Alternative imaging modalities for polymer gel dosimetry

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Abstract. This review summarizes recent work in the area of imaging polymer gel dosimeters using x-ray CT imaging, ultrasound, and radiation-induced changes in gel mechanical properties. In addition, recent work in the area of Raman tomographic imaging of canine bone, in conjunction with past efforts in Raman imaging of polymer gel dosimeters, raises new possibilities for new polymer gel imaging techniques.

1. Introduction
Research and development efforts in the imaging of polymer gel dosimeters has, to date, been focussed on MRI and optical CT techniques. Both of these modalities are capable of imaging irradiated polymer gel dosimeters and efforts continue in developing these modalities further. Each technique does, however, present itself with its own series of technical and implementation challenges. Hence, over the course of the history of gel dosimetry research, efforts have been made in identifying and developing alternative imaging modalities for polymer gel dosimetry. This review aims to provide an overview of these alternative techniques. The review will outline (i) a brief background of x-ray CT polymer gel dosimetry, (ii) an update of work in x-ray CT polymer gel dosimetry since the last review [1], (iii) an update to work in ultrasound and gel mechanical property imaging, and (iv) comment on prospects for Raman imaging of irradiated polymer gel dosimeters.

2. X-ray CT imaging of polymer gel dosimeters
Detailed reviews of work prior to 2008 have been reported previously [1, 2]. Hence, only a brief sketch of work prior to 2008 is given here, and is primarily aimed at providing sufficient background for the reader to understand the basics of the technique.

2.1. Density changes in irradiated polymer gel dosimeters
The underlying principle in x-ray CT polymer gel dosimetry is the fact that irradiated polymer gel dosimeters undergo a slight physical density change in proportion to the dose delivered to the gel. This density change is subsequently manifest as a change in image CT number (H, N_CT, see figure 1).
The first demonstrated clinical application of x-ray CT polymer gel dosimetry was undertaken by Audet et al [4]. Figure 2 illustrates a stereotactic irradiation of polymer gel subsequently imaged using x-ray CT. Overlaid on the image are treatment plan isodose lines.

2.2. Formulation studies to improve dose sensitivity
It can be seen from figures 1 and 2 that x-ray CT imaging constitutes a low contrast imaging modality, due to the minute irradiation-induced density changes with the gel. Trapp et al [5] undertook dose response studies of a number of polymer gel dosimeter formulations and table 1 summarizes the results of this work. From table 1 it can be seen that dose response sensitivity varies as a function of initial composition. However, even for sensitive compositions, minimum detectable dose is high, typically greater than 1 Gy. Furthermore, as shown in figure 3, dose resolution (95% confidence) remains high (several Gy) and, in fact, much higher than, for example, MRI [5]. This fact is largely responsible for the lack of clinical applications of x-ray CT polymer gel dosimetry in the literature.
Table 1: Dosimeter sensitivity when imaged with x-ray CT. From [5].

| Gelatin | Agarose | AA | Bis | Water by % weight | CT-dose sensitivity (H/Gy) | r²     | Standard error (Gy) | P-value | Minimum detectable dose (Gy) |
|---------|---------|----|-----|------------------|--------------------------|--------|----------------------|---------|--------------------------|
| 2       | 3       | 3  | 3   | 92               | 0.78 ± 0.03              | 0.98508| 0.32598              | 1.3E−08 | 1.3                      |
| 3.5     | 3       | 3  | 3   | 90.5             | 0.87 ± 0.03              | 0.98889| 0.31228              | 4.2E−09 | 2.4                      |
| 5       | 3       | 3  | 3   | 89               | 0.71 ± 0.02              | 0.99649| 0.12362              | 7.45E−10| 1.0                      |
| 6.5     | 3       | 3  | 3   | 87.5             | 0.59 ± 0.02              | 0.99060| 0.19520              | 2.14E−09| 3.7                      |
| 8       | 3       | 3  | 3   | 86               | 0.54 ± 0.01              | 0.99682| 0.10337              | 2.8E−11 | 2.5                      |
| 5       | 1       | 1  | 1   | 93               | 0.26 ± 0.02              | 0.96834| 0.13654              | 2.8E−07 | 2.7                      |
| 5       | 2       | 2  | 2   | 91               | 0.40 ± 0.04              | 0.97286| 0.12153              | 1.91E−03| 1.0                      |
| 5       | 5       | 5  | 5   | 85               | 1.14 ± 0.04              | 0.98917| 0.40600              | 3.78E−09| 1.6                      |
| 5       | 6       | 6  | 6   | 83               | 1.43 ± 0.05              | 0.99362| 0.42826              | 1.11E−06| 1.1                      |
| 1       | 3       | 3  | 3   | 93               | 1.2 ± 0.1                | 0.93270| 1.11288              | 5.77E−06| 2.4                      |
| 1       | 4       | 4  | 4   | 91               | 1.3 ± 0.1                | 0.96552| 0.58564              | 7.59E−05| 1.5                      |

Figure 2: Dose resolution (95% confidence) for the formulations of table 1. From [5].

