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# Radiation effects in life sciences

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## Abstract

Topics in radiation effects in life sciences are reviewed with special attention to communality with radiation effects in device physics.

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## 1. Introduction

Radiation plays an important role in life sciences and medicine. On one side, it is the usual way of providing a non-invasive diagnostic tool to image structures in living bodies. In addition, it provides the means to deliver treatment for many forms of cancer during radiation therapy. But radiation is also threatening living organism through several forms of natural and artificial radioactivity on the ground and future human presence in space is limited by radiation damage of cosmic rays. Radioactivity is responsible at least in part for evolution due to spontaneous mutations, and in the future, might be also shape the future of the human race and all living beings. Thus understanding the effects of radiation on living organism leads to improvements in the beneficial

application and to the development of mitigation plans against the detrimental effects of the radiation [1].

Radiation targets DNA, and thus influences and modifies the gene pool. A beneficial role in radiobiology could be the potential to selectively induce DNA faults for cancer research.

## 2. Interaction of charged particles with living cells

Much of Radiobiology is done with photons (UV, X- and  $\gamma$ -rays), because they are readily available either from natural (radioactive materials) or artificial (accelerators) sources of modest size. In addition, they can penetrate a fair amount of material before losing their effectiveness, and thus are easily encapsulated. Charged particles (protons, light and heavy ions) behave different. They can be confined by magnetic and electric field, and thus be accelerated and directed as needed. For clinical application, fairly large accelerators (cyclotrons, synchrotrons) are needed.

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It turns out that the physical properties of charged hadrons make them superior for cancer treatment: they have an energy dependent defined range and a characteristic track structure. Charged particles are the main component of space radiation (trapped in the radiation belts, part of sun eruptions and coming from galactic Super Nova remnants); their energy composition can easily be replicated in accelerators.

The responses of normal tissues to radiation limits medical treatment and space mission operations. Living cells represent a system of extreme sophistication. They will react to radiation damage in several ways: cell and tissue changes of state or cell inactivation [2]. Considering the double-helix of the DNA, we are looking at a large molecule with built-in complete redundancy. The redundant information is being used to repair damage occurring to only one of the two strands, so-called single-strand breaks. What is truly fascinating is the response to heavier damage, which might not be repairable because the underlying redundant information is lost in double-strand breaks. It appears that the cells are pre-programmed to react to certain forms of the heaviest damage, which sometimes depends on the cell cycle it occurs in: the cell starts a controlled program of cell shut-down (“Apoptosis”). This idea of programmed cell death was recognized with the 2002 Nobel Prize in Medicine [3]. Apoptosis seems to be an integral part of the cell communications and is similar to other forms of controlled cell shut-down like falling leaves or losing unneeded extremities.

The ability to deal with radiation damage is similar to what is being implemented in modern electronic circuits in space, for example in dealing with changes in the bit content due to very high instantaneous charge deposit called Single-Event Effects (SEE) [4]. Radiation immunity is achieved by keeping two copies of the program and data in memory. The original and the copies are continually compared to each other, and the corrupted data are eliminated by “majority voting”. In addition, single-event upsets (SEU) are corrected by continuing bit stream repair (“scrubbing”).

It should be pointed out that the DNA is only part of the target for radiation damage in living

cells. Cell membranes, and the information pathways and control systems can also be affected [2]. In addition, injured cells distribute damage to neighbors (“Bystander Effect”) [5,6]. Radiation damage on cells in tissues respond differently than individual isolated cells and record their exposure history (“Microenvironment Effects”). Damage to genome may not be proportional to dose and may not be expressed for up to 50 cell generations (genomic instability) [2].

Because the biological system are highly structured, the definition of the biological effectiveness of radiation has to include not only the description of the radiation, but also the description of the target. The biological effectiveness is assessed with the standard killing method, where the ability of cells to survive radiation and continue to divide is measured [7].

### 3. Quality of radiation

Radiation is a form of energy, and its effects are due to the deposition of energy in the target. Thus the strength of radiation described by the dose  $D$ , defined as absorbed energy per unit mass [8]:

$$D = \frac{\Delta E}{M} = \frac{N}{A} dE/dx \quad (1)$$

where  $N/A$  is the fluence and  $dE/dx$  is the so-called stopping power or energy loss. Table 1 shows the dosimetry for protons in a cube of water of 10  $\mu\text{m}$  dimension as a function of energy [9]. The energy deposited and the number of ionizations created in 10  $\mu\text{m}$  can be substantial. Fig. 1 gives a perspective by how much the energy loss can vary from one particle type to the next.

