Abstract—Advanced radiation techniques such as intensity-modulated radiotherapy (IMRT) for complex geometries in which targets are close to organs at risk have been introduced in radiation therapy, creating a need for procedures that allow easy three-dimensional (3-D) measurement of dose for verification purposes. Polymer gels that change their material properties when irradiated have been suggested for such use. For example, the change in their magnetic properties has been thoroughly investigated with magnetic resonance imaging (MRI). Also, we have previously shown that the mechanical stiffness, i.e., Young’s modulus, of these gels changes with dose. This finding prompted us to assess whether we can image a radiation-induced stiffness distribution with quantitative ultrasound elastography and whether the stiffness distribution is correlated with the dose distribution. A methacrylic-acid-based gel was loaded with scatterers to create an ultrasound echoic signal. It was irradiated to create a rod-like region of increased stiffness with a $10 \times 10 \text{mm}^2$ cross-section. The gel block was compressed in a frame that restricted the movement of the gel to planes orthogonal to the long axis of the irradiated region and ultrasonic echo data were acquired in the central plane during compression. This simplified irradiation pattern and experimental set-up were designed to approximate plane-strain conditions and was chosen for proof of concept. The movement of the gel was tracked from ultrasound images of a different compressional state using cross-correlation, enabling a displacement map to be created. The shear modulus was reconstructed using an inverse algorithm. The role of the magnitude of the regularization parameter in the inverse problem and the boundary conditions in influencing the spatial distribution of stiffness and, thus, final dose contrast was investigated through parametric studies. These parameters were adjusted using prior knowledge about the stiffness in parts of the material, e.g., the background was not irradiated and therefore its stiffness was homogeneous. It was observed that a suitable choice for these reconstruction parameters was essential for a quantitative application of stiffness measurement such as dosimetry. The dose contrast and distribution found with the optimal parameters were close to those obtained with MRI. Initial results reported in this article are encouraging and indicate that with ongoing refinement of ultrasound elastography techniques and accompanying inverse algorithms, this approach could play an important role in gel dosimetry. (jeff.bamber@icr.ac.uk) © 2010 World Federation for Ultrasound in Medicine & Biology.

Key Words: Polymer gel, Dosimetry, Radiation therapy, Ultrasound elastography, Inverse problems, Quantitative elastography.

INTRODUCTION

In radiation therapy, increasingly complex dose distributions with potentially high dose gradients are produced by applying modern and advanced radiation techniques. While conventional one- or two-dimensional (1- or 2-D) dosimetry methods approximately suffice for simple radiation-field verifications, the routine application of modern techniques creates a need for quick, cheap and easy three-dimensional (3-D) dose measurements. Radiation sensitive gels that change their material properties monotonically with radiation dose in combination with magnetic resonance imaging (MRI) for read-out have been shown to offer great potential as a dosimeter in clinical radiation therapy. Their introduction into the clinical routine has been attempted (Crescenti et al. 2007) but has often been frustrated by the high cost and low availability of imaging time on MRI-scanners. Alternative read-out methods, such as systems based on the
determination of the optical density, X-ray attenuation or ultrasound attenuation, have therefore been suggested (Gore et al. 1996; Hiltis et al. 2000; Mather and Baldock 2003; Trapp et al. 2001). The finding that radiation-induced polymerization in such gels also increases their stiffness (Crescenti et al. 2009) has prompted us to carry out the experiments reported herein, to image dose distributions using quasi-static ultrasound elastography (e.g., Bamber et al. 2004; Ophir et al. 1991). Advantages of using ultrasound methods for dosimetry include that ultrasound scanners are widely available in clinics, are low cost and an increasing number possess real-time high-resolution elastography functionality.

