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How to scan polymer gels with MRI?

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Abstract. The absorbed radiation dose fixated in a polymer gel dosimeter can be read out by several methods such as magnetic resonance imaging (MRI), optical CT, X-ray CT and ultrasound with MRI being the first method that was explored. Although MRI was considered as an elegant scanning technique, readily available in most hospitals, it was later found that using a non-optimized imaging protocol may result in unacceptable deviations in the obtained dose distribution. Although most medical physicists have an understanding of the basic principles of magnetic resonance imaging (MRI), the optimization of quantitative imaging sequences and protocols is often perceived as the work of MRI experts. In this paper, we aim at providing the reader with some easy guidelines in how to obtain reliable quantitative MRI maps.

1. Introduction
In the early days of the development of gel dosimetry, magnetic resonance imaging (MRI) was suggested as the method to read-out gel dosimeters. The use of MRI as a non-destructive imaging method of a dosimeter gel was first proposed in 1984 by Gore et al [1] who showed that ferrous sulfate chemical dosimeters initially developed in 1927 [2] could be probed by nuclear magnetic relaxometry and hence by magnetic resonance imaging (MRI) [1]. Gore et al investigated the nuclear magnetic resonance (NMR) relaxation properties of irradiated Fricke or ferrous sulfate dosimetry solutions showing that radiation-induced changes, in which ferrous (Fe^{2+}) ions are converted to ferric (Fe^{3+}) ions, could be quantified using MRI and subsequently showed that Fricke dosimetry solutions dispersed throughout a gel matrix could be used to obtain three-dimensional (3D) spatial information using MRI. It was subsequently shown that irradiated Fricke-type gel dosimeters did not retain a spatially stable dose distribution due to ion diffusion within the irradiated dosimeters [3]. Fricke solutions with various gelling agents such as gelatin, agar, sephadex™ and polyvinyl alcohol (PVA) were investigated. Chelating agents to reduce diffusion in Fricke gels, such as xylene orange (XO), had only limited success [4] and diffusion remained a significant problem in the advancement of gel dosimetry. Different models have been described that explain the mechanism of how the relaxation rates are affected by the paramagnetic substances [1, 5-7]. The spin-lattice relaxation rate (R_1 = 1/T_1) and the spin-spin relaxation rate (R_2 = 1/T_2) in Fricke gels is altered significantly upon irradiation. As R_1 of a non-irradiated Fricke gel dosimeter is small as compared to the R_2 of a non-irradiated Fricke gel dosimeter, the dynamic range of the Fricke gel dosimeter in relative terms is higher for R_1 than R_2. For this reason, R_1 mapping is preferred to R_2 mapping for Fricke gel dosimeters. Also R_1 maps (at least in the early days) can be obtained with a shorter acquisition time than R_2 maps which is of crucial importance in avoiding diffusion related blurring of the dose distribution.
Polymer systems for the use of radiation dosimetry were first proposed as early as 1954, where Alexander et al discussed the effects of ionizing radiation on polymethylmethacrylate [8]. In 1992, Kennan et al reported on NMR longitudinal relaxation studies performed on an irradiated aqueous solution of N,N'-methylene-bis-acrylamide (Bis) and agar, which showed that the relaxation rates increased with absorbed dose [9]. Polymer gel dosimeters are based on the conversion of comonomers to polymer aggregates upon irradiation. This reaction alters the mobility of surrounding water molecules which also results in a change in \( R_1 \) and \( R_2 \) [10]. The dose-response of \( R_2 \) in gelatin based polymer gel dosimeters however is more pronounced than of \( R_1 \). To explain the effect that the radiation-induced polymerization has on the \( R_2 \) relaxation rate, a model of fast exchange [11] is adopted [12–14]. It is shown in later studies that not only the relaxation rate can be used as an imaging parameter but also other MR contrasts such as magnetization transfer [15–17] and chemical shift [18]. For a further explanation of these mechanisms, the reader is also referred to other papers in these proceedings. Different imaging sequences can be used to acquire quantitative images. These imaging sequences may differ in performance in terms of accuracy, precision and speed. It will be shown that for a specific imaging sequence, these three properties are interconnected.

