A Method for Extracting the Relevant MRI Information from Normoxic Polymer Gels Exposed to Low Doses

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Introduction

Different formulations for Polymer gels (MAGIC, BANG, MAGAS, PAGAT, etc.) for three-dimensional dosimetry have been proposed to increase gel sensitivity and stability.[1] The aim of gel dosimetry is to correlate polymerization induced by ionizing radiation at a point in a gel matrix with its location in the matrix. In the present work several factors related to gel sensitivity and methods to increase it had been explored. The working hypothesis is that by extracting information related directly to the polymerization process gel sensitivity can be enhanced. The standard methods for gel data extraction and analysis are MRI relaxometry (R_2) and optical CT transmittance. The former method provides an average relaxation rate which includes contributions not related to the polymer formation and the latter method has important limitations due to gel sample transparency. In what follows, a combined approach which includes all these methods is used to investigate the polymerization process in a normoxic[2] (normal room atmosphere) standard MAGIC gel with 9% of methacrylic acid.[2] Although gel response to a wide range of dose is the aim of our studies, in this presentation only the gel response to low dose will be considered since it is of interest in IMRT applications and it has received little attention in the literature.

Materials and Methods

The different experiments performed using the proposed combined techniques are summarized in Fig. 1.

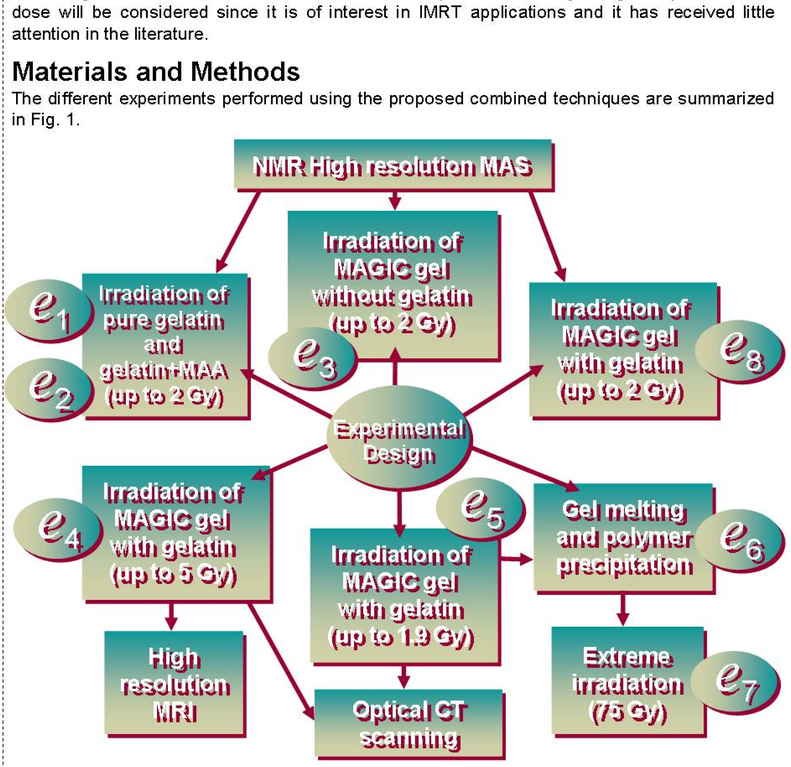

Fig. 1. ***Experimental design*** *(particular tests are labeled as e_i, i=1,... ,8, and the techniques used are showed inside the square boxes).*

• **Experiment 1 (e_1):** Two samples of pure gelatin were prepared, one sample was not irradiated and the other was irradiated to a dose of 2 Gy. Both samples were scanned in a magnetic resonance 600 MHz spectrometer using a high resolution magic angle spinning (HRMAS) technique. The purpose of the experiment was to induce changes in the properties of the gel matrix. To obtain an optimized spectra, D_2O was used as the main solvent. This solvent was also used in experiments e_2 e_3 and e_8.

• **Experiment 2 (e_2):** Four samples combining gelatin and methacrylic acid (in absence of other ingredients) were irradiated to doses from 0 to 2 Gy, and scanned using the same HRMAS technique as in e_1. The purpose of this experiment was to investigate the role of the gelatin in the polymerization process, which still is not well understood.[1,3]

• **Experiment 3 (e_3):** Four samples of MAGIC gel without gelatin were irradiated to doses from 0 to 2 Gy and scanned using the same technique as in e_1.The purpose of this experiment was to further investigate the role of gelatin in the polymerization process.