Quasi-static elastography is performed by compressing the sample externally and acquiring images (for example with ultrasound or MRI) from within the sample during the compression. By comparing images from different compressional states, e.g. by performing a point-wise cross-correlation of the reference and the (incrementally) deformed image, a displacement map is produced. Stiff areas are found to strain less than soft areas because materials of different stiffness strain differently when equal stress is applied on them. Strain may be imaged by taking the derivative of the axial displacement in the axial direction. Strain images are also called elastograms. Many manufacturers of ultrasound scanners have now implemented algorithms to image strain in tissue. However, strain is not only dependent on the local stiffness but also on the stiffness distribution and boundary conditions. Therefore, it does not directly image the stiffness distribution (Kallel et al. 1996). In dosimetry, knowledge of the stiffness distribution is critical because Young’s modulus is directly linked to the dose (Crescenti et al. 2009).

However, recent progress in quantitative elastography may solve that problem. From a measured displacement or strain map, an image of the stiffness distribution can be computed by solving the inverse elastic problem. Most inverse algorithms work by solving a forward problem iteratively (e.g., Dooley et al. 2000, Oberai et al. 2003) wherein a stiffness distribution and boundary conditions are assumed a priori and the corresponding displacement field is evaluated by solving the equations of equilibrium for the material. The distribution of the material properties is modified iteratively, until a satisfactory match between the predicted and measured displacements is achieved. Such algorithms provide an estimate for a relative shear modulus or Young’s modulus distribution. Absolute values can be computed via the knowledge of the stiffness at one point, for example by performing a separate calibration experiment with a homogeneous material of the same stiffness. However, such algorithms suffer from a strong dependence on boundary conditions (Barbone and Bamber 2002; Dooley et al. 2000), which can be difficult to measure or control. Relatively little work has been done so far on the choice of the boundary condition and their effect on the elasticity estimation.

This article describes an evaluation of quantitative ultrasound elastography for radiation-dose imaging, with emphasis on correctly modeling the boundary conditions. For simplification and for proof of concept, a plane-strain experimental set-up and 2-D reconstruction of the shear modulus was selected. A similar approach may also be used in three dimensions.

MATERIALS AND METHODS

Gel preparation

The MAGIC gel composition described by Fong et al. (2001) was chosen for the studies because of its relatively low toxicity compared with other radiation sensitive gels and because external mechanical compression required the handling of uncontained gels. However, the formulation was adapted to create ultrasound echoic signal from everywhere within the gel; employing the technique of Bamber et al. (2004), polyethylene granules of a mean diameter of 119 μm (GUR415; Hoechst, Frankfurt, Germany) were added to the gelatin-in-water solution at 50°C. The solution was then cooled to approximately 35°C in a chamber while repeatedly stirring gently and creating a partial vacuum to extract the air from the solution. Air in the gel would decrease the penetration depth of ultrasound and, if oxygen is present in large quantities, it may also inhibit the radiation-induced polymerization of the gel. Then, solutions of hydroquinone (99%, Sigma-Aldrich, Buchs, SG, Switzerland), ascorbic acid (minimum 99.0%, Sigma-Aldrich) and cupric sulphate pentahydrate (approx. 99%, Sigma-Aldrich) were added, followed by methacrylic acid (approx. 99%, titration, Sigma-Aldrich). The gel solution was gently stirred to achieve a homogenous distribution of all components and poured into a 4 × 4 × 12 cm³ container made in-house from Barex with a wall thickness of 4 mm to set. For calibration purposes, four cylindrical polymethyl methacrylate containers (53 mm diameter, 35 mm height), which were again built in-house, were also filled with this gel.

The samples were kept in a refrigerator at approximately 10°C for 1 day before production and irradiation, for another day between irradiation and MR-measurement and again for 1 day between MR-measurement and elasticity measurement.

Gel irradiation

Before the irradiation, the contained gel samples were warmed to room temperature (21.4 ± 0.1°C) in a water bath, which took approximately 6 h. For calibration, two of the cylindrical samples were each separately placed in the center of a 30 × 30 × 30 cm³ water tank and irradiated to a radiation dose of 20.8 Gy by applying
were chosen to provide an in-plane spatial resolution of 1 mm² and a slice thickness of 5 mm with a good signal-to-noise ratio within less than 30 min.

