# EFFECTS OF X-RAY IRRADIATION ON BODY WATER, AND ELECTRICAL PROPERTIES OF RAT TISSUES

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*Abstract*. *In vivo* measurements for whole body exposed to doses 50–600 rads and *ex vivo* measurements of dielectric properties of excised tissues are carried out at 10 days post-irradiation using multiple frequency bioelectrical impedance analysis (MFBIA). Changes in the extracellular water (*ECW*) and total body water (*TBW*) of rats are estimated. The results show significant increases above non-irradiated rats in intracellular water (*ICW*) by 11.61% ($P = 0.0001$) and *ECW* by 9.95% ($P = 0.0216$) of rats exposed to 600 rads. These significant changes indicate a reduced activity of the ion pumps, which leads to changes in ion distribution between inter- and extra-cellular spaces. Dielectric properties (permittivity and conductivity) of freshly excised samples are measured at frequencies between 100 Hz and 5 MHz using two-electrode technique. The results for liver and muscle tissues reveal differences between non-irradiated and irradiated tissues (600 rads). The irradiation of rats with 600 rads causes 17% ($P = 0.1139$) non-significant decrease in the conductivity and 26% ($P = 0.0091$) significant decrease in the permittivity of liver below that of non-irradiated. While irradiation of rats causes significant increases by 19% ($P = 0.005$) and 25% ($P = 0.0217$)) in conductivity and permittivity of rat muscle tissues, respectively. Also the increase of irradiation doses (50 to 600 rads) causes a decrease on the characteristic frequency (the point of the maximum value for the reactive component of impedance). This indicates that there is a variability of the electrical properties which could be used as indicator to determine the degree of damage of tissue due to irradiation.

*Key words*: Extracellular water, conductivity, permittivity, muscle tissues.

## INTRODUCTION

The radiation affects every component of the exposed tissue and it is likely to damage both the parenchymal and vascular tissues. Previously, the findings did not clarify whether interphase death of parenchymal cells was a direct response to irradiation or resulted indirectly from radiation-induced vascular damage [6, 15, 25, 29]. The severity of radiation damage is dependent on dose with a latent period

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that varies with the type of tissue involved [7, 21, 26, 31]. Factors influencing radiation response include dose, dose rate, radiation quality, field-size and intrinsic radiation sensitivity. Some studies explore the potential of electrical impedance spectroscopy (EIS) to deduce and monitor the progression of radiation-induced tissue injury in the treatment field through frequency-dependent changes in electrical properties [21]. The effect of whole-body X irradiation on the electrical properties of rat tissues has been investigated in considerable detail to elucidate the underlying mechanisms. Bioelectrical impedance analysis is attractive as a method which is minimally invasive, rapid and harmless for the estimation of body composition. Bioelectrical impedance analysis measures the impedance of the body to the flow of an electrical current. The electrical impedance (or conductivity) of a tissue depends upon its fluid and electrolyte content, thus it is related to the amount of water in the body [17, 18]. Multiple frequency bioelectrical impedance analysis (MFBIA) has been used for the measurement and prediction of *TBW* and *ECW* [2, 27]. It must be pointed out that most biological structures are composed of cells and hence exhibit different properties in different types. The dielectric properties of a biological tissue result from the interaction of electromagnetic radiation with its constituents at the cellular and molecular level and the dielectric properties of tissues have been widely reviewed [8, 11, 12, 13, 16, 22, 28, 30]. Both conductivity and relative permittivity vary widely between different biological tissues and the parameters are frequency dependent [4, 10, 24].

## MATERIALS AND METHODS

The experiments are carried out with a total of 54 adult albino rats weighing 130 g on average. The rats are divided into two main groups: 6 rats for controls (non-irradiated) and 12 subgroups each of 4 rats. Each subgroup is confined, in a rectangular plastic box and exposed to X-rays from a clinical therapeutic 6 MV linear accelerator facilities at faculty of Medicine, Alexandria. Each of 12 subgroups exposed to the following doses: 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550 and 600 rads, respectively. At specific 10 days post- irradiation time, *In vivo* measurements, within the alive and anaesthetized rats are carried out, then the other *ex vivo* measurements, with the organ just excised and in the minutes following its extirpation are performed.