The target figure of accuracy that is aimed in gel dosimetry for high-precision radiotherapy is about 3-5% of the maximum dose in regions of homogeneous dose and a spatial error of less than about 2-3 mm in regions of high-dose gradients. This figure of accuracy encompasses the overall dosimetry experiment. The problem in evaluating the overall accuracy of the dose maps obtained with gel dosimetry is that there is no “golden dosimetric standard” to compare with. The most reasonable strategy is to compare doses obtained with gel dosimetry with doses obtained by the most reliable dosimetry techniques that apply to a certain spatial dimension. For example, dose profiles of a single field (photons and electrons) can be compared with dose profiles obtained with an ionization chamber or diamond detector [19–20]. In two dimensions, gel dosimetry can be compared with film dosimetry [19, 21–22]. Dose distributions obtained with gel dosimetry have been compared with those calculated with treatment planning software [21, 23–29]. Errors that compromise the accuracy may occur at different stages of the dosimetry procedure [30].

At the stage of imaging the dosimeter, several imaging artifacts may cause errors in the final dose map. These errors may be classified in dose inaccuracies or in deformations of the dose maps. Studies of these different artifacts have resulted in different compensation strategies. The verification of the treatment plan can be seen as the major purpose of gel dosimetry in radiotherapy quality assurance. Besides the possibility of systematic errors, the dose maps will also contain stochastic noise. To minimize the stochastic noise in the images, the imaging sequence parameters should be optimized.


Although there is a vast amount of scientific literature available on different quantitative scanning methods and compensation of imaging artifacts, for the medical physicist who is planning to start using MRI as a readout technique for polymer gel dosimeters, the implementation of a reliable scanning protocol may seem very complex. Here is a step-by-step procedure that may guide you in implementing a quantitative MRI protocol to scan polymer gels.

2.1. Get yourself familiar with the basics behind magnetic resonance imaging (MRI)

Without studying the quantum mechanical description of nuclear magnetic resonance, it is essential that you familiarize yourself with the basic principles behind magnetic resonance imaging (MRI). Knowledge is the best medicine against beginners fear. There are some nice primers on the basics of MRI [31-35]. It may also be beneficial to allow yourself to play around with the parameters of a basic spin-echo sequence. It should be noted that in order to make the theory of NMR more accessible, some of these works have made compromises on the preciseness of the quantum mechanical model. More advanced textbooks on MRI physics and sequence development will give a more precise description of the quantum mechanical model [36-38].
2.2. Choose a quantitative imaging sequence

Theoretically, any kind of imaging sequence that generates an image in which the pixel intensity is related to absorbed dose in a monotonic fashion is a possible candidate. A dose map can be obtained by calibrating every pixel intensity to the absorbed dose by use of a set of calibration vials that have been irradiated with known doses. In general, due to the inhomogeneity of the radiofrequency ($B_1$-) field, contrast weighted images ($T_1w$, $T_2w$, MTw) suffer from severe image non-uniformity which results in poor accuracy. Eventually, this can be compensated by acquiring an additional $B_1$-field map and using the $B_1$-field map to compensate for the non-uniformity before calibration. However, other artifacts such as eddy currents and $B_0$-field inhomogeneity may also lead to image non-uniformity. A better approach to compensate for image non-uniformity is obtained by using quantitative parametric maps such as $T_1$, $T_2$- and MTR-maps. The contrast mechanism ($T_1$, $T_2$, MTR) should be chosen on the basis of the kind of gel dosimeter that is scanned. In Fricke based gel dosimeters, both $T_1$ and $T_2$ are significantly affected upon irradiation and thus both $T_1$ and $T_2$ maps can be used. In polymer gel dosimeters $T_2$ is more affected than $T_1$ and thus $T_2$-maps and MTR-maps will yield the highest dose resolution. A comprehensive list of possible imaging sequences to acquire parametric maps is provided in [39] and listed in table 1. The parameter of interest is calculated from a set of images that are acquired where one imaging parameter is varied (see table 1).

