A variable echo-number method for estimating R_2 in MRI-based polymer gel dosimetry

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(Received 26 September 2010; revised 2 December 2010; accepted for publication 2 January 2011; published 28 January 2011)

Purpose: Spin-spin relaxation rate R_2 is commonly used to quantify absorbed dose for magnetic resonance imaging (MRI)-based polymer gel dosimetry. R_2 is estimated by applying a parameter fitting algorithm to a train of spin-echo signals. However, a careless application of a large number of echoes can result in anomalous R_2 values because the echo signal intensity decreases to the background signal offset level for a long echo time. In this article, the authors proposed and evaluated a variable echo-number (VAREC) method to remedy the problem.

Methods: The VAREC algorithm uses only echo signals, whose intensities are greater than a preset threshold. Here, the threshold is defined as the standard deviation of Gaussian noise times a multiplier α . The authors implemented three R_2 estimation methods in an in-house program: The nonlinear least-squares algorithm (NLLS), the VAREC method, and the maximum likelihood estimator with the Rician signal intensity distribution (MLE_R). Those methods were used to estimate the R_2 values of test phantoms with known R_2 values and BANG3-type polymer gels, which were irradiated to 12 different doses ranging from 0 to 50 Gy. The R_2 values were measured by using a 32-echo CPMG pulse sequence on 3 T MRI scanners. The R_2 values of the VAREC method were compared with those of NLLS and MLE_R.

Results: The R_2 values of the NLLS method incorrectly decreased to the zero-dose level for doses greater than 10 Gy. The R_2 values of the VAREC method with $\alpha=2$ agreed with those of MLE_R within the measurement uncertainty. The uncertainties of the R_2 values were the smallest for $\alpha=2$ or 3 among various α values.

Conclusions: The VAREC algorithm is simple, fast, and robust for the R_2 estimation. The authors recommend this method with $\alpha=2$ or 3 for R_2 estimation using multispin echo MRI protocols. © 2011 American Association of Physicists in Medicine. [DOI: [10.1118/1.3544659](https://doi.org/10.1118/1.3544659)]

Key words: quantitative MRI, CPMG, polymer gel dosimetry, maximum likelihood estimator, R_2 , radiation dose

I. INTRODUCTION

Polymer gel dosimeters are a promising tool to obtain true three-dimensional (3D) dose distributions.¹ The dose information recorded in the polymer gel can be deciphered by measuring the dose-dependent changes in physical parameters of the polymer gel. At present, magnetic resonance imaging (MRI) and optical computed tomography (optical-CT) are two of the most advanced and well-studied modalities for this purpose. These methods have advantages and disadvantages; hence, both techniques will be used for some time until a clear “winner” appears between them. The current study was focused on the MRI technique.

The changes in magnetic properties of polymer gel upon irradiation can be detected by measuring the spin-lattice relaxation time T_1 or the spin-spin relaxation time T_2 of the polymer gel.² The magnetization transfer ratio was also used to quantify the absorbed dose.^{3,4} Among those parameters, T_2 , or the spin-spin relaxation rate $R_2(=1/T_2)$, is the most sensitive to dose variation; hence, a majority of MRI-based polymer gel dosimetry studies has used the R_2 value for dose measurements.¹

R_2 values can be estimated by measuring the magnitude signals of multiple spin echoes produced in a phantom. Under an assumption of a monoexponential decay of the echo signal intensity, we can estimate R_2 by applying a parameter fitting algorithm to the train of echo signals. The R_2 value of the irradiated polymer gel depends on both the absorbed dose and the characteristics of polymer gel and ranges from 1.0 s^{-1} to as large as 80 s^{-1} . The number of data points sampled over the decaying signal influences the accuracy and precision of the estimated R_2 value.⁵ Usually, one should use as many echoes as possible for high precision dosimetry if an adequate MR pulse sequence is available. For the past ten years, investigators in the polymer gel dosimetry field used multispin echo pulse sequences, typically, the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence, with 4–64 echoes.^{6,7} Since the shortest echo-time spacing is limited by the machine hardware to about 10 ms, we generally end up sampling the signal for a time length much longer than T_2 . When the decay signal is sampled over a time interval much longer than the length of T_2 , however, the signal intensity reaches the image magnitude background signal offset level.

Then, the accuracy of the R_2 estimation suffers, usually leading to the underestimation of R_2 values with large uncertainties. In fact, it was theoretically shown before that the uncertainty of the estimated R_2 values is the smallest for an optimum number of spin echoes used for the estimation.⁸ In addition to the number of echoes, the echo-time spacing also influences the precision of the estimated R_2 and consequently the dose resolution.^{9,10} However, the echo-time spacing will be fixed in this study because varying the echo-time spacing for every voxel is not practical. It is noted that several authors recently studied new mathematical methods considering the effect of signal noise on the R_2 estimation.^{11,12}

In this article, we proposed a numerical algorithm to automatically select the number of echoes used for R_2 estimation without knowing the R_2 value beforehand. The new algorithm excludes the echo signal whose intensity is below specific signal intensity (or a threshold) from the R_2 estimation process. This algorithm is named as a variable echo-number (VAREC) method because the optimum number of echoes varies depending on the R_2 value of a voxel being analyzed. The idea for limiting the number of echoes used for R_2 estimation to avoid the effect of noise is not new.^{8,13,14} The proposed method is a practical solution in selecting the voxel-dependent maximum number of echo signals for the R_2 estimation. In this study, we demonstrated the feasibility of the VAREC method and examined the effect of the threshold value on the estimated R_2 value and its uncertainty.