### *IN VIVO* MEASUREMENTS OF WHOLE BODY

The weighing of the rats was recorded to the nearest 0.1 g, then the rats were anesthetized with ether. Hair was removed from the dorsal surface of the head and body for electrode placements. The needle electrodes were placed subdermally on the body to give the most reliable results [14]. Bioimpedance is measured with stainless steel needles electrodes. The rat is positioned on a nonconductive surface

to eliminate interference of electrical induction. Body orientation was with the dorsal surface upwards. On the midline, the source insertion electrodes on rat body are inserted 5 mm subcutaneously. The sites of insertion as described by Hall *et al*., 1989 [13] and applied by Cornish *et al*., 1992 [2]. The needle electrodes are inserted subcutaneously along the dorsal midline of the body. One distal drive electrode was in-line with the superior edge of the orbit, and the other was inserted 3 cm from the base of the tail. Detector electrodes were positioned; one was in-line with the posterior opening of the pinna, and the other was in-line with the iliac spines. Body length was measured between positions of electrodes. MFBIA is as a method to predict total body water (*TBW*) and extracellular water (*ECW*) by measuring the impedance at the characteristic frequency and at zero frequency, respectively [3]. This cannot be readily measured practically, but it may be estimated by extrapolation of Cole-Cole parameters obtained over a range of frequencies. For each rat, the impedance (*Z*) is measured over the frequency range 2 KHz to 5 MHz for 73 frequency points. The electrical impedance (or conductivity) of a tissue depends upon its fluid and electrolyte content. Total body impedance will thus be related to the amount of water in the body [9, 27, 33]. The wideband of electrical impedance data measurement for each rat is fitted to the Cole-Cole expression given [1] as:

$$Z^* = R_0 + \frac{\left(R_0 - R_\infty\right)}{1 + \left(\mathrm{j}\omega\tau\right)^{1-\alpha}} \tag{1}$$

where ω is the angular frequency, $R_\infty$ is the high frequency resistance, $R_0$ is the low frequency resistance, τ is the relaxation time constant, α is the parameter that allows for the broadening of the dispersion. Total body water (*TBW*, g) and extracellular water (*ECW*, g) are predicted from the MFBIA measurements using the prediction equations for rats of Cornish *et al.*, 1992 [3]:

$$TBW = 309.9 \times \frac{L^2}{Z_\mathrm{c}} + 30.0\,,\ ECW = 108.3 \times \frac{L^2}{R_0} + 13.8 \tag{2}$$

$$ICW = TBW - ECW \tag{3}$$

where $L$ is the measuring electrode distance (cm), $Z_\mathrm{c}(\Omega)$ is the impedance at the characteristic frequency and $R_0$ (Ω) is the resistance at zero frequency. The ratio of *ICW/ECW* is also estimated.

## *EX VIVO* MEASUREMENTS OF EXCISED TISSUES

All the rats are sacrificed, and the tissues of liver and muscle are excised from each sacrificed animal. Electrical impedance of each excised tissue is measured between 100 Hz and 5 MHz for 93 frequency points using a capacitor

cell technique as shown in (Fig. 1). It consisted of two circular parallel silver electrodes with a silver chloride coating, having a diameter of 1.0 cm (surface area = 0.785 $cm^2$). Silver-silver chloride provides a good contact transfer with minimum polarization. The two electrodes are enclosed in chamber made of Plastic Glass (Lucite). One of the electrodes is fixed at the bottom of chamber and the other electrode is adjustable to accommodate a variety of tissue sample sizes.

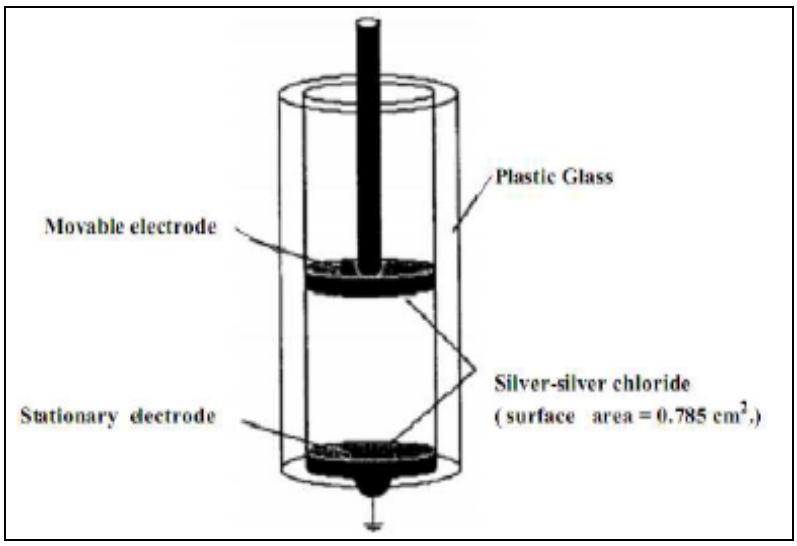



Fig. 1. Capacitor cell consisted of two circular parallel silver electrodes.

