Timing considerations for preclinical MRgRT: effects of ion diffusion, SNR and imaging times on FXG gel calibration

M Welch1, WD Foltz2,3 and DA Jaffray1,2,3,4
1Dept. of Medical Biophysics, University of Toronto, Toronto, ON, Canada
2Radiation Medicine Program, Princess Margaret Hospital, Toronto, ON, Canada
3Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
4The TECHNA Institute for the Advancement of Technology for Health, Toronto, ON, Canada

E-mail: mattea.welch@rmp.uhn.ca

Abstract. Sub-millimeter resolution images are required for gel dosimeters to be used in preclinical research, which is challenging for MR probed ferrous xylene-orange (FXG) dosimeters due to ion diffusion and inadequate SNR. A preclinical 7 T MR, small animal irradiator and FXG dosimeters were used in all experiments. Ion diffusion was analyzed using high resolution (0.2 mm/pixel) T1 MR images collected every 5 minutes, post-irradiation, for an hour. Using Fick’s second law, ion diffusion was approximated for the first hour post-irradiation. SNR, T1 map precision and calibration fit were determined for two MR protocols: (1) 10 minute acquisition, 0.35mm/pixel and 3mm slices, (2) 45 minute acquisition, 0.25 mm/pixel and 2 mm slices. SNR and T1 map precision were calculated using a Monte Carlo simulation. Calibration curves were determined by plotting R1 relaxation rates versus depth dose data, and fitting a linear trend line. Ion diffusion was estimated as 0.003mm2 in the first hour post-irradiation. For protocols (1) and (2) respectively, Monte Carlo simulation predicted T1 precisions of 3% and 5% within individual voxels using experimental SNRs; the corresponding measured T1 precisions were 8% and 12%. The linear trend lines reported slopes of 27 ± 3 Gy*s (R2 : 0.80 ± 0.04) and 27 ± 4 Gy*s (R2 : 0.90 ± 0.04). Ion diffusion is negligible within the first hour post-irradiation, and an accurate and reproducible calibration can be achieved in a preclinical setting with sub-millimeter resolution.

1. Introduction
Technological advances have revolutionized preclinical radiation studies, resulting in accurate and highly conformal dose delivery with sub-millimeter precision. Novel radiotherapy studies are possible with these systems [1], including MR-guided preclinical radiotherapy (MRgRT) verification.

Sub-millimetre resolution with MR probed FXG gel dosimeters is limited by ion diffusion, inadequate signal-to-noise ratio (SNR), which limits T1 precision, and increased imaging time; high field pre-clinical MRI systems provide an advantageous resolution/SNR/imaging time trade-off. In this paper, high field pre-clinical MRI is used to approximate the rate of ion diffusion and to investigate the feasibility of accurate and reproducible dose calibration with R1 (1/T1).

2. Materials and Methods

2.1 Gel Preparation
FXG dosimeters were used in all experiments and prepared according to the recipe outlined by Babic et al [2]; final concentrations were 0.3 mM ferrous ammonium sulphate (Cat.No.203505,
Sigma-Aldrich Ltd, Oakville, Canada), 0.05 mM xylenol orange (Cat.No.398187, Sigma-Aldrich Ltd), 65 mM sulfuric acid (Cat.No.258105, Sigma-Aldrich Ltd) and 6% by mass 300 Bloom Porcine gelatin (Cat.No.G2500, Sigma-Aldrich Ltd) in de-ionized water. This recipe was chosen because of the reduced ion diffusion coefficient resulting from the addition of xylenol-orange [3]. Gelatin was added to a portion of the water and allowed to swell for 10 minutes at room temperature. The mixture was then heated to 50°C, and held at this temperature for approximately 15-20 minutes to dissolve the gelatin. A stock solution containing ferrous ammonium sulphate and xylenol-orange was added to the sulfuric acid and remaining water. The gelatin mixture was cooled to 35°C and the rest of the chemicals were added. The cooled solution was poured into 50 mL centrifuge tubes 3 cm in diameter, covered and allowed to set overnight in a refrigerator.

2.2 FXG Gel Irradiations
The FXG gels were irradiated one day post manufacturing using an X-Rad 225Cx small animal irradiator (Precision X-Ray Inc., North Branford, CT, USA). Centrifuge tube caps were removed and the tops of the gel were treated. 1x1 cm square beams (225 kVp, 13 mA) were delivered to a surface dose of 10 Gy (2.85 Gy min⁻¹) for ion diffusion experiments. 1 cm circular beams (225 kVp, 13 mA) were delivered to a surface dose of 4 Gy (2.88 Gy min⁻¹) for calibration experiments.

