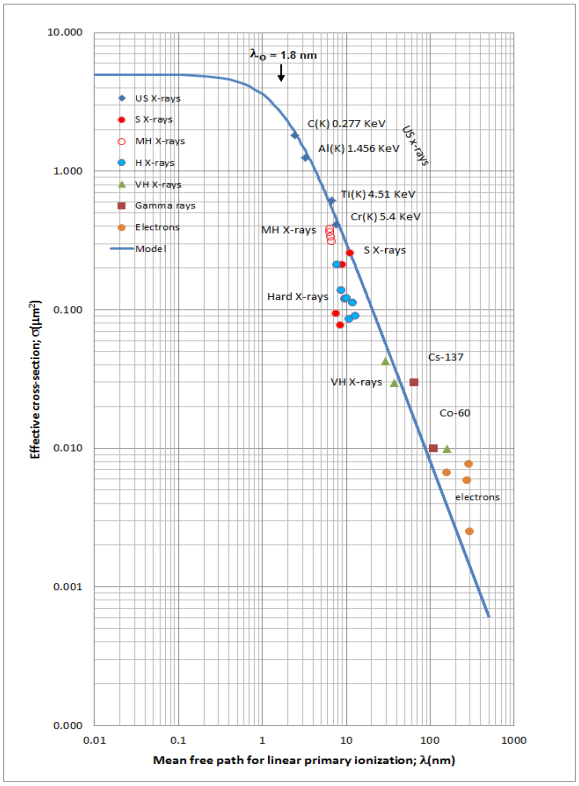

Figure (2). The effective cross section σ(μm^2) for mammalian cells vs. mean free path for primary ionization λ(nm) for SIR's (Alkharam, 2022). Only the sparsely ionizing data are extracted in the figure. The model carried in this research has been modified to match with the one used in this paper.

The grouping of data of both directly ionizing radiation and indirectly ionizing radiation and their action on mammalian cells as observed in both Figures 1-2; indicate damage to cells is independent of both the type of radiations and the type of cells. That is nothing to say more than a unified action of either types of ionizing radiation (HCP's and SIR's) on mammalian cells. The search of a simple mathematical model to fit data of both types of ionizing radiations leads to the following semi-empirical relation:

$$\sigma(\lambda) = \frac{\sigma_o}{\left(1 + \left(\frac{\lambda}{\lambda_o}\right)^n\right)}$$

where σ_o is the saturation cross section, λ_o is the value of the mean free path at inflection point (the spacing between the DNA strands), and n is a numerical value to be find for best fitting model.

The result of fitting these relations is presented by the solid lines in Figure 1 (red curve) and Figure 2 (blue curve). Both models are presented infn the same log-log scale for effect cross sections vs. mean free path for linear primary ioniztion in Figure 3 to asses the size of damage by both types of radiations and to compare their effectvness on mammalian cells.

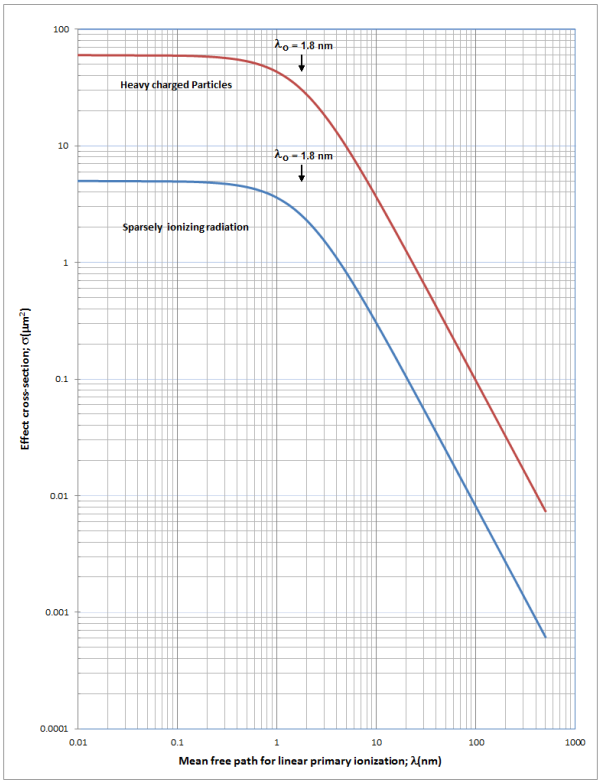

Figure (3). The unified model of radiation action on mammalian cells for both HCP's and SIR's as indicated by the solid lines.

Both curves show saturation damage for $\lambda \leq 1.8$ nm of different scales. The linear portions of the two curves have the same slope with gradient of -1.59 ± 0.06.

The merit of these values; for n = 1.6 the saturation cross sections of HCP's at $\sigma_o = 60 \pm 4$ μm^2, and of SIR's at $\sigma_o = 5 \pm 0.3$ μm^2, and an infliction point at λ_o = 1.8 ± 0.4 nm, indicate that the size of this damage have got to be related to nanometric dimensions. In other words, ionizing radiation initially induce dab's and ssb's in the DNA strands.

related to nanometric dimensions. In other words, ionizing radiation initially induce dab's and ssb's in the DNA strands.

HCP's is responsible for the induction dsb's in the DNA directly. The fact that only the DNA dsb leads to cell death, shows that HCP's have greater capability than SIR's to destroy normal or cancerous cells. The damaging capability of HCP's to mammalian cells is about 12 times of SIR's.

4 Conclusions

In this study, a simple model that unifies the action of radiation on mammalian cells was presented. The main features of this model is; its unique specification of the cellular damage in terms of biophysical parameters that relates molecular events such dsb's of the DNA to macroscopic biological effects such as cell death. In simple mathematical form; $\sigma(\lambda)=\sigma_o/(1+(\lambda/\lambda_o)^n)$, the model indicate that the maximum damage is represented by σ_o which equivalent to the geometrical cross section, $\sigma_g = 60\ \mu m^2$ of the cell nucleus. This maximum damage can only take place if the ionizing radiation have mean free path greater than 1.8 nm. The inflection point as indicated by the parameter λ_0, gives an insight of where the damage becomes prominent; for $\lambda < 1.8$ nm the damage is saturated and caused by dsb's of the DNA whereas for $\lambda > 1.8$ nm the damage could be repaired whether initiated by dsb's or ssb's of the DNA. Further investigations are needed to indicate the rules of water radicals in cellular damage. A more sophisticated model will be vital to further demonstrate the unification action of ionizing radiation on mammalian cells in terms of detailed physical parameters.

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Conflict of Interest: The author declares that there are no conflicts of interests.

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