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ISSUES ON THE ELECTRON LINEAR ENERGY TRANSFER, IN HEAD TISSUES, MODULATED BY MAGNETIC AND ELECTRIC FIELDS

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ABSTRACT

Ionizing radiation has been employed in conjunction with various clinical modalities for therapeutic purposes. Often, surgery, chemo and radiation therapies have been combined on the arsenal against cancer. Nontraditional techniques, as Tumor Treating Fields (TTF) that uses low-intensity variable electric fields, have also been employed for the treatment of brain tumors, such as Glioblastoma Multiforme (GBM), with promising results in reducing the harmful radio and chemotherapy effects, while maintaining the same tumor control rates. The combination of electromagnetic field and chemotherapy has already been part of clinical investigations; however, experimental and theoretical studies coupling electric and magnetic fields with high-energy electron radiotherapy are missing. Herein, a theoretical analysis involving the electron's LET in conjunction with static electric and magnetic fields (E, H) was addressed in order to investigate the relevance of the use of external electromagnetic fields in radiotherapy. The theoretical findings reinforce the possibility of application of the coupling of magnetic field with electron radiotherapy, opening a horizon for future experimental and clinical studies.

Keywords: **Electrons, Electromagnetic, Fields, TTF.**

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1. INTRODUCTION

Cancer is a common name of a set of more than one hundred diseases, which have the neoplasic growth of cells, able to invade surrounding tissues and organs. The cancer cells tend to be very aggressive and uncontrollable, which may develop solid tumors, infiltrate on neighboring tissues, and flow through lymphatic or vascular systems reaching distant organs or tissues in the body [1].

Glioblastoma Multiforme (GBM) is the most common type of glioma, a brain cancer. It accounts for approximately 15% of all primary brain tumors. This type of cancer starts in the glial cells that give support to the neurons in the cortex. GBM patients have the poorest prognosis of all malignant brain tumor patients, with a median survival of about fourteen months [2]. Due to its fast growth and mortality, one can suppose that the conventional radiation therapy and chemotherapy do not work properly, which makes necessary the search for alternative treatment methods. One of them is a technique called Tumor Treating Fields (TTF). The TTF technique consists in the use of electromagnetic fields along with chemo or radiation therapy. In some places in the USA and Europe, there are hospitals testing the TTF using 200 kHz electric fields along with chemotherapy, which leads to a decrease in the progression rate and an increase in the overall patient survival [3, 4, 5, 6]. Therefore, GBM is the first kind of tumor to receive treatment based on the coupling of electromagnetic fields and radiation.

There are researchers studying the effects of magnetic fields in cancer cells to understand how they affect their properties. They addressed the nucleic acid productions and the gene expressions [7]; membranes and channel properties [7]; intracellular component’s orientation [7]; free radical pair’s formation [8]; ATP levels [9]; effects of magnetic fields in proteins [10] and enzymes [11]; cells growth and viability [12], among others themes. The methodologies were applied using a great variety of static and dynamic electric and magnetic fields, in the order of few mT to 9 Tesla.

Yet, the combination of varying electric and magnetic fields together or high intensity static magnetic field on the radiation therapy is not very well understood. Therefore, there is the necessity of pursuing a theoretical model and follow a series of experiments using electromagnetic fields along with radiation therapy.

Let us define Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE). LET is the amount of energy that an ionizing particle transfers to the medium by unit of travelling distance. While RBE is the ratio of the amount of a relevant biological effect from the radiation in study to the same from the reference radiation of X-ray 200 kV, in equivalent conditions of absorbed dose on the human tissues. Both of these physical quantities, LET and RBE, are related as described in the literature [13], and depicted on Figure 1.

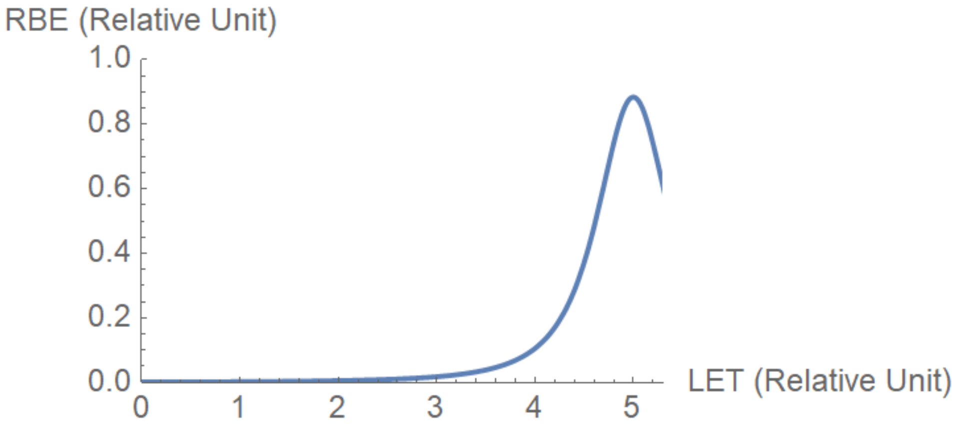

Figure 1: *Arbitrary representation of the RBE with dependence on LET, provided by data from literature [13].*

Herein, the present goal is to investigate if the coupling of the electromagnetic fields and the high energetic electrons will change the LET and the RBE, under the hypothesis that the magnetic and electric fields will alter the trajectory of charged particles in the human tissue but not the collision phenomena. Therefore, energy loss and trajectory may be treated separately, and coupled by a correction factor.