2.3 MR Imaging
Imaging of the FXG gels were performed pre and post-irradiation using a 7T MR unit (BioSpec 70/30 USR, Bruker Corp., Ettlingen, DE) and 7.2 cm inner diameter cylindrical quadrature RF volume coil provided by the manufacturer; the tubes were aligned in the magnet using pre-existing markings on the centrifuge tubes. The room temperatures were not specified; however, the gels were placed in a temperature controlled 21 °C water bath prior to pre-irradiation imaging for an hour. The variation in dosimeter response due to temperature was considered minimal given that the increase in Fe³⁺ ions in an aqueous solution increases by approximately 0.12% per degree Celsius [4]. The following imaging protocols were used:

2.3.1 High resolution T₁ weighted imaging. To monitor ion diffusion, a 1 minute image acquisition was designed using a spin echo sequence with TR 1000 ms and TE 7 ms to collect twenty, 5 mm thick, axial slices. The field of view (FOV) was 28 mm by 28 mm on a 140 by 140 acquisition matrix.

2.3.2 T₁ Mapping. Two variable TR spin echo sequences were designed for R₁ dose calibration (TE 6ms; TR 750, 1000, 1500, 2000, 3000 and 5000 ms). Protocol #1: A 10 minute image acquisition with twenty 3 mm axial slices and an in-plane FOV of 32.5 mm by 32.5 mm on a 100 by 100 matrix. Protocol #2: A 45 minute image acquisition consisting of two 22.5 minute image acquisitions with contiguous slice packages providing the same longitudinal volume coverage with 2 mm slice thickness. A FOV of 32.5 mm by 32.5 mm on an acquisition matrix of 128 by 128 was used.

2.4 Ion Diffusion Analysis
Ion diffusion was estimated using T₁ weighted high resolution images (Sec. 2.3.1) collected every five minutes, post-irradiation, for an hour. Beam profile noise reduction was achieved by averaging together ten coronal beam profiles (figure 1). As described by Olsson et al [5], Fick’s second law was used to approximate ion diffusion for the first hour post-irradiation. To encompass the extent of the beam concentration a sigma was chosen to include approximately 95% of the total concentration.
2.5 Precision of T1 Estimates
Several factors effect T1 precision, these include the TR sampling strategy, SNR and thermal noise [6]. SNR at the longest TR was found by dividing the average signal amplitude within a ROI in the gel by the standard deviation of the noise, after Rayleigh noise statistics correction. T1 precision for the SNR was then calculated by Monte Carlo simulation using in-house Matlab scripts (250 repetitions of T1 regression with SNR ranging from 20 to 1000). Experimental T1 precision was estimated using pre-irradiation T1 maps and the mean and standard deviation of T1 within a central circular ROI.

2.6 Calibration Curve Fitting Analysis
Calibration curve fitting was analysed with the imaging protocols outlined in Sec. 2.3.2 and 2.3.3. Previously collected dose rate information was assumed linear and interpolated to obtain dose information at depths corresponding to the slice depths of the MR images. Post-irradiation R1 (1/T1) relaxation rates at a given depth were represented by the average of an 11 x 11 pixel area spliced out of the centre of the irradiated column of the gel. The change in relaxation rates was found by subtracting the pre-irradiation R1 relaxation rates from the post-irradiation R1 relaxation rates; these changes were plotted against the depth dose information and a linear trend line was fit to the resulting graphs (figure 2). The $R^2$ values and slopes of the trend lines were analysed to determine the quality and reproducibility of the fit.

3. Results

3.1 Ion Diffusion
The ion diffusion coefficient reported when using Fick’s second law of diffusion was approximated at 0.003mm$^2$ in the first hour post-irradiation; a rate undetectable by the image resolution used in these experiments.
3.2 T1 Precision Analysis
SNR at TR 5000 ms was approximately 75 for Protocol #1 and 49 for Protocol #2, as one would expect given 2.5-fold larger voxels for Protocol #1 and two-fold signal averaging for Protocol #2. Based on Monte Carlo analysis, SNR of 75 and 49 should correspond to T1 map precision from thermal noise on the order of 3 and 5%, respectively, and were found to be 8% and 12%, respectively.