• **Experiment 4 (e_4):** Eleven samples of MAGIC gel were prepared following the standard recipe[2] by adding the methacrylic acid at 37°C. One sample was not irradiated and the other ten samples were irradiated either in a ^{60}Co beam or in a 6 MV photon beam to doses from 0 to 5 Gy. The samples were then scanned in a 7-Tesla MRI Bruker BioSpec spectrometer using a high resolution technique and also a Carr-Purcell-Meiboom-Gill sequence (broad band) with 132 echos separated by 9 ms.

• All relaxation signals amplitude and related quantities were analyzed with a stochastic algorithm for the inversion of the Laplace transform (which is an ill-posed inverse problem)[5,6] as depicted in *Fig. 2*. This signal analysis makes the decomposition procedure independent of artifacts due to changes in local magnetic fields. The relaxation rate might be displaced but the associated area is invariant.

• The relaxation signal amplitude dependence on the number of solvated water molecules could lead to a significant **signal loss** or **signal quenching** if the relevant sites for solvation of water molecules or hydrogen atoms are lost in chemical reactions with free radicals. This **signal loss** could lead also to important changes in $T_{2,exp}$ which are difficult to detect in the absence of a proper relaxometric analysis.

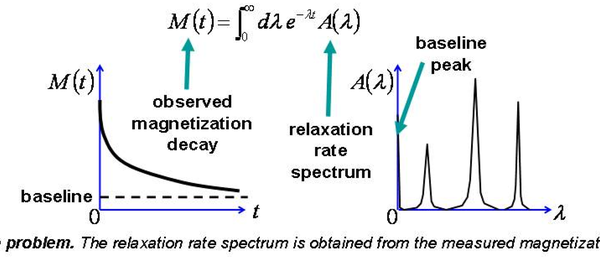

Fig. 2. ***Inverse problem.*** *The relaxation rate spectrum is obtained from the measured magnetization.*

• The average R_2 values are dependant on the fraction contributions from the average relaxation rates of the mobile, gelatin and polymer pools.[4] The average R_2 values can be expressed as function of the different fractions by the following equation:

$$\frac{1}{T_{2,exp}} = \frac{f^H_{mob}}{T_{2,mob}} + \frac{f^H_{poly}}{T_{2,poly}} + \frac{f^H_{gela}}{T_{2,gela}}$$

• **Before irradiation** the mobile pool contains the protons from water and monomers.
• **During irradiation** the monomers were gradually transferred to the polymer pool and gelatin pool remain unchanged. This process is represented in *Fig. 3*.

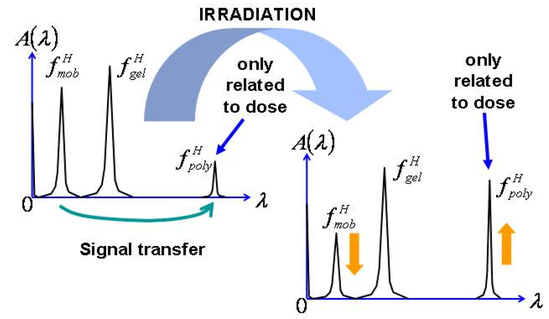

Fig. 3. ***Fractions changes during the irradiation process.*** *Note the increase of the polymer fraction.*

•The ten samples were also scanned in an optical CT. Optical density provides an independent and significant way to check the **loss of solvation sites** since the gel optical properties (dielectric constant) depend strongly on the water structure at those sites[7,8]. The polymers in MAGIC Gel (polymethacrylic acid and gelatin) provide the natural frame for the formation of water structures. In this sense the data that can be extracted from a relaxometric analysis and optical CT should be equivalent.

• **Experiment 5 (e_5):** Eleven samples of MAGIC gel were prepared following the standard recipe[2] but adding the methacrylic acid at 45°C. Ten samples were irradiated in a ^{60}Co beam to doses from 0 to 1.9 Gy and scanned only with optical CT.