2. MATERIALS AND METHODS

Primarily, the analysis of the particle's trajectory was described by its motion equations, following the determination of how the path may affect the LET calculated by the Bethe-Bloch's formula. The second step was to show whether there is a change in the LET values following the mathematical models and the computer simulations. The hypothesis was that the changes in LET drive us to affirm that the RBE is also changed due to the relation between the two quantities.

The effectiveness of the electron radiation on the tissue can be quantified by the absorbed dose on the tissue, which is the absorbed energy per mass unit (measured in Gray) in the material that absorbed such energy. The absorption is intrinsically linked with the electron's LET, which is related to the energy transferred to the tissue. The present model pursued the mathematical development of the electron stopping power modified by an arbitrary controlled magnetic field.

2.1. Motion Equations

Different of electric fields, magnetic forces do not change the kinetic energy of an electron. However, an exotic trajectory occurs if uniform magnetic and electric fields are present, permeating the medium in the r-direction and acting on a charged particle [14]. Suppose that an H vector in the x-direction and an external E vector in the z-direction are present. A charged particle is moving from the origin; what non-collision path will it follow?

The position and velocity of the particle at any time t can be described by the vectors:

$$\boldsymbol{r} = (x(t), y(t), z(t));$$
$$\boldsymbol{v} = (\dot{x}, \dot{y}, \dot{z});$$
$$\boldsymbol{a} = (\ddot{x}, \ddot{y}, \ddot{z}) \tag{1}$$

Starting from Lorentz's force, applying Newton's second law, and separating the coordinates, the following differential equations are addressed:

$$\boldsymbol{v} \times \boldsymbol{H} = H\dot{z}\hat{\boldsymbol{y}} - H\dot{y}\hat{\boldsymbol{z}};$$
$$\boldsymbol{F} = Q(\boldsymbol{E} + \boldsymbol{v} \times \boldsymbol{H}) = Q(E\hat{\boldsymbol{z}} + H\dot{z}\hat{\boldsymbol{y}} - H\dot{y}\hat{\boldsymbol{z}}) = m\boldsymbol{a} = m(\ddot{x}\hat{\boldsymbol{x}} + \ddot{y}\hat{\boldsymbol{y}} + \ddot{z}\hat{\boldsymbol{z}}) \tag{2}$$

Separating the y and z coordinates, the differential equations are found:

$$\ddot{x} = 0, \ddot{y} = \omega\dot{z};\ \ddot{z} = \omega\left(\frac{E}{H} - \dot{y}\right);\ \omega \equiv \frac{QH}{m}\ (cyclotron\ frequency) \tag{3}$$

This is a coupled differential equation system. The solution is:

$$x(t) = C_1 + C_2 t;$$
$$y(t) = \frac{1}{\omega}[C_4 sin(\omega t) - C_6 cos(\omega t) + C_6] + \left(\frac{E}{H}\right)t + C_3;$$
$$z(t) = \frac{1}{\omega}\left[C_4 cos(\omega t) - C_6 sin(\omega t) - C_4 + \frac{E}{H}\right] + C_5 \tag{4}$$

Consider a particle starting from the origin with an initial speed$\boldsymbol{v_0} = (\dot{x}_0, \dot{y}_0, \dot{z}_0)$. These initial conditions determine the constants C_1, C_2, C_3, C_4, C_5 and C_6.

$$C_1 \equiv 0;\ C_2 \equiv \dot{x}_0;\ C_3 \equiv 0;\ C_4 \equiv \frac{H\dot{y}_0 - E}{H};\ C_5 \equiv -\frac{E}{H\omega};\ C_6 \equiv \dot{z}_0 \tag{5}$$

2.2. Energy loss per unit of unidirectional length

Based on the Bethe-Bloch's equation [15, 16], the energy loss per unit of length, in the arbitrary x-direction is:

$$-\frac{dE}{dx} = K\frac{Z}{A}\frac{z^2}{\beta^2}\left[\frac{1}{2}ln\left(\frac{2m_e\gamma^2c^2\beta^2W_{max}}{I^2}\right) - \beta^2 - \frac{\delta(\beta\gamma)}{2}\right] \tag{6}$$

Where:

$K = 2\pi N_A r_e m_e c^2$

$N_A = Avogadro's\ number;$

$r_e = classic\ electron\ radius;$

$m_e = electron\ mass;$

$c = speed\ of\ light;$

$\beta = relative\ velocity = \frac{v}{c};$

$\gamma = Lorentz\ Factor = (1-\beta^2)^{-\frac{1}{2}};$

$z = Atomic\ number\ of\ incident\ particle, -1\ for\ electrons\ and\ 1\ for\ positrons;$

$M = Mass\ of\ incident\ particle, m_e\ for\ electrons;$

$Z = atomic\ number\ of\ medium;$

$A = mass\ number\ of\ medium;$

$I = mean\ excitation\ energy;$

$\delta = density\ correction;$

And,

$$W_{max} = \frac{2m_e\gamma^2c^2\beta^2}{\left[1 + 2\gamma m_e + \left(\frac{m_e}{M}\right)^2\right]} \tag{7}$$

In which W_{max} is the maximum energy transfer per collision, and v is the module of the velocity.

Taken the motion equation, Eq. 4, it is possible to calculate the amount of loss dE into the differential path, dr, on the helical trajectory. Here, the assumption was that collisions might not remove the particles from the helical trajectories imposed by the E and H fields. In order to generalize Eq. 6, in a 3-dimensional motion and obtain an analytical and simplified expression for dr, the following relations are applied:

$$r = \sqrt{x^2 + y^2 + z^2} \rightarrow \frac{dr}{dx} = \frac{\dot{x_0}t}{\sqrt{x^2 + y^2 + z^2}} \rightarrow dx = dr\frac{\sqrt{x^2 + y^2 + z^2}}{\dot{x_0}t} \quad (8)$$

$$dx = dr\ C_F\ (C_F \equiv correction\ factor) \quad (9)$$

Where C_F is defined as:

$$C_F \equiv \frac{\sqrt{x^2 + y^2 + z^2}}{\dot{x_0}t}$$

$$= \frac{1}{\dot{x_0}t}\left\{2\left(\frac{H\dot{y}_0 - E}{H\omega}\right)^2 + \left(\frac{\dot{z}_0}{\omega}\right)^2 + 2\left(\frac{\dot{z}_0}{\omega}\right)^2\frac{Et}{H} + \left(\frac{Et}{H}\right)^2 + \dot{x_0}^2t^2 + \left(\frac{\dot{z}_0}{\omega}\right)^2 cos(2\omega t)\right.$$
$$- 2\frac{\dot{z}_0}{\omega}\left(\frac{H\dot{y}_0 - E}{H\omega}\right)sin(2\omega t) + \left[4\frac{\dot{z}_0}{\omega}\left(\frac{H\dot{y}_0 - E}{H\omega}\right) + 2\left(\frac{H\dot{y}_0 - E}{H\omega}\right)\left(\frac{E}{H}\right)\right]sin(\omega t)$$
$$\left. + \left[\left(\frac{H\dot{y}_0 - E}{H\omega}\right)^2 + \frac{\dot{z}_0}{\omega}\left(\frac{Et}{H} - \frac{\dot{z}_0}{\omega}\right)\right]cos(\omega t)\right\}^{\frac{1}{2}} \quad (10)$$

The Bethe-Bloch's formula, considering the presence of uniform electric and magnetic fields, becomes, by replacing the dx value given on the Eq. 9 on the Eq. 6:

$$-\frac{dE}{dr} = C_F K\frac{Z}{A}\frac{z^2}{\beta^2}\left[\frac{1}{2}ln\left(\frac{2m_e\gamma^2c^2\beta^2W_{max}}{I^2}\right) - \beta^2 - \frac{\delta(\beta\gamma)}{2}\right] \quad (11)$$

It is important to observe that the equation is now relative to dr taken the direction of the motion trajectory in x, dx.

3. RESULTS AND DISCUSSION

3.1. Motion Trajectories

Let us simulate the motion equations, depicted in Eq. 4, for the particle's path of a particle with mass m_e and charge *e*, in a 15 T magnetic field (H), and a 1000 N/C electric field (E). It is possible to observe the helical motion around a straight line along the x-axis, similar to the cycloid motion that occurs in two-dimensions if the particle is initially at rest. Figure 1 shows the descriptive particle motion.