At closer inspection, there are several effects for which the direct proportionality to dose breaks down. One of them is the “low-dose” effect, which shows increased damage for low dose when compared to high dose [10,11]. The most well-known case is that of survivors of the Hiroshima A-bomb: at very low dose the mortality is higher than expected from high-dose data [12]. A similar effect occurs in radiation damage of electronic devices, which show saturation at high dose and

Table 1  
Radiobiological effectiveness of protons of different energy in a 10  $\mu\text{m}$  cube

P energy (MeV)	dE/dx (keV/ $\mu\text{m}$ )	No. of p for 1 Gy (10 $\mu\text{m}$ $\times$ 10 $\mu\text{m}$ )	No. of ions/10 $\mu\text{m}$	RBE (rel. to $^{60}\text{Co}$ $\gamma$ )
4	9.6	65	2760	2
10	4.6	135	1336	1.4
50	1.3	496	363	1.1
200	0.5	1377	131	1
1000	0.2	2798	64	1

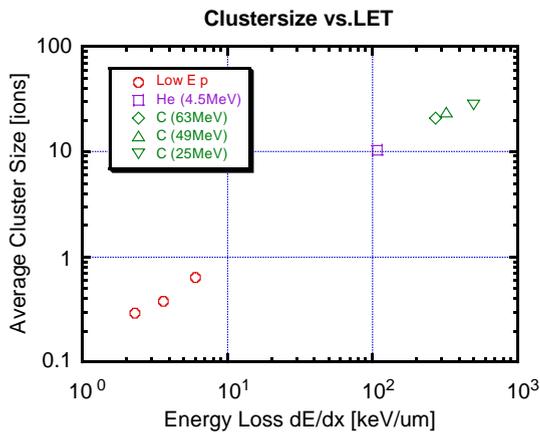


Fig. 1. Average cluster size in propane gas as a function of the linear energy transfer LET (energy loss) of ionizing radiation (low energy protons,  $\alpha$ 's and carbon ions) [20].

thus exhibit larger damage at low dose than one would expect from high-dose data [13].

Radiation effects in biological systems depend on the dose rate, as does degradation in bipolar transistors under certain biasing condition [14]. Another effect beyond strict dose proportionality is the “adaptive response”, where the damage in tissue previously irradiated is lower than in unirradiated tissue [15,16]. And there is annealing, where previous damage is reduced by the repair mechanism in the cell, much like the annealing of radiation damage in transistors and silicon detectors [13].

One of the most important findings is that charged particles produce unique radiation effects such that the normalization with respect to X-rays is not valid. While the X-rays interact mainly by absorption, which is a localized random process, the principal interaction of charged particles in matter interact is ionization, in which energy is

deposited in a structured way along the track [17,18]. Thus the biological effectiveness to generate damage depends critically on the correlation between the structure of the ionization and the structure of the biological samples. The relative effectiveness of different radiation fields is measured by the “relative biological effectiveness” (RBE), defined as the total dose ratio of X-rays or  $^{60}\text{Co}$   $\gamma$ -rays and charged particles giving the same surviving fraction. The RBE will depend on the type and energy of the charged particle as shown in Table 1 for protons, but also on the target and the repair mechanism which might be active. In addition, it will depend on the total dose administered because the dose dependence of the survival fraction are different for X-rays and charged particles. This is the reason why dose equivalent (“Quality”) and normalization factors (RBE) are not always valid when relating radiation damage of X-rays and charge particles [2]. This fact is well known in device physics, where the dose is a useful quantity only for surface damage, but can not be applied to displacement damage by hadrons, responsible for the increase of the leakage current and the change in doping concentration, where the relative damage from different kind of particles is expressed in the Kerma in the non-ionizing energy loss (NIEL) [19].

In both radiobiology and device physics, the linear energy transfer (LET) play an important role. It describes the amount of localized energy, which can be transferred to the target. High  $z$  heavy ions deposit large amounts of energy within small volumes and thus have a large probability to damage the DNA. In tissue, one is mainly interested in the size of ion clusters generated by the radiation. It was found that at small LET, small cluster size of less than five ions are created

which lead to single-strand breaks which can be repaired, while at larger LET, clusters of about 10 ions are created which generate multi-strand breaks, which damage DNA irreparably. The relationship between mean cluster size and LET is shown in Fig. 1 for rarefied propane gas, which has a chemical composition like DNA [20]. In device physics, large LET from charged particles generates SEE, where the high concentration of ionization generates SEU, and single-event latch-up (SEL) [21].

As in device physics, the only accurate independent variable for radiation is to characterize the radiation field by type, fluence and energy of the particles instead of dose or LET.

#### 4. Applications of silicon detectors in radiobiology

The X-ray absorption coefficient in silicon is energy dependent and fairly low at energies interesting for life sciences (above 20 keV), and thus the use of silicon strip detectors (SSD) with customary thickness of a few hundred microns is somewhat limited in the detection of X-rays, except where detector orientation relative to the beam creates very large effective thickness' [22–24]. On the other hand, SSD have high efficiency for the detection of charged particles and are thus a good detector choice in charge particle radiobiology [25]. They allow simultaneous particle-by-particle determination of the position with high-spatial resolution (in the few micron range), of the angle using a detector pair and of the energy or LET using the energy deposit in silicon with wide dynamic energy range. They have a fast response, supporting high particle rates and permitting self-triggering, and are radiation tolerant. They can be adapted to most geometries and are compatibility with physiological conditions of cells. Their simple operation (e.g. low voltages, no gain, no consumables) and compactness make them suitable for use in life sciences.