Mechanical compression and acquisition of ultrasonic radio-frequency data

For elastography, the gels had to be compressed mechanically while simultaneously acquiring radio-frequency (RF) image data. To do so, the contained gels were warmed to room temperature (19.4 ± 0.1°C) in a water bath sufficiently long (> 6 h) to guarantee a homogeneous temperature within all gels. The homogeneous calibration gels were then compressed along the axis of the cylinder with a mechanical testing device (Instron 3342 with load-cell 2519-103; Instron, Bucks, UK) applying a precompression just sufficient to make good contact between the lubricated compressor plate and the gel and a subsequent strain-rate of 2% per second up to a maximal strain of 8%. As this was a quasi-static compression, the result was independent of the strain-rate. It was verified that at the maximal strain, the stress-strain relation was still linear and that the gel was not damaged and repeatable and reproducible compression tests were possible. Young’s modulus $E$ was then determined from $E = \frac{\text{stress}}{\text{strain}}$. The inhomogeneously irradiated sample was compressed along the y-direction (Fig. 1) using the same technique. For that procedure, the gel rested in a mechanical frame, which allowed expansion in the x-direction but prevented motion in the z-direction. During the compression, a sequence of RF ultrasonic echo image frames was acquired at a frame rate of 14 Hz in the central x-y plane with a scan depth of 6 cm (Z.one ultrasound scanner with L10-5 linear array; Zonare Medical Systems Inc., Mountain View, CA, USA).

The transversal relaxation rate and Young’s modulus of the two homogeneously irradiated and two unirradiated samples were thus determined with MRI and elasticity measurements. As shown previously, the relationship between the transversal relaxation rate and dose, and Young’s modulus and dose in the dose range of 0 to 20 Gy is close to linear and can be approximated as such (Crescenti et al 2009). Under the assumption of linearity, the linear parameters for these relationships were determined from the measurements of the four homogeneous samples for this gel batch. This approximate calibration was regarded as sufficient for our purposes in this initial study but we recognize that in any future application of the method, even if the measured parameters are linearly related to dose, it will be desirable to obtain a calibration using more than two dose points.

### Table 1. MRI parameters for the acquisition of transversal relaxation time (T₂) weighted images of the gel

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>2D T₂-weighted multi-spin-echo sequence</td>
</tr>
<tr>
<td>Field of view</td>
<td>256 mm</td>
</tr>
<tr>
<td>Relative field of view</td>
<td>100%</td>
</tr>
<tr>
<td>Matrix size</td>
<td>$256 \times 256$ pixels</td>
</tr>
<tr>
<td>Echo times</td>
<td>20, 40, 60, 80, 100, 120, 140 and 160 ms</td>
</tr>
<tr>
<td>Repetition time</td>
<td>2 s</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>84 Hz</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm</td>
</tr>
</tbody>
</table>
Inverse reconstruction of Young’s modulus

With the ultrasonic scatterers present in the gel, a speckle pattern was obtained. The speckle pattern is generated by superposition of the RF echoes from all scatterers. The presence of such a pattern enabled the computation of displacement between two RF images via cross-correlation. Each of the two images was acquired with the gel at a different compressional state, e.g. with a difference of 0.29% overall strain. A series of 18 of such displacement maps was averaged, resulting in a lower noise but smoothed displacement map (75 × 101 matrix with a pixel size of 0.473 mm in x-direction and 0.317 mm in y-direction). This displacement map was denoted as the displacement vector \( \mathbf{u}_{\text{meas}} \) for further mathematical computation.