2.3. Image filtering
Aside from formulation studies, efforts to improve the dose resolution have been attempted through post-acquisition image filtering. Hilts and Duzenli [6] undertook a comprehensive study of a number of image filters applied to CT images of irradiated polymer gel. Table 3 illustrates the improvements in dose resolution for a range of filters and kernel sizes. While some filters look promising, it should be noted that (i) the filters can widen penumbral regions and (ii) a filters performance can vary based on the particular image in question.
2.4. X-ray dose considerations

A further issue with implementing x-ray CT imaging for polymer gel dosimetry is the fact that CT imaging itself imparts radiation dose to the gel, potentially altering the dose information within the gel. This problem was studied by Baxter et al [7] who showed that, for imaging a single position within the gel and using standard imaging protocols (140kVp, 200mAs, 16 averages), CT imaging imparts <0.5Gy to the gel. Figure 4 illustrates CT dose deposite within a gel for a range of imaging methods (single position, SP; volumetric; varying slice thickness). It can be seen that care must be taken in certain scenarios, as CT dose can become a non-trivial contribution to gel dose. Ensuring that the gel is inactivated prior to imaging will alleviate any problems of CT dose within the polymer gel.

Figure 4: CT dose within a polymer gel dosimeter imaged within a single slice (SP) or volume. Different slice thicknesses are shown. From [7].
2.5. Recent studies in x-ray CT polymer gel dosimetry

2.5.1. Gel sensitivity: As can be seen from prior development, aside from preliminary applications, the low contrast of x-ray CT polymer gel dosimetry has precluded researchers to undertake clinical applications using CT imaging. Rather, efforts have concentrated on improving the gel dosimeter sensitivity to radiation, with the aim of improving resulting image dose resolution. Koeva et al [8] undertook a series of experiments in an attempt to improve the dose sensitivity of polymer gel dosimeters. They substituted the crosslinker (bis-acrylamide) with a range of alternative crosslinkers, with the aim of reducing the primary cyclization of the bis-acrylamide crosslinker. Unfortunately, no suitable alternative crosslinkers were found in this investigation, with all tested crosslinkers giving rise to much lower gel radiation dose sensitivities. A second avenue was to incorporate a co-solvent into the manufacture process, thereby increasing the total solubility of the crosslinker. It has been previously shown [9] that increasing the total monomer/crosslinker content of the gel linearly increases the radiation dose sensitivity. However, the solubility limit of bis-acrylamide in water, the primary gel constituent, is 3%, beyond which bis-acrylamide precipitates out of solution. This presents an upper limit of dose sensitivity in traditional gel recipes. The addition of co-solvent, then, is aimed at increasing the bis-acrylamide solubility limit in the gel solution. Koeva et al investigated several co-solvents, with solubility limits given in table 4. Table 5 demonstrates the improvements in gel dose sensitivity, as measured with NMR, for gels with varying amounts, and types, of co-solvent. Figure 5 illustrates the improvement in gel sensitivity, as measured with x-ray CT imaging, for gels with isopropanol co-solvent. The addition of co-solvent clearly improves dose sensitivity.

Table 4: Solubility limits for bis-acrylamide for gels prepared with a range of co-solvents. From [8].

| Water: cosolvent volumetric ratio | Glycerol (Gly) | Isopropanol (IPA) | N-propanol (NPA) | Sec-butanol (SBA) |
|----------------------------------|---------------|------------------|-----------------|------------------|
| 10:0                             | 3             | 3                | 3               | 3                |
| 9:1                              | **4.5**       | 7                | 7               | **9**            |
| 8:2                              | 5             | 8                | 10.5            | 14               |
| 7:3                              | 5             | 10               | **14**          | **19**           |
| 6:4                              | 5             | 10               | 17              | 23               |

Table 5: Dose sensitivities, as measured with NMR, for gels with and without co-solvent. From [8].

| Recipe | %T | %C | Cosolvent | THPC (mM) | Dose sensitivity (s⁻¹ Gy⁻¹) | Standard error (s⁻¹ Gy⁻¹) |
|--------|----|----|-----------|-----------|----------------------------|---------------------------|
| 1      | 6  | 50 | No cosolvent | 5         | 0.069                      | 0.001                     |
| 2      | 10 | 50 | No cosolvent | 10        | 0.113                      | 0.004                     |
| 3      | 6  | 50 | 10% Gly    | 10        | 0.069                      | 0.009                     |
| 4      | 8  | 50 | 10% Gly    | 10        | 0.132                      | 0.009                     |
| 5      | 6  | 50 | 10% Iso    | 5         | 0.111                      | 0.006                     |
| 6      | 10 | 50 | 10% Iso    | 10        | 0.157                      | 0.008                     |
| 7      | 14 | 50 | 10% Iso    | 10        | 0.187                      | 0.017                     |
| 8      | 10 | 50 | 30% Iso    | 10        | 0.155                      | 0.006                     |
The first co-solvent for dose sensitivity enhancement to be studied in detail was glycerol [10]. It was shown that increasing glycerol concentrations within gel solutions increases irradiated gel dose sensitivity. As well, increasing total monomer/crosslinker concentration within a gel of given glycerol concentration also increases dose sensitivity, as expected (figure 6). However, increasing glycerol concentration has the effect of altering the shape of the resultant dose response curve, hence rendering calibration of dose response more difficult than in traditional dosimeters. Furthermore, the increase in dose sensitivity when using glycerol as co-solvent is not great enough to sufficiently improve the dose resolution of the system. Hence, current focus is in the investigation of isopropanol as co-solvent (see work presented at this conference).