To facilitate measurements, a computer-controlled automatic scanning and data recording are performed with an impedance LCR meter (HIOKI 3532-50 LCR meter 42 Hz to 5 MHz HiTester, Japan). The measured complex impedance is:

$$Z_{\mathrm{m}}^{*} = R_{\mathrm{m}} + \mathrm{j}X_{\mathrm{m}} \tag{4}$$

where $R_{\mathrm{m}}$ and $X_{\mathrm{m}}$ are measured resistance and reactance of impedance data which are converted to their volume independent tissue property equivalents by exploiting (the two-parallel plane electrodes) as

$$Z_{\mathrm{m}}^{*} = (R_{\mathrm{m}} + \mathrm{j}X_{\mathrm{m}}) \cdot \frac{A}{d} \tag{5}$$

The parameters, conductance (*G)* and capacitance (*C)* in terms of *Z*-components are:

$$G = \frac{R_{\mathrm{m}}}{R_{\mathrm{m}}^2 + X_{\mathrm{m}}^2}, \; C = \frac{X_{\mathrm{m}}}{\omega(R_{\mathrm{m}}^2 + X_{\mathrm{m}}^2)} \tag{6}$$

From these parameters, the conductivity (σ) and relative permittivity (ε') which, depending on the nature of the sample and relating to cell constant factor $\left(\frac{d}{A}\right)$, can be calculated as:

$$\sigma = \frac{d}{A}.G\ ,\ \varepsilon' = \frac{d}{A}.\frac{C}{\varepsilon_0} \tag{7}$$

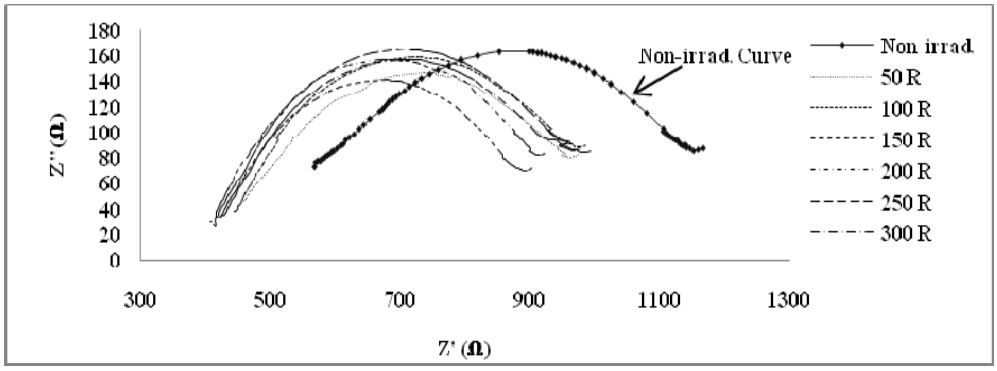
where $d$ and $A$ are the average separation between the electrodes and the surface area of electrode unit, (approximately the thickness length and cross-sectional area of the sample) and ω is the angular frequency of the field (radians per second) and $\varepsilon_0$ is the permittivity of free space ($8.85 \times 10^{-12}$ F/m).