Once the displacement vector \( \mathbf{u}_{\text{meas}} \) was found, the distribution of the material properties was determined by solving the inverse elasticity problem iteratively using the algorithm described in Oberai et al. (Oberai et al. 2003, 2004). In this approach, a vector of material parameters was sought that would minimize the scalar \( \pi \), which contains the difference between the measured and predicted displacements,

\[
\pi = \frac{1}{2} \left| \left| \mathbf{u} - \mathbf{u}_{\text{meas}} \right| \right|^2 + \frac{\alpha}{2} R(E). \tag{1}
\]

In the equation above \( \mathbf{u} \) is the vector of the nodal values of the predicted displacement field that is obtained by solving the equations of equilibrium for an incompressible, linear, isotropic elastic solid in the state of plane strain. The variable \( E \) is the vector of the nodal values of Young’s modulus (in contrast to the scalar value of \( E \) for the homogenous material above). The idea is to find the value of \( E \) that minimizes \( \pi \). Also in the equation above, \( R \) is the regularization functional. Its job is to ensure that, in the presence of noisy measurements, the recovered material distribution retains certain physical characteristics such as smoothness. In our examples we selected the total variation diminishing (TVD) functional (for example see Vogel 2002) as a regularization term. This restricted the total absolute change in the recovered Young’s modulus distribution while allowing this change to be very steep. The parameter \( \alpha \) is the regularization parameter that controls the importance of the regularization term \( R(E) \) relative to the displacement matching term \( \left| \left| \mathbf{u} - \mathbf{u}_{\text{meas}} \right| \right|^2 \). If \( \alpha \) is large, the solution is smooth; however, the corresponding displacement matching term is large. On the other hand if \( \alpha \) is small the solution may be noisy while the displacement matching term will be small. By varying \( \alpha \) over several orders of magnitude, the largest possible value was sought that does not cause the displacement matching term to increase much beyond the value obtained with \( \alpha = 0 \). To determine the value of \( E \) that minimizes \( \pi \), a Quasi-Newton method (Broyden-Fletcher-Goldfarb-Shanno method in particular) was applied. This method requires the gradient of the scalar \( \pi \) with respect to each entry of \( E \) at all iterations. This gradient was efficiently evaluated by solving an adjoint elasticity equation as described in Oberai et al. (2004). At every iteration of the optimization algorithm, for a given distribution of the material parameter, two linear elastic problems were solved to determine the predicted displacement field and the adjoint field. This required the knowledge of boundary conditions in axial and lateral directions on all edges. In the axial \((y-)\) direction, for all edges, the predicted displacement field was set equal to the measured displacements. However, there was no reliable estimate of the lateral component of the measured displacement field, so this could not be imposed as a boundary condition in the lateral \((x-)\) direction; but as the traction on the vertical edges was small (the gel could freely expand), the traction was set to zero in the lateral direction on these edges. Further, since the top and bottom surfaces were lubricated, the lateral traction on these edges, which was shear traction, was also set to zero. Results for these conditions, shown below, demonstrated a need for change to this assumption. The contact of the top and bottom surface was then modeled using uniform springs in the lateral \((x-)\) direction all along the top and bottom surfaces. The stiffness of these springs (representing traction/friction at the surface), relative to the stiffness of the material, determined the extent of lateral displacement on these surfaces. The optimal value of the stiffness for these springs was determined by requiring the recovered material stiffness to be homogeneous close to the top and bottom surface. This homogeneity was expected because the gel was not irradiated close to the edges. It was also confirmed with MRI.

The finite element method was used for solving the linear elasticity problems for determining the predicted and the adjoint displacement fields. It is well known that the standard finite element formulation fails for the incompressible materials we are working with. This problem was overcome by using selective reduced integration (SRI) while evaluating the stiffness matrix (see Hughes 2000 for example).

RESULTS

The calibration experiments with the homogeneous gels provided data for the relationship between the transversal relaxation rate and dose (Fig. 2) and Young’s modulus and dose (Fig. 3). As mentioned above, the assumption of linearity for doses up to 20 Gy is justified from previous work (Crescenti et al. 2009). The y-axis intercepts were 4.27 s\(^{-1}\) and 2.23 kPa\(^{-1}\) and the slopes were 0.99 s\(^{-1}\)Gy\(^{-1}\) and 0.29 kPa\(^{-1}\)Gy\(^{-1}\) for the MRI (Fig. 2) and mechanical calibration (Fig. 3), respectively.
Figure 4 shows the dose distribution obtained by applying the relationship between Young’s modulus and dose to the relative elastic modulus distribution computed with the inverse elasticity algorithm. The figure gives the reconstruction for the assumption of completely slippery boundary conditions and for a regularization parameter $\alpha$ of $10^{-2}$. Because of observed boundary artefacts (incorrectly high dose values at the top and bottom boundary) seen in Figure 4, further reconstructions were performed. This time, friction at the surfaces was assumed to be present (simulated with spring elements) and the spring constants were adjusted in the model to produce a homogeneous background. The dose distribution shown in Figure 5 resulted. The same value of the regularization parameter was used as in Figure 4 to allow direct comparison.