II. METHODS AND MATERIALS

II.A. Test phantoms

We used BANGkit from MGS Research (Guilford, CT).¹⁵ The polymer gel was made of BANG[®]3 polymer gel (water+gelatin+methacrylic acid), 1 mole of ascorbic acid-L, and 0.1 mole of CuSO_4 . The polymer gel was prepared without any effort to minimize oxygen contamination and this is justified because of its normoxic nature. The polymer gel was contained in 24 small glass vials (2 cm diameter and 9 cm long cylinders) and a 200 ml plastic container (9 cm diameter and 10 cm long) for experiments. The phantoms containing the polymer gel were left under room temperature (about 22 °C) for 1 day before irradiation. MRI scanning was done after the irradiated gel phantoms were left overnight in a MRI scanner room.

To evaluate the accuracy of T_2 measurements using a specific MRI pulse sequence, we used two test phantoms with known T_1 and T_2 values. The first phantom (bottle phantom) was a 2 L cylindrical bottle filled with liquid (99.6% weight of water and 0.4% weight of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$), of which T_1 and T_2 values were 110 and 100 ms (or $R_2 = 10 \text{ s}^{-1}$), respectively. The second phantom (clear phantom) was a 17.4 cm diameter spherical container filled with liquid (99.87% weight of water and 0.13% weight of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$), of which T_1 and T_2 values were 280 and 270 ms (or $R_2 = 3.7 \text{ s}^{-1}$), respectively.

FIG. 1. The spatial arrangement of polymer gel phantoms used for MRI scans. The doses to calibration vials in the outer layer were 0, 1, 2, and 4 Gy (clockwise). The doses to calibration vials in the inner layer were 6, 8, 10, 15, 20, 30, 40, and 50 Gy (clockwise). Two vials received the same dose. The dose at the center of the large 200 ml phantom was 45 Gy. This image was acquired at the first echo time $TE = 13.6 \text{ ms}$.

II.B. Irradiation of BANG polymer gel

Polymer gel phantoms were irradiated with a 6 MV photon beam from a Varian 2300C/D Clinac (Varian Medical Systems, Palo Alto, CA). Small cylindrical vials were irradiated in a $37 \times 37 \times 37 \text{ cm}^3$ cubic water tank to achieve uniform medium. The long axes of the cylindrical vials were placed perpendicularly to the beam axis. Two parallel opposing lateral beams with a $20 \times 20 \text{ cm}^2$ field size were used for irradiation. Two vials were irradiated at the same time. There were 11 pairs, which were irradiated to various doses, i.e., 1, 2, 4, 6, 8, 10, 15, 20, 30, 40, and 50 Gy. One pair of unirradiated vials was used as a control. A 200 ml phantom was irradiated in air using a pair of $4 \text{ cm} \times 4 \text{ cm}$ opposing parallel photon beams from four directions orthogonal to each other. The dose at the overlapping region was 45 Gy.

II.C. MR scanning

Polymer gel phantoms were scanned using a Magnetom Trio A Tim 3 Tesla (3T) MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the Center for Magnetic Resonance Research (CMRR). Twenty-four calibration vials were placed around the 200 ml phantom for the scanning as depicted in Fig. 1. The entire phantom assembly was securely placed inside a 12-channel head matrix coil. The phantoms were scanned twice. For the first scan, we used an inversion recovery pulse sequence to measure the T_1 value of the polymer gel. For the subsequent R_2 measurement scan, the repetition time was set to four times the T_1 value.

The CPMG pulse sequence as implemented in Siemens MRI scanners (denoted as *cp_mc*) was used for R_2 measurements. The imaging parameters were set as follows: The echo-time spacing (ΔTE) = 13.6 ms, the number of echoes = 32, the field-of-view (FOV) = $25.6 \text{ cm} \times 25.6 \text{ cm}$, the pixel size = $1 \text{ mm} \times 1 \text{ mm}$, the slice thickness = 2 mm, and the number of acquisitions (NEX) = 1. The measured T_1 value of the polymer gel was 1.8 s; hence, the repetition time (TR) was set to 7 s. The interleaved acquisition method was used to acquire 15 imaging slices within one repetition time period.