## RESULTS AND DISCUSSION

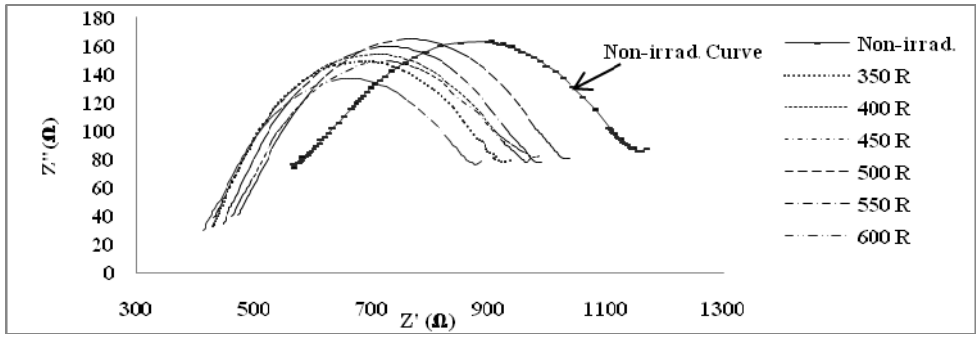
Impedance measurements of whole body for non-irradiated and irradiated rats are carried out and presented in two plots. Fig. 2a and Fig. 2b show spectral data for whole body in the complex impedance plane for groups exposed to doses (50–300 R) and doses (350–600 R) respectively. At low frequency impedance (right portion of plot) in both figures, it shows the separation between the curves of non-irradiated and irradiated rats themselves. There is no clear systematic separation between the curves of irradiated rats themselves. A slight shift in the real component of impedance can be noticed at high frequency (left portion of plot) between the curves of non- and irradiated rats and it is clearly evident in both figures (2a, b). This shift of high frequency impedance suggests that there is a change in the ionic properties of the intra and extracellular material. The studies, using external beam irradiation techniques, indicate greater levels of inflammation, and recorded larger shifts in high frequency impedance [21, 23]. The impedance spectra (Fig. 2a, b) are fitting the Cole-Cole equation (1) to extract the Cole parameters, τ, α, $R_\infty$, $R_0$ and using them to estimate characteristic impedance ($Z_c$) and the water compartments (*TBW*, *ECW*) as shown in Table 1.

The first column in Table 1 represents several different doses studied. In Table 1 it can be noticed that the relaxation time (τ) of all irradiated rats are in a higher value than the value of non-irradiated rats which indicate a decrease in characteristic frequencies as doses increase. From this table it is also noticed that the distribution parameters (α) of all irradiated rats are in a higher value than that value of non-irradiated rats. This demonstrates a clear difference in the heterogeneity of the tissues which may be due to a direct or indirect effect of irradiation. The characteristic impedance ($Z_c$) (or an impedance which has a

maximum reactance) of all irradiated rats is in a lower value than the value of non-irradiated rats (682.92 Ω). The three (4rd, 5th, and 6th) columns in Table 1 give characteristic impedance, total body water (*TBW* (*g*) = *ECW* + *ICW*) relative to its whole weight (*W*′ (g)) and extracellular water (*ECW*), respectively. The last column, in this table, gives the ratio value of an intracellular (*ICW* = *TBW* – *ECW*) to extracellular water (*ECW*). The ratio value for non-irradiated rats in this study is (2.44), which is very close to the previously reported values given by Yokoi [33] and Nielsen [19]. They found that the ratio (*ICW* / *ECW*) of normal rats was (2.42). In this study, the ratio values of irradiated rats have values greater than of the non-irradiated ones (> 2.45).




**a)**




**(b)**

Fig. 2. Plots of spectral data for whole body in the complex impedance plane grouped by non-irradiated and irradiated rats. (a) exposed to doses (50–300 R) and (b) exposed to doses (350–600 R) at specific time 10 days post-irradiation.

*Table 1*

Cole-Cole parameters and water content calculations. Each reading is the mean of determinations carried out on non- and irradiated rats

| Dose (rads) | τ(s) | α | $Z_c$ (Ω) | *TBW* (g/100 g) | *ECW* (g/100 g) | *ICW/ECW* |
|---|---|---|---|---|---|---|
| 0 (n=6) | 7.28E–06 | 0.538 | 682.92 | 61.42 | 17.8 | 2.45 |
| 50 (n=4) | 8.22E–06 | 0.524 | 545.47 | 67.06 | 18.12 | 2.7 |
| 100 (n=4) | 1.07E–05 | 0.452 | 560.87 | 71.44 | 20.11 | 2.55 |
| 150 (n=4) | 8.64E–06 | 0.497 | 518.86 | 71.65 | 19.62 | 2.65 |
| 200 (n=4) | 1.12E–05 | 0.441 | 515.52 | 72.57 | 19.29 | 2.76 |
| 250 (n=4) | 9.98E–06 | 0.498 | 534.61 | 72.53 | 19.97 | 2.64 |
| 300 (n=4) | 1.28E–05 | 0.5 | 556.51 | 71.19 | 19.88 | 2.58 |
| 350 (n=4) | 1.24E–05 | 0.509 | 545.87 | 71.4 | 19.4 | 2.68 |
| 400 (n=4) | 1.17E–05 | 0.475 | 551.36 | 71.47 | 20.25 | 2.53 |
| 450 (n=4) | 9.68E–06 | 0.446 | 566.53 | 69.37 | 18.68 | 2.71 |
| 500 (n=4) | 1.11E–05 | 0.445 | 590.68 | 75.36 | 20.72 | 2.64 |
| 550 (n=4) | 1.19E–05 | 0.487 | 519.78 | 72.38 | 19.44 | 2.72 |
| 600 (n=4) | 2.09E–05 | 0.404 | 531.24 | 76.81 | 21.74 | 2.55 |

