Dose rate and fractionation dependence of methacrylic acid based polymer gels using optical and MRI techniques

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Abstract. Polymer gels formulated with methacrylic acid as the main monomer source have been investigated for several decades. However, there is some discrepancy in the literature regarding their dose rate and fractionation dependence. This study investigated whether the read-out technique, optical versus MRI, affected the measured dependence for dose rate and fractionation.

1. Introduction
Polymer gels are a type of 3D dosimeter that react to the absorption of radiation dose with the polymerization of monomers as a result of the byproducts of radiolysis of water molecules. The linking and crosslinking of monomers produce a measurable, localized 3D dose distribution that can be measured with computed tomography (CT), optically, or with magnetic resonance imaging (MRI) techniques [1-7]. A variety of monomers have been investigated for polymer gel applications, most notably beginning with N,N’-methylene-bis-acrylamide (bis) monomers [8], acrylamide and bis monomers (BANANA, BANG®, and PAG) [1, 9-12], acrylic acid and bis monomers (BANG®-2) [13], methacrylic acid monomers (BANG®-3, BANGkit™, and MAGAT) [14], and methacrylic acid and ascorbic acid (MAGIC) [15].

Mixed reports of dose rate (DR) dependence and fractionation (fx) dependence exist for polymer gels and particularly for those containing methacrylic acid, such as BANG®-3, BANGkit™, MAGAT, and MAGIC gels. These reports use a variety of read-out methods: CT, optical, and MRI. As a polymer gel reacts due to absorption of radiation, the change in gel density is expected to be directly proportional to the change in CT number [3]. Similarly, the optical density (OD) of an irradiated polymer gel is expected to increase with radiation dose. However, the relationship of OD versus dose is dependent on the wavelength at which the measurements are taken [4, 16]. Polymer gels exhibit a stronger change and mono-exponential decay in spin-spin relaxation response (time constant T2) compared to spin-lattice relaxation response (time constant T1) and was first described by Zimmerman and later called the fast exchange model [17, 18]. As a result, the changes in polymer gels read-out using MRI are typically reported as T2 or transverse relaxation rate R2 (=1/T2) values.

Reports of dose rate dependence include a threshold beginning at 6 Gy while others have indicated a range for which their dose rate dependence occurs (30 cGy/min to 400 cGy/min) [2, 19-21]. A summary of these findings is below in Table 1 with their respective read-out methodologies. The literature thus far agrees that methacrylic acid-containing gels do not exhibit any energy dependence, which could confound some of the reported dose rate dependence [21, 22].
Table 1. Dose rate (DR) dependence in literature for methacrylic acid containing polymer gels.

| Reference               | Gel          | Read-out Method | DR Dependence | Range            |
|-------------------------|--------------|-----------------|---------------|------------------|
| Sathiyarat et al 2018   | MAGAT        | CT              | Y             | 250-1500 cGy/min |
| Massillon-JL et al 2010 | BANG3®-Pro-1 | Optical (635 nm) | N             | 3.7-15.2 cGy/min |
| Sathiyarat et al 2018   | MAGAT        | Optical (400 nm) | Y             | 250-1500 cGy/min |
| De Deene 2004          | nMAG         | MRI             | Y             | 25-1000 cGy/min  |
| Bayreder et al 2006     | MAGAT        | MRI             | Y             | 60-500 cGy/min   |
| De Deene et al 2006     | nMAG         | MRI             | Y             | 30-400 cGy/min   |
| Murakami et al 2007     | BANGkit™     | MRI             | Y             | 68-408 cGy/min   |
| Vredevooog 2012         | BANG3®-Pro-2 | Optical (785 nm) | Y             | > 6 Gy           |
| Karlsson et al 2007     | nMAG         | MRI             | N             | 44-1000 cGy/min  |
| Pavoni et al 2012       | MAGIC-f      | MRI             | Y             | 200-500 cGy/min  |
| Roed 2017               | BANG3®-Pro   | MRI             | N             | 60-425 cGy/min   |
| Khan et al 2018         | MAGIC        | MRI             | Y             | 60-1800 cGy/min  |

Similarly for fractionation dependence, mixed reports exist with both optical and MRI read-out methodologies. A summary of this literature can be found below in Table 2.

Table 2. Fractionation (fx) dependence in literature for methacrylic acid containing polymer gels.

| Reference               | Gel          | Read-out Method | fx Dependence |
|-------------------------|--------------|-----------------|---------------|
| Massillon-JL et al 2010 | BANG3®-Pro-1 | Optical (635 nm) | N             |
| Vredevooog 2012         | BANG3®-Pro-2 | Optical (785 nm) | Y             |
| Karlsson et al 2007     | nMAG         | MRI             | Y             |
| Pavoni et al 2012       | MAGIC-f      | MRI             | N             |
| Roed 2017               | BANG3®-Pro   | MRI             | Y             |

For the above reasons, this work used a methacrylic acid-based polymer gel (MAGAT) formulation for comparisons of dose rate and fractionation dependence when read-out with optical and MRI techniques.