**Table 1:** Overview of important quantitative MR imaging sequences for $R_1$ (= $1/T_1$), $R_2$ (= $1/T_2$) and magnetization transfer ratio (MTR) imaging. The variable that is changed to acquire different contrast weighted images is shown in the third column. If the variable is varied automatically within the sequence, the parameter is shown between squared brackets. The meaning of the availability is as follows: (*) The imaging sequence is not provided by the manufacturer. The sequence should be developed in house. (**) The sequence is available but significant changes to the imaging parameters are required. (****) The imaging sequence is readily available on all clinical MRI scanners.

<table>
<thead>
<tr>
<th>Sequence type</th>
<th>Conditions</th>
<th>Variable</th>
<th>Post-processing</th>
<th>Availability</th>
<th>Spatial accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single spin-echo (SE)</td>
<td>TE short</td>
<td>TR ($\times 2/\times N$)</td>
<td>Fit</td>
<td>***</td>
<td>Very good</td>
</tr>
<tr>
<td>Saturation recovery (SRGE/SRSE)</td>
<td>TR long, TE short</td>
<td>TM ($\times 2/\times N$)</td>
<td>Fit</td>
<td>***</td>
<td>Good / Very good</td>
</tr>
<tr>
<td>Inversion recovery (IRGE/IRSE)</td>
<td>TR long, TE short</td>
<td>TI ($\times 2/\times N$)</td>
<td>Fit</td>
<td>***</td>
<td>Good / Very good</td>
</tr>
<tr>
<td>Driven Equilibrium Single Pulse Observation of $T_1$ (DESPOT)</td>
<td>-</td>
<td>FA ($\times 2/\times N$)</td>
<td>Fit</td>
<td>*</td>
<td>Good</td>
</tr>
<tr>
<td>Look-Locker (LL, TOMROP)</td>
<td>FA small</td>
<td>TI ($\times 2/\times N$)</td>
<td>Fit</td>
<td>*</td>
<td>Good</td>
</tr>
<tr>
<td>Steady-State Free Precession (SSFP)</td>
<td>TR &gt;&gt; $T_2$</td>
<td>FA ($\times 2/\times N$)</td>
<td>Anal. / Fit</td>
<td>**</td>
<td>Good</td>
</tr>
<tr>
<td>IR - Very fast acquisition (EPI, GRASE, HASTE)</td>
<td>TR long</td>
<td>TI ($\times 2/\times N$)</td>
<td>Fit</td>
<td>**</td>
<td>Poor</td>
</tr>
</tbody>
</table>
2. Quantitative $R_2$ imaging sequences ($R_2 = 1/T_2$)

<table>
<thead>
<tr>
<th>Single spin-echo (SE)</th>
<th>TR long</th>
<th>TE ($\times 2/N$)</th>
<th>Anal. / Fit</th>
<th>***</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast spin-echo (FSE, TSE, RARE)</td>
<td>TR long</td>
<td>TE ($\times 2/N$)</td>
<td>Anal. / Fit</td>
<td>***</td>
<td>Good</td>
</tr>
<tr>
<td>Multiple spin-echo (MSE, MC-SE)</td>
<td>TR long</td>
<td>$[\Delta TE(N)]$</td>
<td>Fit</td>
<td>***</td>
<td>Very good</td>
</tr>
<tr>
<td>Steady-State Free Precession (SSFP)</td>
<td>TR $&lt;&lt; T_1$</td>
<td>FA = $90^\circ$</td>
<td>[2 echoes]</td>
<td>Anal.</td>
<td>**</td>
</tr>
</tbody>
</table>

3. Quantitative magnetization transfer (MT) imaging sequences

<table>
<thead>
<tr>
<th>MT pulse prepared spin echo imaging sequence</th>
<th>TR long</th>
<th>MT pulse amplitude</th>
<th>Anal.</th>
<th>**</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed MT steady state</td>
<td>TR short</td>
<td>MT pulse amplitude</td>
<td>Anal.</td>
<td>**</td>
<td>Good</td>
</tr>
<tr>
<td>Stimulated echo preparation</td>
<td>-</td>
<td>TM</td>
<td>Anal.</td>
<td>*</td>
<td>Very good</td>
</tr>
</tbody>
</table>

2.3. Develop image processing software for calculating parametric maps from a set of base images

The parametric maps are calculated from a set of base images with different image contrast. This is achieved by an adequate software program which is most often developed ‘in house’. The importance of the choice of an appropriate cost-function to be minimized has been emphasized in [40]. It has been shown that the use of a chi-square minimization results in a more precise $R_2$ map as compared to a least-square minimization. In order to test the image processing software, a synthetic base image data set may be generated on which stochastic (or structural) noise may be added in order to test its performance.