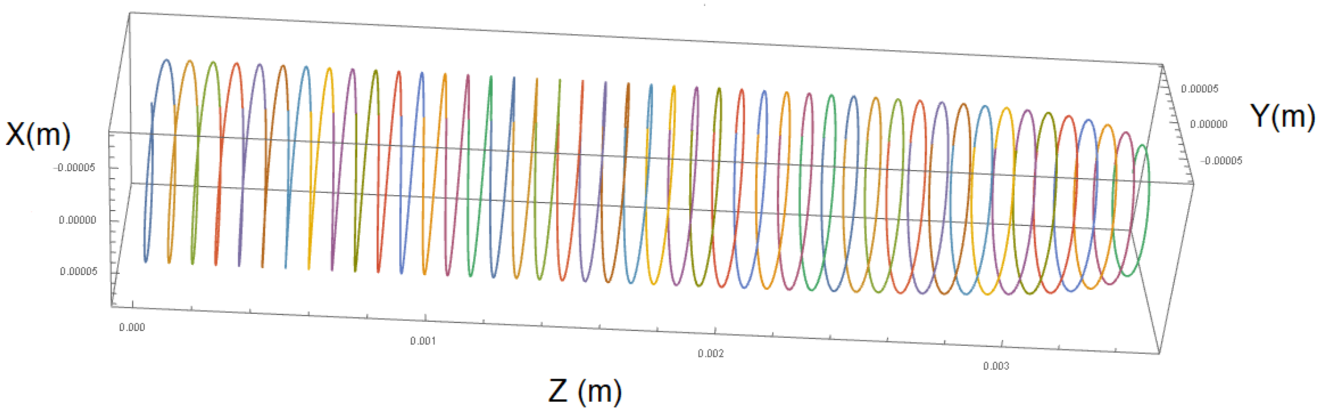

Figure 2: *Part of a 5 MeV particle helical motion when modulated by a 15 T magnetic field and a 1000 N/C electric field, in water, with an arbitrary and positive initial direction that is non-parallel to H (z-axis).*

3.2. Energy Loss per Unit of Length per unit of trajectory

We have considered a unique unidirectional trajectory, without dispersions, or angular changes in the direction of the particle after collision. The value of the correction factor, observed on the Eqs. 9, 10 and 11, depends on the three velocity coordinates, which will depend on the initial motion direction. In the example depicted on Fig. 2, considering a speed of 0.9957c that corresponds to a 5 MeV energy, a time of interaction in the order of 3.5 ps, a 15 T magnetic field and a 1000 N/C electric field, the theoretical correction factor is 1.03137. This value is greater than 1, indicating an increase of the LET by 3,1% in this case. Indeed, such value depends only on the value of the H and E fields, and the mass and charge of the incident particle (Eq. 10). In addition, it is not related to the density effect of the material (Z^2). H and E have no uncertainty because both are theoretical input values; the mass and energy of the electron have both very small uncertainties; for these reasons the theoretical uncertainty of C_F can be assumed as negligible

.

3.3. Analysis of the LET and RBE

The Relative Biological Effectiveness (RBE) is directly proportional to LET, until a maximum point, as depicted in Fig. 1. The LET is calculated by the collision dE/dx, which is the same used in Bethe-Bloch's formula observed on Eq. 6. In the presence of the magnetic and electric fields, such parameters will be changed, as shown by the correction factor obtained on Eq. 10. If the LET is increased by 3% (using the values given above), it will cause a slight change on the RBE as well, since both quantities are related.

Our assumption of a helical motion all over the path may not be supported for the full domain of electrical energy and magnetic and electric fields. It is a challenge to follow the charged particle trajectory on a long range into the tissue, since collisions change the direction of the velocity in relation to the H and E fields, altering the forces caused by the electric and magnetic fields. Therefore, the changes in LET will be randomly follow the changes in the directions after collisions. A Monte Carlo code shall be addressed to study the charged particle motion and collisions in the medium, in which magnetic and electric fields are present, predicting particles motion and collisions in non-uniform E and H fields.

In the example presented herein, the energy deposition per unit of path will be greater than its value without the magnetic field, slightly increasing the LET on the tissue by about 3% of its magnitude and decreasing the length of the trajectory (obtained directly using the Eq. 10 an the Eq. 11). The result refers to the theoretical analysis of LET under static electric and magnetic fields. Future experiments may confirm its relevance on real human tissue.

4. CONCLUSION

The findings demonstrated that the energy loss in function of the path length, expressed by Bethe-Bloch’s equation, assumes different values according to the presence of electric and magnetic fields.

In addition, it is possible to affirm that a change on the LET, by an insertion of external magnetic and electric fields, will lead to a change in the RBE due to their close relation, depicted by Fig. 1. Indeed, it is necessary to confirm whether the changes are relevant or not to real biological systems through *in vitro* experiments.

The *in vitro* experiments shall be addressed in the near future, based on the Semiconductor Physics Lab (Physics Department – ICEX/UFMG) and in the Radiobiology Lab (Nuclear Engineering Department – EE/UFMG). A superconducting magnet shall provide the magnetic field intensity. The B value, and both the cell culture type and the radioactive source intensity are yet to be chosen.

This model and the incoming experiments shall be addressed on the radiotherapy field, to provide reliable data to support the combined use of the conventional electron therapy and electromagnetic fields.

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