2. Materials and Methods

2.1. MAGAT gel fabrication and read-out methodologies

The MAGAT formulation used to make the polymer gels in-house was as follows: 8 wt% 300 bloom gelatin (Sigma-Aldrich), 6% methacrylic acid (MAA) (ACROS Organics), 5mM tetrakis (hydroxymethyl) phosphonium chloride (THPC) (Sigma-Aldrich), and 86 wt% deionized water. Gelatin served as the gel matrix; MAA was the source of monomers; THPC was an oxygen scavenger; and water was the source of radicals to initiate the polymerization process during irradiation. Gelatin was soaked in water until fully dissolved then heated gradually to 50°C. After maintaining 50°C for an hour, the temperature was lowered to 40°C and MAA and THPC were added. The mixture was stirred while the temperature was further gradually lowered to 35°C, poured into cuvettes or jars, and moved to 4°C for complete gel solidification. After at least 10 hours at 4°C, the gels were then acclimated to room temperature (~21°C) over at least another 10 hours. All MAGAT gels in this study were irradiated within 24 hours of creation in order to reduce the risk of oxygen contamination, especially for the cuvettes.

For the optical read-out method of this study, the gels were poured into standard size cuvettes with an optical path length of 1 cm (Thermo Fisher Scientific) for optical density (OD) read-out in the visible range using a GENESYSTM 10S UV-VIS spectrophotometer (Thermo Fisher Scientific). The cuvettes were topped with plastic paraffin film to reduce oxygen contamination. The absorption spectra (350-700 nm, 1 nm wavelength steps) of all cuvettes were measured prior to irradiation and 22 hours post-
irradiation. The xenon lamp light beam dimensions were 2 mm (wide) by 7 mm (tall), and the central point of measurement in the cuvette was 8.5 mm from the bottom of the cuvette (away from the region of possible oxygen contamination at the top of the cuvettes). The net OD was calculated by subtracting the OD of un-irradiated samples from that of irradiated samples. Three intra-batch cuvettes were averaged for each given data point. A single batch was used for all of the optical measurements and was the same as one of the MRI read-out method batches.

For the MRI read-out method of this study, the gels were poured into cylindrical polyethylene terephthalate (PET) plastic containers that were 45 mm in diameter and filled to a height of 90 mm. Similar to the optical read-out samples, all MRI read-out gels were imaged prior to irradiation and 22 hours post-irradiation using two different sequences: T2-Weighted (T2W) and T2 map series. The T2W images were acquired with the following parameters: acquired voxels 1x1x3 mm³, reconstructed voxels 0.63x0.63x1.50 mm³, turbo spin echo, 5 averages (NSA or NEX), TR = 2100 ms, and TE = 439 ms. The T2 map was calculated with images acquired with the following parameters: acquired voxels 1x1x3 mm³, reconstructed voxels 0.42x0.42x3.00 mm³, turbo spin echo, 5 averages, TR = 240 ms, TE = 5.5 + n*11 (8 echoes = 5.5, 16.5, 27.5, 38.5, 49.5, 60.5, 71.5, and 82.5 ms). The first echo of each T2 map series (TE = 5.5 ms) was not used for the T2 map calculation since it may not have been acquired in a steady state. The T2 of each sample was calculated in ImageJ using the QuickVol II plugin, where T2 is calculated by a linear regression model [30]. The goodness of fit for calculating T2 using this model measured by R² was on average 0.914±0.004. The final reported R² values were calculated as 1/T2. The temperature of these samples was also measured immediately prior to irradiation to ensure room temperature equilibration using an infrared thermometer (Cen-Tech™). Three batches were used for the MRI read-out comparison and with one gel per batch per data point (three inter-batch gels averaged for each given data point).

2.2. MR-linac irradiation set-up
An integrated 1.5 T magnetic resonance imaging and 7 MV linear accelerator system (pre-clinical MR-linac, Elekta AB, Stockholm, Sweden) was used for all irradiations and MR imaging of the gels in this study. The radiation isocenter and MR isocenter of the pre-clinical “2ATL” MR-linac system are located 143.5 cm from the linac target and approximately 14.2 cm above the surface of the couch. The cuvettes were centered within a 1.3 cm thick acrylic slab with 4.4 cm of solid water on top for build-up to reach a total of 5 cm depth at the center of the cuvettes (Figure 1a). The MRI gels were set-up on top of solid water such that 4 cm of gel was below the isocenter height and 5 cm of gel was above the isocenter height (with the region of interest and measurement at 5 cm depth) (Figure 1b). All samples received a total dose of 3 Gy at 5 cm depth using a 20x20 cm² field with gantry angle 0°.

![Figure 1. Irradiation set-up with MR-linac for a) cuvettes in a central cut-out of an acrylic slab and b) cylindrical PET gels.](image)
The dose rate dependence was investigated using two methods: changing the gun duty cycle (GDC) (changing the photon fluence rate) and changing the distance of the samples relative to the source. The first method (GDC) changes the average dose rate but not the instantaneous dose rate. For the first method, GDC of 100% (400 MU/min), 87% (348 MU/min), 50% (200 MU/min), and 14% (56 MU/min) were used. The second method (by distance) changes both the average and instantaneous dose rates. For this method, dose rate was changed using the distance from the source-to-center-of-sample from 100% (143.5 cm) to 87% (153.7 cm) and to 130% (125.9 cm). Both the minimum and maximum dose rates using the second method were limited by the size of the MR-linac bore.