• **Experiment 6 (e_6):** Gel from e_4 and e_5 were melted at 28°C to produce polymer precipitation.

• **Experiment 7 (e_7):** One sample irradiated to 0.5 Gy from e_5 was again irradiated to 75 Gy.

• **Experiment 8 (e_8):** Four samples of MAGIC gel were irradiated to doses from 0 to 2 Gy and scanned using the HRMAS technique. The aim of this experiment was to obtain spectral information about the gel standard composition. This information complements the one obtain from e_1 and e_2.

Results

• e_1 results show no changes in the HRMAS absorption spectra of pure gelatin before and after irradiation. Gelatin seems to be inert when it is exposed to low doses.

• e_2 spectroscopic results did not show polymerization at 1 Gy. This could be explained as: (1) The polymer spectrum was masked by the one of gelatin. (2) A **signal quenching** has taken place.

• e_3 results show that the polymer to monomer ratio ϕ (number of ^{1}H spins ratio) was very high in the non-irradiated sample. This implies that the gelatin plays a significant role as a moderator in the diffusion process of methacrylic and polymethacrylic acid. There is evidence of **loss or quenching of signal** around 1Gy (see *Figs. 4* and *5*).

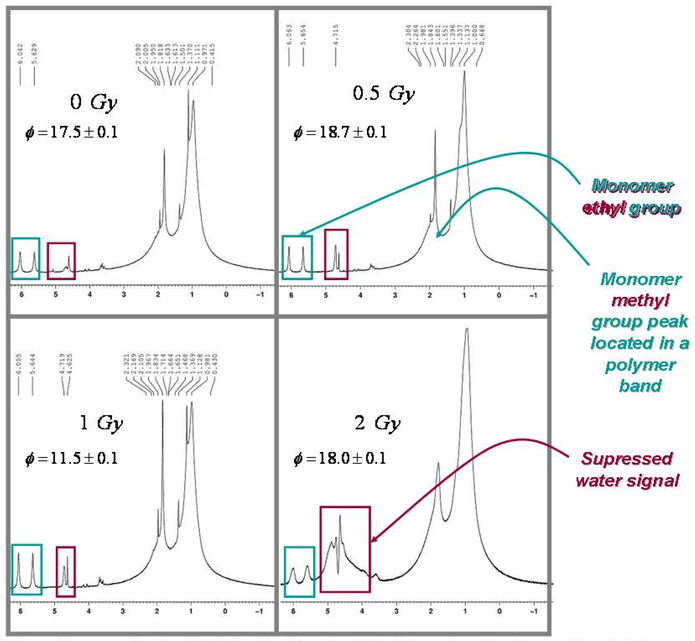

Fig. 4. ***NMR absorption spectra for MAGIC gel without gelatin.*** *There is a signal quenching at 1 Gy.*

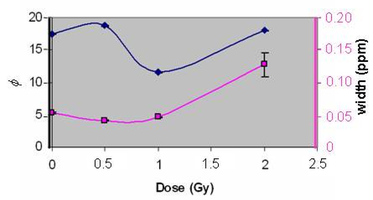

Fig. 5. ***Polymer to monomer ratio ϕ (blue curve) and signal width (red curve) related to the monomer peaks in the absorption spectra in Fig 4 for the MAGIC gel without gelatin.*** *Note that above 1 Gy there is a parallel increase in both quantities, resulting from a significant monomer trapping and that the magnitude of this effect, measured as a peak broadening, is proportional to ϕ .*

• e_4 results demonstrate that there is a loss of water solvation sites as a function of dose. The observed polymer fraction by relaxometric analysis and by optical density are proportional to each other as expected. The optical densities obtained in e_4 (blue) and e_5 (red) are shown in *Fig. 6*. Note that close to 1 Gy (blue) and to 0.1 Gy (red) there is a signal quenching.