The relationship of the magnitude of the displacement matching term (first term on the right side in eqn [1]) and the inverse of the regularization parameter is given in Figure 6, for a large range of the regularization parameter ($\alpha$ from $10^{-5}$ to $10^{0}$) in a logarithmic scale. The optimal value for the regularization parameter was found to be approximately $10^{-2}$, which produced a displacement mismatch that was much smaller than that for larger values of $\alpha$ and was close to the mismatch obtained when $\alpha$ approached zero. The effect of changing
the regularization parameter on the reconstructed dose distributions is illustrated in Figures 5 and 7.

Figures 7a and b (together with Fig. 5) visualize the variation introduced by a different choice of the regularization parameters. In Figure 7, the parameter was set to $10^{-2}$ and $10^{-3}$, while in Figure 5 it was set to $10^{-2}$. The same optimal value for the spring constant was used in all these figures.

Figure 8 shows the reference dose distribution, which was obtained by measuring the transversal relaxation rate $R_2$ with MRI and by using the relationship between $R_2$ and dose shown in Figure 2. For easier visualization and direct comparison of the dose contrast, gradient and fluctuation, dose plots through the center of the high-dose regions in the Figures 5, 7 and 8 are given in Figure 9, in x-direction (a) and y-direction (b).

**DISCUSSION**

As seen in Figures 4, 5, 7 and 9, the choices of both the boundary conditions and the regularization parameter greatly influence the dose estimation. The latter influences the magnitude of the stiffness/dose contrast, the smoothness of the image and the maximum stiffness/dose gradient throughout the body of the model. A wrong choice of the boundary conditions introduces errors at the edges; however, they propagate from the edges into the body. This error was minimized by using a priori knowledge of the expected stiffness distribution. Here, the background could be assumed to be homogeneous because it had not been irradiated, which was also verified with MRI (Fig. 8). This knowledge was used to fine-tune the spring constant of the lateral springs at the top and bottom surface, which compensated for the inability to create perfectly slippery boundaries. Most artefacts (Fig. 4) that were created by erroneous assumption of perfect slip at these boundaries disappeared except in the bottom right corner, where a new artefact emerged (Fig. 5). This is probably due to nonuniform friction along the bottom surface of the gel, which was assumed to be uniform in the reconstruction with the same spring-constant for all spring elements.

The optimal value of the regularization parameter was selected from the graph of the displacement mismatch term versus the regularization parameter (Fig. 6). In this curve, it is observed that as the regularization parameter is increased (from a very small value), the corresponding displacement mismatch is not altered significantly. However, at a certain value of the parameter ($10^{-2}$ in our case), the value of the mismatch term increases steeply. This represents the
maximum value of the regularization parameter that can be used without compromising the closeness of the predicted and measured displacement fields. This is the “optimal” regularization parameter we have used in our calculations. An alternative to this approach would be to use the L-curve, however, the L-curve is known not to work very well in the case of TVD regularization. Figures 5, 7 and 9 show that a correct choice of the regularization parameter is essential, if a correct absolute value for the stiffness is needed, as for example in dosimetry. Good regularization helps to avoid a transfer of measurement-noise into the dose image and knowledge of homogeneity in the background may help in adjusting the regularization parameter. However, as the regularization parameter is increased, it will eventually also lower the dose contrast and smooth dose gradients. The smoothing occurs mostly in y-direction as is clearly visible in Figure 9b, where the dose shoulders get wider for larger values of \( \alpha \). For larger values of the regularization parameter \( \alpha \), less noise is visible in the background, however, the shape and the dimension of the highly irradiated and, hence, stiff square inclusion are not recovered accurately (see Fig. 7b). Further, errors due to incorrect boundary conditions appear to penetrate deeper into the gel; e.g., in Figure 7b, where the largest value of \( \alpha \) was used, the above mentioned falsely stiff artefact at the bottom right corner almost connects with the truly stiff central area. Amongst the data shown here, the optimal value of the regularization parameter \( \alpha = 10^{-2} \) was found to produce a dose distribution closest to the reference, with a dose contrast that was approximately 10% higher than the reference (Fig. 9). A slightly stronger regularization parameter could have improved the dose accuracy and reduced the remaining noise at the sides but at the cost of even more dose-gradient smoothing in the vertical direction.