2.4. Optimize the imaging sequence parameters for optimal precision

If the range of $R_1$, $R_2$ or MTR values is known in advance, the variable imaging parameters (column 3 in table 1) can be optimized to yield the highest achievable dose resolution. Tables of optimal scanning parameters for different $R_2$ ranges for a single-echo sequence and a multi-spin echo sequence are provided in [40] and [41] respectively. Theoretical derivations can be made for other imaging sequences using similar mathematical formalisms as provided in [40]. In most applications, a dose resolution $D_{p=95\%} = 2\%$ is required which results in a signal-to-noise ratio (SNR) in the dose map of approximately $138$ ($D_{p=95\%} = 1.96\sqrt{2}\sigma_p(D_{\text{max}} - D_{\text{min}}) = 0.02$).

The dynamic range of the parametric map can be easily assessed using a series of standard contrast agent solution. The $R_1$ and $R_2$ are linearly proportional with the molar concentration of the contrast agent. To change both $R_1$ and $R_2$ of the test phantoms independently, a mixture of two contrast agents (e.g. Gd-DTPA and FeSO$_4$) or a mixture of a contrast agent and a gelling agent can be used.
2.5. Test the spatial and dosimetric accuracy of the imaging sequence

It has been well described that imaging artifacts may compromise the accuracy of the acquired dose maps [30, 42-45] both spatially as in dose. It is therefore vital that before a gel dosimeter is scanned, the performance of the imaging sequence in terms of accuracy is investigated. A simple test consists of scanning a ‘blank’ phantom (phantom with a non-irradiated gel) with similar spatial dimensions as the gel dosimeter phantom. It is important to leave the ‘blank’ phantom in the scanner room for at least 24 hours before scanning in order to equilibrate at the scanner room temperature. Quantitative parametric maps should be calculated from the ‘blank’ images and the signal homogeneity should be assessed. To isolate stochastic and structural deviations in the image, a voxel based analysis method can be used as described elsewhere [39]. The structural deviations should be below the tolerated error in the quantitative parametric MR maps. The tolerated error is obtained from the tolerable dose error as

\[ \varepsilon_P = \frac{\partial P}{\partial D} \varepsilon_D \]  

where \( P = R_1, R_2 \) or MTR and \( \varepsilon_P \) and \( \varepsilon_D \) are the tolerated error in the parameter \( P \) and in dose respectively.

Figure 1: Antropomorphic ‘blank’ gel dosimetry phantom with fiducial markers (a) and corresponding sagittal slice (b) A sagital reconstructed from a stack of 105 transverse slices (c) reveals the effect of temperature drift during scanning. Transverse scanning was performed in three interleaved blocks. The ring shaped cranial artifact is attributed to oxygen effects.

At this point, it is advisable to test the image uniformity for several RF coils and check if the addition of a water load improves the homogeneity. Also, it is recommended to perform this uniformity test with the same imaging parameters as in the actual dosimetry experiment, as some artifacts may be phantom related. Also temperature drift as a result of the RF energy from the imaging sequence is dependent on the number of imaging slices and number of acquisitions [44]. If temperature drift results in non-uniformity in the imaged volume, either the repetition time should be increased to decrease the overall specific absorption rate (SAR) or the sequence should be modified to obtain central k-space ordering [44]. Only if the error in the parametric map is below the tolerable error, it is recommended to proceed to the next step.