In addition to the figures available in Table 1, Fig. 3 represents the curves of an intracellular (*ICW*) and extracellular (*ECW*) fluid as a function of doses. It is evident from this plot that *ICW* increased over non-irradiated. The increased difference in *ICW* values between non- and irradiated rats (600 R), normalized to non-irradiated value in percent, based on statistical analysis is 11.61% ($P$ = 0.0001). Whereas, the increased difference in *ECW* is 9.95% ($P$ = 0.0216). These differences are considered to be statistically significant (probability associated with Student's t-test). The significant changes indicating reduced activity of the ion pumps lead to changes in ion distribution between inter- and extra-cellular spaces. Or more specifically, functional abnormality of sodium-potassium pump activity leads to little depolarization of the cell, resulting in inflow of water and sodium, and causing cell swelling. Fig. 4 shows characteristic frequency as a function of doses for non- and irradiated rats. It can be noticed that an increase of the irradiation doses (50 to 600 rads) causes a decrease on the characteristic frequency. This indicates that there is a variability of the electrical properties of irradiated tissues as a function of dose.

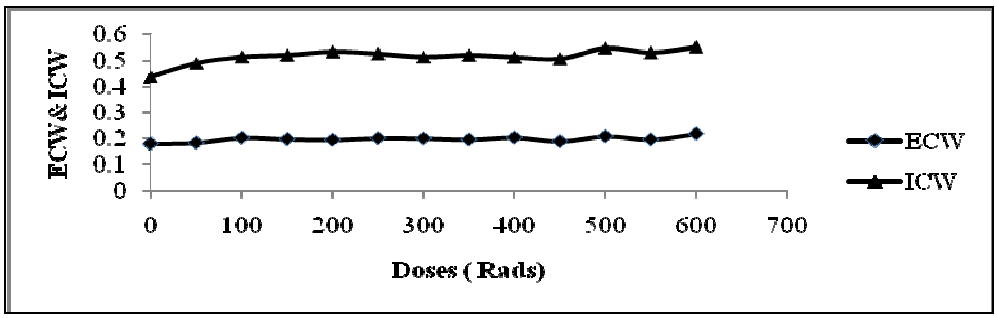



Fig. 3. Extracellular and intracellular water with respect to body weight as a function of irradiation. The *ICW* & *ECW* curves represent the average response of all non- and irradiated rats.

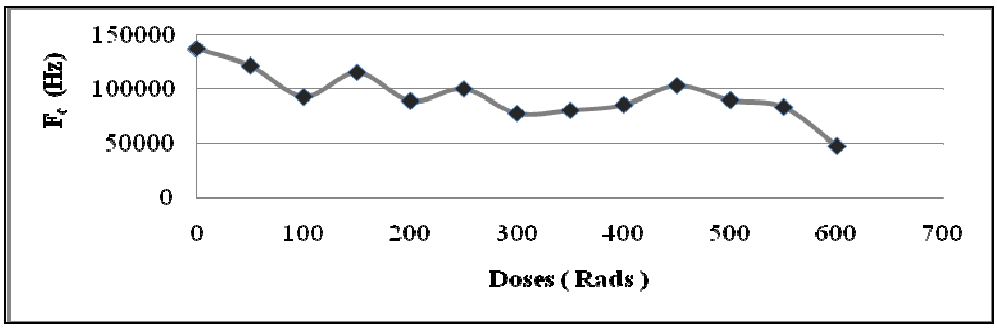
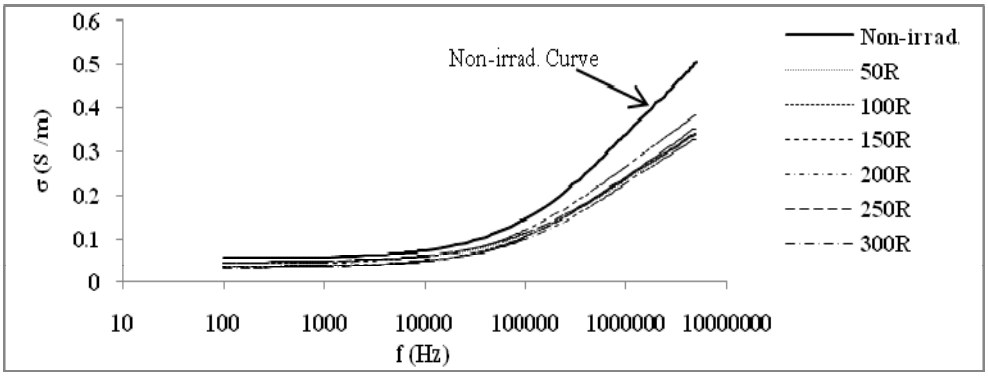