3.3 Calibration Fit
Protocol #1 had a mean linear trend line with $R^2$: 0.80 ± 0.04 and slope: 27 ± 3 Gy*s (figure 2. A). Protocol #2 had a mean linear trend line with $R^2$: 0.90 ± 0.04 and slope: 27 ± 4 Gy*s (figure 2. B).

4. Discussion

4.1 Ion Diffusion
Olsson et al [5] reported an ion diffusion coefficient of 0.19mm$^2$ hour$^{-1}$ for a standard agarose dosimeter; the use of xylenol-orange as a chelator in these experiments would result in a slower ion diffusion coefficient. The resolution of the images used (0.2mm/pixel) is not high enough to detect ion diffusion in the first hour post-irradiation. Higher resolution and longer wait times post-irradiation would be needed in order to quantify the diffusion coefficient accurately [7]. The diffusion reported in these experiments may be the result of image noise or ion development not associated with diffusion. Furthermore, the changes in beam profile width seen over time in figure 1 may be due to the continued development of Fe$^{3+}$ ions post-irradiation [8].

4.2 T1 Precision Analysis
The measured T1 map precision was higher than predicted from SNR, which may reflect spatial heterogeneity in gel characteristics or systematic biases in the T1 data acquisition. However, the variable TR approach should be robust to RF and static field inhomogeneity; additionally inter-slice interference was reduced by selection of RF pulses with sharp excitation and refocusing profiles. The 95% confidence limits for the T1 maps are 16 and 24% within individual voxels (2 standard deviations), corresponding to 3.4 and 5.7 Gy at a slope of 27 Gy*s. Further improvement to T1 precision can be gained by binning voxels, increasing scan time or using a more sensitive receive coil.

4.3 Calibration Fit
The two imaging protocols used in this study verify that lower resolution T1 maps improved SNR and T1 mapping precision without penalty to calibration; improvements to calibration linearity may be achieved through further T1 mapping optimization. Reproducibility of the fit is also increased when using shorter imaging times, which can be attributed to gel sensitivity.

Gel composition within each imaging protocol is identical; however, it may vary between imaging protocols due to gel batch number. Likely, the varying trend line slopes for Protocol #2 reflect auto-oxidation, because the delay to experimentation for gel 1 was two hours less (1.5 hours in total for imaging, 0.5 hours for set up and irradiation) than for gel 2. This time lapse for Protocol #1 gels would have been less than an hour, giving less time for auto-oxidation. In order to validate these assumptions, further tests need to be conducted regarding auto-oxidation and the effects on sensitivity.

4.4 Clinical MR-Guided RT
MR-guided RT is an emerging field within IGRT. The excellent soft tissue contrast and motion characterization opens new doors in treatment planning, resulting in more aggressive plans with higher tumour conformity that would benefit from 3-Dimensional (3D) dosimetry. MRgRT systems are currently being constructed [9] with minimal preclinical testing. 3D ferrous xylenol-orange gel dosimetry is a proven method utilizing MR [10]. Therefore, it is proposed that a preclinical simulation of the MRgRT workflow using 3D FXG gel dosimeters be performed.
5. Conclusion
The results support potential preclinical MR-guided RT gel dosimetry. The low ion diffusion coefficient and T1 mapping precision provided by imaging Protocol #1 improves the accuracy and reproducibility of the dose calibration. Increased SNR should be considered for dose calibration within individual voxels. Further experiments will establish the effects of auto-oxidation on gel sensitivity, define the ion diffusion coefficient more accurately, and verify preclinical radiation treatment plans.

6. Acknowledgements
The authors thank Shawn Stapleton and Kevin Alexander for valuable discussions regarding project direction and experimental design. This work is supported by the Natural Sciences and Engineering Research Council of Canada, TECHNA, Garron Family and PMCF.

7. References
[1] Kahn J et al 2012 Rad. Onc. 7 223
[2] Babic S et al 2008 Phys. Med. Biol. 53 1637-50
[3] Bero M A et al 2001 Rad. Phys. Chem 61 433-5
[4] Shortt K R 1989 Phys. Med. Biol. 34 1923-6
[5] Olsson LE et al 1992, Phys. Med. Biol. 37 2243-52
[6] Nishimura DG 2012 Principles of Magnetic Resonance Imaging pp 19, 159-162 and 163-164
[7] Baldock C et al 1994, J. Roy. Soc. Med. 87 806-8
[8] Olding T and Schreiner L J 2011 Phys. Med. Biol. 56 1259-79
[9] Jaffray D A et al 2010 SPIE 7622 02
[10] Gore J C et al 1984 Magn. Reson. Imaging 2 224