2.5.2. Energy and modality dependence: Recent work by Sellakumar et al [11] has been undertaken to study the x-ray CT imaged dose-response dependence on radiation energy and type (photon, electron). Figure 7 illustrates typical dose profiles for a photon and electron beam. Also shown are the dose response curves for PAGAT gel exposed to a range of photon and electron beam energies. Calibration curves were obtained from the measured depth dose curves. It can be seen that there is little dependence of the calibration curve on the incident beam energy. However, it is pointed out that even small differences can lead to clinically relevant errors.
Figure 7: X-ray CT imaged PAGAT depth dose curves for a 15 MV photon beam (top left panel) and 15 MeV electron beam (top right). Also shown are constructed dose response curves for a range of incident photon (bottom left panel) and electron (bottom right panel) energies. From [11].

2.6. Summary
X-ray CT offers a quick, robust, and practical imaging modality for polymer gel dosimetry. Traditionally plagued with low sensitivity and low dose resolution, efforts in the development of x-ray CT polymer gel dosimetry have centred around the improvement of the dose resolution of the system. Further studies have been undertaken on determining the incident energy-response characteristics.

3. Ultrasound and mechanical property imaging
Ultrasound imaging of polymer gel dosimeters was first proposed by Mather et al in 2003 [12] and is based on the change in ultrasonic properties of irradiated polymer gel. The application of the modality to polymer gel imaging, while promising, is largely in the development phase.

It has been shown that the ultrasonic speed and attenuation within irradiated polymer gel dosimeters is dose dependent and, furthermore, highly dependent on the type of polymer gel undergoing irradiation (see figure 8) [12, 13].
Figure 8: Ultrasonic speed (left panel) and attenuation (right panel) for irradiated PAG and MAG polymer gel dosimeters. From [12].

Mather and Baldock [14] further demonstrated the ability of time-of-flight ultrasound in imaging irradiated polymer gel dosimeters (see figure 9).

Figure 9: Ultrasound image (left panel) and profile through image (right panel) of irradiated polymer gel dosimeters. From [14].

More recently, Crescenti et al have characterized the dose-dependent variation of Young's modulus in irradiated polymer gel dosimeters (figure 10) [15]. They have been able to use elastography measurements to then image an irradiated polymer gel dosimeter (figure 11) [16]. These results are encouraging and demonstrate the possibility of mechanical-property-based imaging of irradiated polymer gel dosimeters.
Figure 10: Variation in Young’s modulus in irradiated polymer gel dosimeters [15].

Figure 11: Elastography image (left panel) of an irradiated polymer gel dosimeter (left panel). Elastography and MRI profiles through irradiated polymer gel dosimeter (right panel). From [16].

4. Raman imaging
Raman spectroscopy, for the purposes of imaging irradiated polymer gel dosimeters, was first proposed by Rintoul et al [17]. They utilized the fact that Raman spectroscopy can be used to determine the dose-dependent decrease in monomer concentrations within irradiated polymer gel dosimeters. Using principle component analysis, they were able to reconstruct a depth-dose dependence within an irradiated polymer gel dosimeter (figure 12).
Figure 12: Reconstruction of a 6MeV depth-dose curve measured using Raman spectroscopy. Ion chamber measurements are shown for comparison. From [17].

While the results of figure 12 are not an "image" per se, this was an early demonstration of the possibility of extending Raman techniques for imaging purposes. However, recently Schulmerich et al [18] have demonstrated the potential if Raman microscopy for tomographic reconstructions of canine bone, as illustrated in figure 13. Bone depths varied between 2 - 4 cm. Hence, it could be envisioned that Raman microscopic imaging for polymer gel dosimetry would be potentially applicable to, for example, brachytherapy seed dose-distributions.

Figure 13: Raman tomographic reconstruction of canine bone From [18].

5. Conclusions
While MRI and optical CT imaging remain the primary modalities for imaging polymer gel dosimeters, alternative modalities such as x-ray CT imaging and ultrasound (and associated mechanical properties) imaging are currently under development. Both show promise in the imaging of dose distributions within irradiated polymer gel dosimeters. Finally, Raman tomographic imaging, while not tested explicitly on polymer gel dosimeters, offer an intriguing possibility for high resolution "micro"-imaging of select dose distributions.

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