Fig. 4. Characteristic frequency ($F_c$) for whole body of non-and irradiated rats as a function of doses at 10 days post-irradiation time. Each point is the mean value from 6 non-irradiated and 4 irradiated rats.

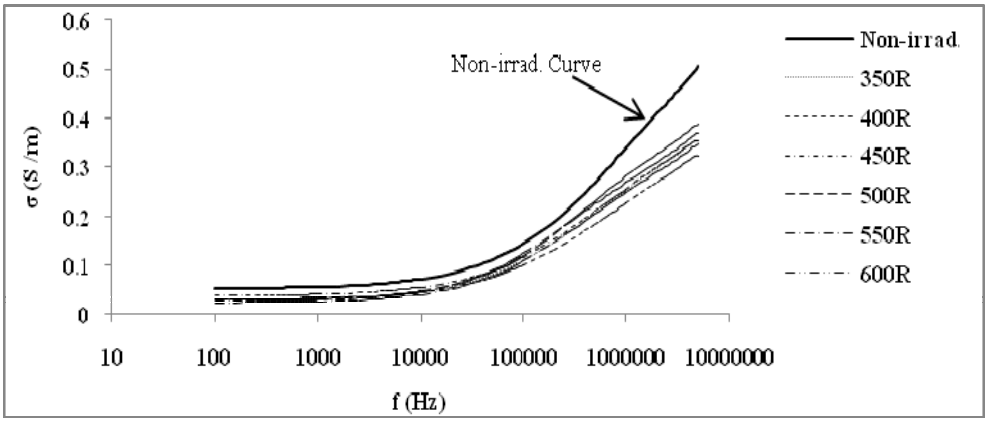
## CONDUCTIVITY AND PERMITTIVITY

The dielectric properties of liver and muscle tissues are analyzed and discussed. Fig. 5 (a, b) and Fig.6 (a, b) represent the conductivity curves for liver and longitudinal muscle (ML) tissues respectively. Each figure represented in both plots, figure (a) for doses between 50–300 rads) and (b) for doses between (350–600 rads). In Fig. 5a, b, the conductivity spectra of the liver show a separation between the curves for non- irradiated and irradiated tissues. In both figures (a, b) they appear to decrease by a similar amount at low frequency, gradually dropping (reducing) below the non-irradiated curve at high frequency (>100 kHz). The reduction conductivity would be explained by a change in tissue biochemistry in which an increase in their density would be consequently a decrease in high frequency conductivity. In Fig. 6a, b, the conductivity spectra of irradiated ML tissue at low and high frequency are elevated in both figures (a, b). At low frequency, the conductivity appears (Fig. 6a, b) to increase by a similar amount,

suggesting that low frequency conductivity would not be affected by a change in cell structure. At high frequency the conductivity (Fig. 6a, b) appears to increase gradually resulting a wide shift between non- irradiated and irradiated tissues. This wide shift at high frequency conductivity can be explained by a change in the conductivity of the inter- and/or intra-cellular fluid or alternatively, a decrease of small membrane-bound structures. The Cell injury as a consequence of cellular alterations may result from the inflammatory response in muscle tissue, due to direct or indirect effect of radiation. There are no decisive differences in the mechanisms of production of this damage [5, 13, 20, 32].