It is encouraging that, by adjusting the boundary condition (Figs. 4 and 5) and optimizing the regularization parameter (Figs. 5 to 7), an optimized image (Fig. 5) with a dose contrast and distribution similar to the reference dose distribution measured with MRI (Fig. 8) was found. While this is encouraging, these results indicate that quantitative elastography still needs improvement for application to clinical gel dosimetry. Examples of ways in which the calibration may be improved include the use of more than two dose levels, increasing the number of samples and reduction of the influence on the calibration of various other sources of error, including that due to inhomogeneous polymerization as extensively discussed in Crescenti et al. (2009). Other improvements of the method could involve better control of the boundary conditions when imaging the sample, for example ensuring almost perfect slip. Alternatively, one
could acquire displacement data in both directions, along and perpendicular to the axis of compression. This would make the requirement of perfect slip at the boundaries dispensable. Another problem associated with boundary conditions is that they are imposed strongly in the inverse problem. Thus, any noise in the measurement of the boundary conditions has a great impact on the reconstruction. In this regard it will be interesting to develop inverse problem algorithms that do not rely on or circumvent imposing any boundary conditions.

Potential for improvement also lies in the use of 3-D image data (and therefore displacement maps), which would allow 3-D inverse-elasticity algorithms to be applied without making the simplifying assumption of 2-D plane strain. This also coincides with the final goal of gel dosimetry of providing an accurate and simple method to measure complex 3-D dose distributions.

However, the development of such 3-D inverse algorithms for elastography is still ongoing and phenomena for experimental verifications and performance tests, especially with complex stiffness distributions, are difficult to produce as of now. A new potential application of radiation sensitive gels, therefore, lies in the fact that almost any stiffness distribution can be achieved with appropriate irradiation. Indeed, some stiffness distributions, such as those with small gradients, may be difficult or impossible to achieve by any other method. A reference dose distribution and, hence, stiffness distribution, could be verified with other methods such as MRI. Thus, these gels may be used to assess the performance of elastography techniques. The gel used here requires careful handling because of its toxicity and its life-time is very limited once taken out of a container but other choices for the composition of the gel may improve these attributes.

**CONCLUSION**

The objective of our studies was to evaluate whether quantitative elastographic methods offer potential for imaging dose in radiation sensitive gels based on radiation-induced stiffness contrast. For proof of this concept, quantitative elastographic studies were performed under simplified conditions, applying 2-D iterative reconstruction of the stiffness distribution to data obtained from a plane strain experiment. By applying a stiffness versus dose calibration using samples of gel from the same batch as that employed for dose imaging, it was found that the reconstructed dose contrast and distribution obtained were close to those measured with MRI, with the peak dose contrast being approximately 10% too high. While this was encouraging, it was also observed that a good choice of the regularization parameter in the iterative algorithm was essential for minimizing noise and for maximizing the accuracy of the dose contrast and the dose gradient. It was also observed that the boundary conditions can greatly influence the dose reconstruction close to the edges. Overall, we conclude that whilst the performance is not yet sufficient for clinical dosimetry, inverse elastographic imaging is a new technique with many clear opportunities for improvement from which gel dosimetry could benefit.

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