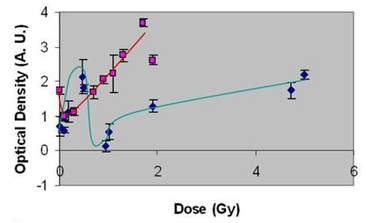

Fig. 6. ***Optical densities for e_4 and e_5.*** *The signal quenching can be displaced by choosing the proper initial conditions, particularly by using higher temperatures during gel preparation. Note that beyond the quenching region the slope is steeper (higher gel sensitivity) for the red curve due* to the presence of more polymer before irradiation. *Both curves were normalized at 0.1 Gy.*

• e_4 results show a strong gel response in the range from 0.1 to 0.5 Gy. As mentioned before, relaxometry analysis lead to the same result. The digital images shown in *Fig. 7* were obtained in a Sagittal plane of samples irradiated in a ^{60}Co beam to doses in the range from 0.1 to 0.5 Gy.

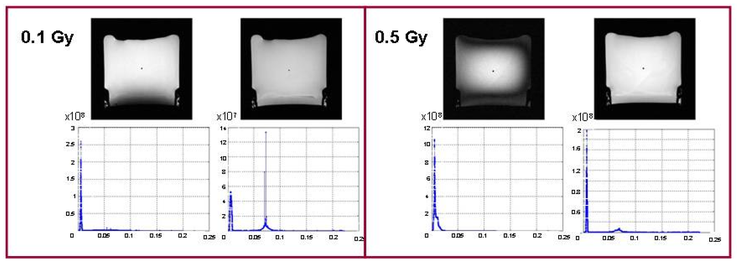

Fig. 7. ***Changes observed at the center of the sample jars.*** *Figure shows the transverse relaxation spectra* calculated using a stochastic algorithm for the inversion of the Laplace transform[5,6] *for the non-irradiated samples. (first and third from the left) show the peak related to the methacrylic acid monomer. The spectra from irradiated samples (second and fourth from the left) demonstrate the changes in polymerization by the presence of a second band of relaxation rates. Note the difference in the peak areas due to the difference in dose.*

Dose (Gy) ^{60}Co	*Experimental R_2 (s^{-1})*	*Polymer Fraction (%)*
0.1	7.1 ± 0.6	9.3 ± 0.4
0.5	7.5 ± 0.6	16.0 ± 0.7

Table. 1. ***Comparison of the Experimental R_2-based and proposed polymer-fraction based methods.***

• Measurements were made in the center of the samples jar in a 2x2 pixels ROI. *It is clear that the* ***experimental R_2*** *is not able to discriminate changes at low dose used in e_4 .*

• The main difference between the results of e_4 and e_5 is due to the difference in the initial amount of polymer formed prior to irradiation.

•To verify that there was more polymer formed before irradiation in e_5 versus e_4, polymer precipitation was induced by melting the gel at 28°C (e_6) this resulted in the formation of a thicker layer in e_5 (see *Fig.8a and Fig. 8b*). Samples were irradiated to 0.1 Gy (closest to the no irradiation conditions).

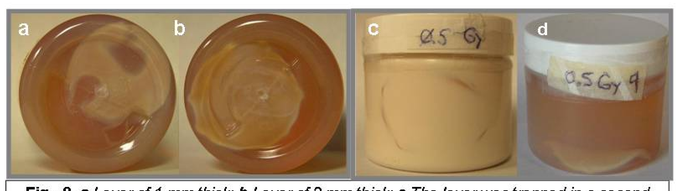

Fig. 8. ***a*** *Layer of 1 mm thick;* ***b*** *Layer of 2 mm thick;* ***c*** *The layer was trapped in a second polymer network;* ***d*** *Sample before second irradiation.*

e_7 results are shown in *Fig. 8c and Fig. 8d*. There is a formation of structures that seems to correspond to two different materials.

• The HRMAS absorption spectra obtained in e_8 shows no polymer spectrum above the gelatin background for doses up to 2 Gy and only monomer spectra is observed. This result is very similar to the one obtained in e_2 and e_4.

Discussion

Our Interpretation of the experimental results are:

1. Lateral crosslinking of linear polymethacrylic acid in the absence of gelatin leads to a loss of hydrogen atoms.
2. In standard MAGIC gel there is additionally crosslinking between gelatin and methacrylic acid, phenomenon already suggested in the literature.[1,3] This can also lead to a loss of hydrogen atoms.
3. Additionally, 1 and 2 lead to signal loss due to the absence of water solvation.
4. The degree of methacrylic acid polymerization prior to irradiation is closely related to the sensitivity of the dosimeter and there is enough room for optimization in the dosimeter response to low doses.

Acknowledgements

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