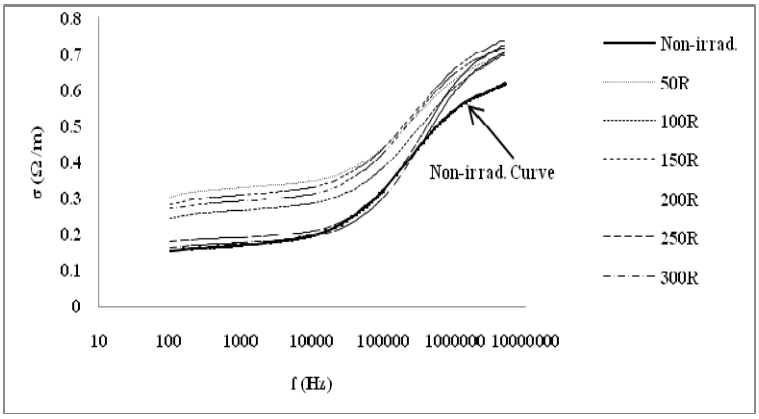



**(a)**

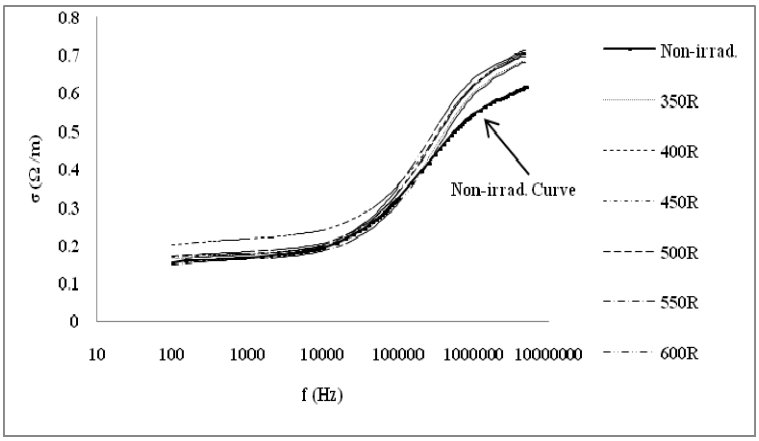



**(b)**

Fig. 5. Conductivity values of the liver as function of frequency for non-irradiated and irradiated rats. (a) exposed to doses (50–300 R) and (b) exposed to doses (350–600 R).




**(a)**

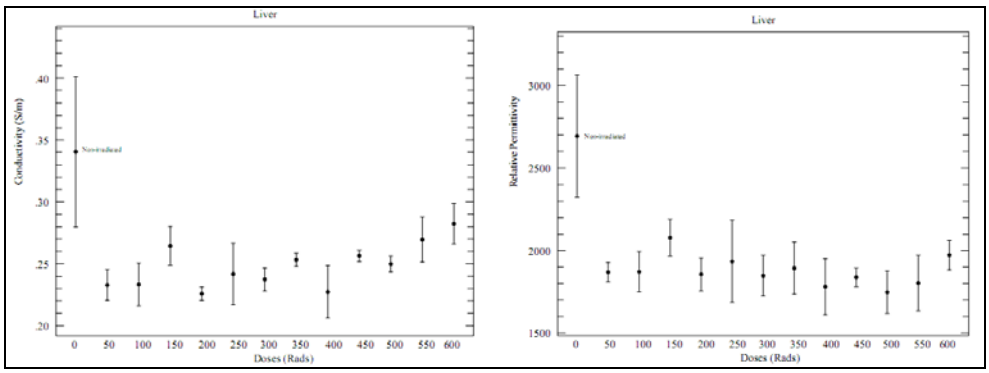



**(b)**

Fig. 6. Conductivity values of ML as function of frequency for non- and irradiated rats. (a) exposed to doses (50–300 R) and (b) exposed to doses (350–600 R).

More careful analysis of measurement variability in dielectric properties for tissues is important to demonstrate some changes in conductivity and permittivity for liver and longitudinal muscle tissues [7]. To do so, Fig. 7a, b show the comparison of conductivity and permittivity for liver tissues as function of doses at (1 MHz). In Fig. 7a, it can be noticed that the conductivity values at high frequency (1 MHz) for irradiated liver tissues are in range value (0.23 to 0.28 S/m). These values are lower than the value of non-irradiated tissues (0.34 S/m). With regard to the relative permittivity of the liver as in Fig. 7b, it has appeared that the permittivity values of all irradiated liver tissues decrease from $\varepsilon'_{50R} = 1870$ to $\varepsilon'_{600R} = 1800$, but remain lower than non-irradiated value ($\varepsilon'_{non\text{-}irrad.} = 2693$). The data

comparison chart results of an analysis of variance (ANOVA) statistical test is presented in Figure 7a, b for conductivity and permittivity respectively. An (ANOVA) test are performed on the 1 MHz conductivity and permittivity values, for liver and a multiple comparison test (with $P < 0.0001$) is used to further analysis which resulted in statistically different conductivity and permittivity readings. An ANOVA test showed significant differences between the magnitudes of the conductivity gained by groups ($P < 0.0001$). Based on statistical analysis, (Probability associated with Student's t-test), the percentage difference in conductivity values for liver at high (1 MHz) frequencies between non- and irradiated tissue (600 R), normalized to non-irradiated value is (–17.10%). This decrease difference is considered to be not statistically significant ($P = 0.1139$). In case of permittivity for liver as in Fig. 7b, the normalized value of relative permittivity at 1 MHz is (–26.78%). This decrease difference is considered to be statistically significant ($P = 0.0091$).