A geometric quality control QC phantom can be used to check the geometric accuracy [30,39]. It should be emphasized that geometric distortions originating from magnetic field distortions caused by susceptibility differences are phantom dependent. A magnetic field map can be acquired and used to correct the geometric image distortions [46-47].

If dose maps are to be acquired in different image orientations, it is also advisable to scan the ‘blank’ phantom with different slice orientations. Although at most modern MR scanners, eddy currents are minimized by actively shielded gradient coils, with some magnetic field gradient intensive imaging sequences, eddy currents may still render the dose-R2 response curve dependent on the slice orientation and other sequence parameters [42].
2.6. Preparation of the gel dosimeter experiment
The gel dosimeter phantom and calibration vials are constructed. To minimize any systematic error introduced by the calibration vials, it is recommended to irradiate at least 15 to 20 calibration vials. The actual gel dosimeter phantom is provided with fiducial markers and scanned with CT or MRI to obtain the image data set on which the treatment is planned. The gel dosimeter phantom may be anthropomorphically shaped or may consist of a gel recipient inserted in an anthropomorphic cast. The isocenter on the treatment planning can be located with respect to the fiducial markers which facilitates the localization of the isocenter laser markers onto the anthropomorphic phantom. Once the isocenter is determined, the isocenter laser lines are marked on the gel dosimeter phantom and the gel dosimeter phantom is irradiated according to the treatment plan. The calibration vials are irradiated with known doses of which the maximum dose is higher than the maximum dose in the treatment plan.

2.7. Transfer of the gel dosimeter to the MR scanner and scanning
Immediately after irradiation, the gel dosimeter phantom is transferred to the MR scanner room and left there for at least 24 hours in order to equilibrate at the MR scanner room temperature. The calibration vials are fixed onto the gel dosimeter phantom and scanned together with the gel dosimeter phantom. It may be helpful to make a special holder for the calibration vials.

Figure 2: A collection of 20 gel measured dose maps out of a stack of 105 transverse dose maps and a 3D reconstructed rendered volume showing the position of the test tubes (b). A coronal dose map demonstrates the sparing of the brain stem (c).

2.8. Post-processing and data interpretation
If all base images are acquired, they are converted in parametric maps. Subsequently, the parametric maps are converted into dose maps using the average values collected in regions-of-interest (ROIs) within the calibration vials. The acquired dose maps are then co-registered with the original (CT) reference image data set (treatment planning) using a rigid transformation on the basis of the fiducial markers that are visible in both data sets. When both image data sets are co-registered, a comparison of the treatment planning dose grid and the gel measured dose distribution can be performed.

Based on clinically relevant dose tolerance and distance to agreement criteria, gamma-maps [48] can be created and dose volume histograms (DVHs) can be generated for both the treatment planning dose distribution and the gel measured dose distribution.
3. Conclusion

In contrast to other imaging modalities, MR scanning of polymer gel dosimeters provides many degrees of freedom. Several quantitative MR properties (such as $T_1$, $T_2$ and MTR) can be imaged and several different MR sequences can be used to acquire these properties. Whatever property or sequence is used to generate a quantitative parametric MR image data set, the accuracy and precision should be assessed and optimized using ‘blank’ phantoms (i.e. phantoms similar to the actual gel dosimeter phantom but filled with a non-irradiated gel).

Figure 3: Gel measured (a), calculated (treatment planning) dose maps (b) and corresponding gamma plots (c).

The actual gel dosimetry experiment should be performed in a similar way as the patient treatment. The treatment planning should be performed on a reference image data set obtained from the gel dosimeter phantom and calibration vials should be irradiated with known doses. The gel measured dose distribution can be co-registered with the simulated (treatment planning) dose distribution on the basis of fiducial markers.

Figure 3: Gel dosimetry is performed in different steps. Errors can occur in each of the steps, leading to a decrease in the overall precision and accuracy. The accuracy and precision of each step can be determined independently.
To obtain a picture of the overall accuracy of polymer gel dosimetry, also the fabrication and irradiation have to be included in the analysis (figure 3). This can be achieved through a reproducibility study of the complete gel dosimetry experiment from gel fabrication to dose distribution analysis with a well-characterized dose distribution (such as from a single square profile).

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