##### 4.1. Nanodosimetry

The dependence of the clusters size on the LET is the subject of the field of Nanodosimetry [20], in

which the interaction of high LET particles with DNA is simulated by the cluster generation in a low-pressure gas, allowing to map the nanometer scale of the organic molecules into millimeter distance between ionizations along the track in the active volume of the detection apparatus. In our application of Nanodosimetry, a telescope of SSD is used to track the charged particles inside the low-pressure volume and correct for the position dependence of detection efficiency of the ionization yield and cluster size [26].

##### 4.2. Particle tracking silicon microscope

The nanometers scale of the chromosome structures is too small to be resolved on a individual scale to investigate radiation effects. Conventional radiobiological experiment are thus based on a statistical approach where cells are randomly traversed by a broad particle beam and an average effect is observed in survival. The use of micro-beams [27] allows now to pinpoint the location of the damage to the 30  $\mu\text{m}$  scale and identify the dose per cell. They still allow confusion between single and multiple particles when the rates are relatively high. We are developing a particle tracking silicon microscope (PTSM) which will track the location of every particle within a specific cell and measures their energy/LET. One potential target is the gametogenesis in the adult hermaphrodite of nematode *C. elegans* [28] with cells of few microns separation as shown in Fig. 2. It is the organism on which the 2002 Nobel Prize winning work was performed [3].

##### 4.3. Proton computed tomography

Proton radiation therapy [29] is a highly precise form of cancer therapy, because the large energy deposited at the end of the range is very localized [30]. This is achieved by tuning the beam energy to have the beam stop inside the cancer, which requires accurate knowledge of the amount and density of the tissue traversed and verification of the correct patient position with respect to the proton beam to avoid damage to critical normal tissues and geographical tumor misses. In existing

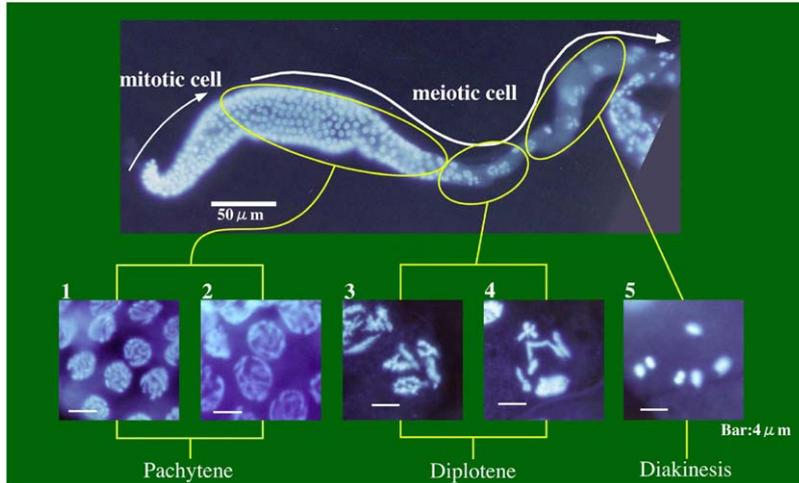


Fig. 2. Cell structure of the nematode *C. elegans*, indicating that the spatial separation of different cell types is several 100  $\mu\text{m}$  [28].

proton treatment centers dose calculations are performed based on X-ray computed tomography (CT) and the patient is positioned with X-ray radiographs.

The use of X-ray CT images for proton treatment planning ignores fundamental differences in physical interaction processes between photons and protons and is therefore inherently inaccurate. Further, X-ray radiographs depict only the skeletal structures of the patients but do not show the tumor itself. Ideally, one would image the patient directly with proton CT by measuring the energy loss of high-energy protons that traverse the patient [31]. This method has the potential to significantly improve the accuracy of proton radiation therapy treatment planning and the alignment of the target volume with the proton beam.

We have starting a program to investigate the feasibility of Proton Beam Computed Tomography (pCT), using SSD for position, angle and energy measurement [32,33]. Our studies indicate that the reconstruction is aided greatly by the superior position resolution (and small thickness) of the SSDs, but that the energy resolution of SSDs at low proton energies (100–200 MeV) of about 10–20% is not good enough, but should be replaced by an energy measurement with 1% resolution.

## 5. Conclusions

Studying radiation effects in life sciences and in device physics offers similar problems: One needs to define both the quality of radiation and the properties of the specific target.

- What is the correct variable (fluence or dose)?
- Are there single-event effects (LET and SEE)?
- Are there normalization factors (RBE/“Q” and Kerma).
- Are there low-dose effects?
- Are there dose rate effects?
- What role does the microenvironment play (Bystander effect and Latch-up).
- Does relaxation exist (Adaptive response and Annealing).
- What is the target (DNA/cells/interfaces and transistors/circuits/data transmission).

Living cells are well engineered (in the EE language: they had many cycles of DRCs and VHDL verification!) and have built-in mechanisms to deal with radiation damage, either repair or apoptosis.

Up to now, most of the radiation damage data is statistical due to the small size of the targeted DNA. In special cases, we will be able to build instruments to replace this approach with more

specific data from particle-tracking measurements using silicon detectors.

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