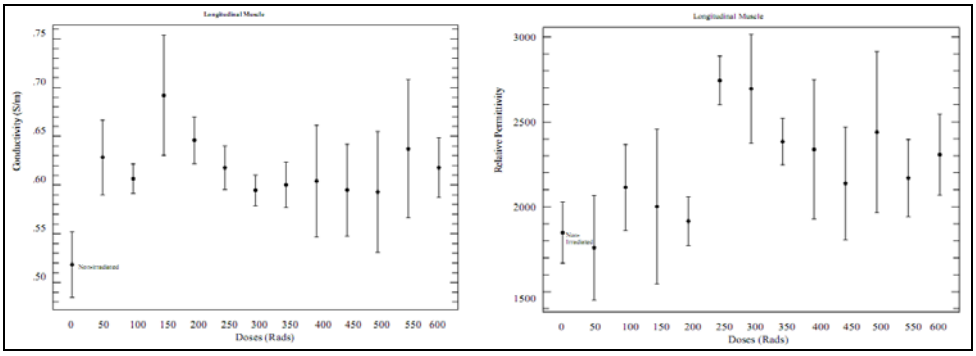



**(a)** **(b)**

Fig. 7 (a) Conductivity and (b) permittivity of livers at 1 MHz for non- and irradiated tissues, the errors bars shown on the graphs cover the range of means and indicate the variation within the particular group of four animals on any given dose. Means for each animal group are indicated by points along the error bars.

In case of muscle tissues, the analysis of data at high frequency (1 MHz) reveals that there exist differences on the conductivity and permittivity (Fig. 8a, b) between non- irradiated and irradiated tissues. In Fig. 8a), it has clearly appeared that the conductivity values of irradiated tissues at different doses are higher than non-irradiated value (0.518 S/m). The analysis of variance and a multiple comparison test on the 1 MHz conductivity values showed a significant difference between the magnitude of the conductivity gained by groups ($P = 0.0047$). When frequency (1 MHz) conductivity values for the non- and irradiated groups are compared, the conductivity is observed to increase with dose (Fig. 8a). The mean conductivity values for irradiated groups were significantly higher than for non-

irradiated group. Based on Student's t-test, the increased difference in conductivity values between non- and irradiated (600 R) tissues normalized to non-irradiated value is 19.21% ($P$ = 0.0046). This difference is considered to be statistically significant. In figure 8(b), data comparison chart results of (ANOVA) statistical test on the 1 MHz permittivity values showed a significant difference between the magnitude of the permittivity gained by groups ($P$ = 0.0006). The percentage difference in permittivity values between non-irradiated and irradiated (600 R) tissues normalized to non-irradiated value is 24.83% ($P$ = 0.0217). This difference is also considered to be statistically significant. According to this, the statistical significant differences observed in muscle tissues in both conductivity and permittivity indicated that the effects due to whole body exposure (50–600 R) do permanent damage and it early appeared in the muscle tissues than in other tissue (liver).




**(a)** **(b)**

Fig. 8 (a) Conductivity and (b) permittivity of longitudinal muscles at 1 MHz for non- and irradiated tissues, the error bars shown on the graphs cover the range of means and indicate the variation within the particular group of four animals on any given dose. Means for each animal group are indicated by points along the error bars.

## CONCLUSION

This work highlights how water compartment distribution and electrical properties of rat tissues are changed due to the effect of radiation. *ECW* and *TBW* are predicted using the prediction equations for rats of Cornish. By tracking variations in both *ECW* and *ICW*, Figures 2–4 demonstrate statistically a significant difference in *ICW* or *ECW* values between non-irradiated and irradiated rats (600 R). These significant changes may indicate that there is a reduced activity of the ion pumps, leading to changes in ion distribution between inter- and extra-cellular spaces. Figures 5–8, for liver and muscle tissues indicating that the decrease differences in dielectric properties for liver are non significant but the

increase difference in muscle tissues are significant. The effects due to whole body exposure have appeared early on muscle tissues than in others tissues (liver).

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