The fractionation dependence used the same set-up as for the 100% dose rate (and used 400 MU/min). The total dose of 3 Gy was divided into three different fractionation schemes: 1 fx (3 Gy), 2 fx (1.5 Gy + 1.5 Gy), and 3 fx (1 Gy + 1 Gy + 1 Gy). Each of these fractions had a 5 minute interval in between.

3. Results and Discussions

3.1. Optical absorption spectra and results

The optical absorption spectra of the MAGAT samples were measured prior to and 22 hour post-irradiation between 350 and 700 nm. Wavelengths of 400, 635, and 785 nm have been reported in the literature using spectrophotometers or optical CT methods for similar methacrylic acid containing polymer gels. Figure 2 demonstrates that the apparent relationship between OD or net OD and radiation dose can vary depending on the wavelength selected. In order to compare with existing literature, wavelengths of 400, 500, and 650 nm were selected for further analysis. A larger separation between the OD of the irradiated and un-irradiated samples existed for 500 and 650 nm compared to 400 nm. 400 nm was also closer to the ultraviolet region where the signal became noisier.

When changing the average dose rate by changing the gun duty cycle, measurements taken at 400 nm were increased by up to 7%, at 500 nm by up to 33%, and at 650 nm by up to 51% at 14% dose rate when compared to 100% dose rate (Figure 3). When changing the average and instantaneous dose rate by changing the distance, measurements taken at 400 nm did not change, at 500 nm up to 4%, and at 650 nm up to 5% at 130% dose rate when compared to 100% dose rate (Figure 3). When changing the number of fractions, measurements taken at 400 nm were increased by up to 11%, at 500 nm up to 46%, and at 650 nm up to 86% (Figure 3).

3.2. Optical versus MRI read-out measurements

When changing the average dose rate by changing the gun duty cycle, T2W measurements were decreased by up to 15% (50% DR), and R2 values were increased by up to 6% (14% DR) (Figure 3). When changing the average and instantaneous dose rate by distance, T2W measurements were decreased by up to 6% (130% DR), and R2 values were decreased by up to 1% (130% DR) (Figure 3). When changing the number of fractions, T2W measurements were decreased by up to 9% (2 fx), and R2 values were increased by up to 3% (3 fx) (Figure 3). The temperature of all MRI read-out gel samples increased on average by 2.6±0.7°C after absorption of 3 Gy. This temperature change is solely attributed to the polymerization process occurring immediately after irradiation began. For this reason and to allow for a stable polymerization state, all samples were imaged 22 hours post-irradiation.

Comparing the optical to MRI read-out results, the R2 values correlated more closely with the 400 nm optical results. However, the T2W measurements had a larger standard deviation and did not follow any trends of change with dose rate or fractionation, which could be due to differences in signal gain factor during image acquisition. Changing the average dose rate by changing the GDC appeared to have a slightly greater effect on the MAGAT response compared to changing both the average and instantaneous dose rate by changing the distance, especially when comparing both 87% dose rates. Radicals formed during the radiolysis of water contributed to both the polymerization of monomers (contributing to increased response of gel) and to the termination of polymer chains (contributing to decreased response of gel). The overall trends in the changes in response agreed with the literature,
where the response of MAGAT was expected to be increased (greater OD, smaller T2W and T2 values, greater R2 values) with decreasing dose rates, due to the production of fewer radicals and fewer polymer chains being terminated by radicals. Similarly, with multiple fractions delivering the same total dose (and therefore the same total number of radicals generated), an increased number of fractions resulted in fewer radicals contributing to polymer chain terminations (versus polymerization) due to the time in between each fraction and therefore an increased response of MAGAT.

![Graph](image1)

**Figure 2.** a) Spectra of un-irradiated and irradiated cuvettes of MAGAT gel and b) dose-response curves for 400 nm, 500 nm, and 650 nm.

4. Conclusions
The results of this study demonstrated that R2 MRI measurements can be correlated to optical measurements but depend highly on the wavelength selected for optical measurements. As vendors continue to provide optical CT scanners dedicated to 3D dosimetry, this study emphasizes that regardless of the dosimeter, careful assessment of the characterization steps should be taken dependent on the wavelength used and compared to other conventional methods in order to make accurate dose comparisons between the dosimeter read-out measurements and treatment plan calculated doses.

Future work should investigate repeating this study at different dose levels since this specific MAGAT formulation may have a different dose threshold for dose rate and fractionation dependence.
for optical and MRI read-out techniques. Energy dependence should also be characterized to ensure that it is not confounding the dose rate dependence results.

**Figure 3.** a) Normalized measurements for dose rates modulated by the gun duty cycle (GDC) relative to 100% (# MU/min in parenthesis), b) normalized measurements for dose rates modulated by distance relative to 100%, and c) Normalized measurements for fractionation relative to 1 fraction (fx).

5. References

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