Two test phantoms (the bottle phantom and the clear phantom) were scanned with a Siemens 3T MRI scanner at Nagoya University in Japan. The hardware configuration including the scanner model was identical to that used at CMRR. The CPMG pulse sequence (cp_mc) with 32 echoes was used for the $R2$ measurements. The scanning parameters were as follows: $\Delta TE = 13.3$ ms, $FOV = 26$ cm $\times$ 26 cm, the pixel size = 1.016 mm $\times$ 1.016 mm, the slice thickness = 5 mm, $NEX = 1$, and $TR = 5$ s. Five imaging slices were acquired.

The magnitude of the background signal can be measured in a small region outside the image of the phantom. By assuming that the magnitude signal obeys the Rayleigh distribution in image regions with no NMR signal, the measured image magnitude background signal offset M_{BG} can be related to the standard deviation of the true Gaussian noise σ by^{13,16,17}

$$M_{BG} = \sqrt{\frac{\pi}{2}} \sigma = 1.253 \sigma. \quad (1)$$

This equation was used to obtain σ from M_{BG} .

Strictly speaking, Eq. (1) is only applicable to the echo signals acquired by using single-receiver system (or coil). For multiple-receiver systems (or multichannel phased array coils) such as the 12-channel head coil used for the current study, the equation must be modified.^{11,19} One of major advantages with a multiple-receiver system is a potential reduction of noise. Hence, the true signal-to-noise ratio (SNR) of images taken with a multiple-receiver system may be larger than SNR estimated by assuming a single-receiver system along with Eq. (1). In this study, however, all equations were formulated by assuming a single-receiver system for simplicity. The precise effect of advanced coil designs on the proposed $R2$ estimation method will be investigated in the future.

II.D. $R2$ estimation methods

In general the probability distribution of the magnitude of spin-echo signal can be represented by the Rician distribution. Hence, a parameter estimation problem can be formulated using the maximum likelihood estimation (MLE) method, for which the following objective function is maximized:^{13,18}

$$L(\rho_0, R2) = \prod_{n=1}^N \frac{M_n}{\sigma^2} \exp \left[-\frac{M_n^2 + S^2(t_n)}{2\sigma^2} \right] I_0 \left[\frac{M_n S(t_n)}{\sigma^2} \right] \varepsilon(M_n). \quad (2)$$

Here, σ is the standard deviation of the Gaussian noise, N is the total number of echoes, I_0 is the zeroth-order modified Bessel function, and ε is the unit-step Heaviside function. M_n is the image magnitude of echo signal measured at the n th echo time t_n . $S(t_n)$ is the true signal intensity $S(t)$ at echo time t_n . By assuming a monoexponential decay of the echo signal intensity, we can express $S(t)$ by

$$S(t) = \rho_0 \exp(-R2 \cdot t), \quad (3)$$

where the pseudodensity ρ_0 is the signal intensity at echo time $t=0$.

The parameters ρ_0 and $R2$ in Eq. (3) can be estimated by directly solving the MLE problem given by Eq. (2). In this study, we solved this problem by using a simplex search method, which does not require the derivatives of the objective function. The function “fminsearch” in MATLAB (MathWorks, Inc., Natick, MA) was used for the solution. This solution method is denoted as MLE_R. Recent publications^{11,12} showed that the MLE_R method provides accurate $R2$ values even for images with a low SNR; hence, we used the $R2$ values of MLE_R as reference values, which were compared to the $R2$ values obtained by other methods. With the MLE method, the lower bound of the variance of estimated $R2$, or the uncertainty of $R2$, is given analytically by using the Cramer–Rao lower bound (CRLB) formula.^{5,12,13,18} The CRLB formula can be used to quickly obtain an estimate of the uncertainty of the measured $R2$ value at every voxel.

The MLE_R solution can be simplified when the echo signal intensity is much larger than the standard deviation of the noise (or typically SNR is greater than 3). In this case, the Rician distribution can be approximated by the Gaussian distribution,^{13,17} so the MLE problem given by Eq. (2) is equivalent to the nonlinear least-squares (NLLS) estimation.¹³ Furthermore, by assuming that σ is independent of the signal intensity, the NLLS problem becomes estimating the parameters through minimization of the following objective function F :

$$F(\rho_0, R2) = \frac{1}{N} \sum_{n=1}^N \{S(t_n) - M_n\}^2. \quad (4)$$

We solved this minimization problem using the “lsqcurvefit” function with the Levenberg–Marquardt algorithm as implemented in MATLAB. We denote this method as NLLS, with which all multiple echo signals were used for the $R2$ estimation.

For the proposed new solution, we further modified the NLLS solution as follows. It was previously demonstrated that the logarithm of the MLE function Eq. (2) has only one maximum.¹⁸ Hence, a faster solution is first to take the partial derivatives of Eq. (4) with respect to the parameters ρ_0 and $R2$. The stationary condition of the function warrants that the derivatives are zero at the minimum. Consequently, we obtain a set of nonlinear equations for two unknowns. Those equations can be easily solved by applying a standard root finding routine for a nonlinear equation. For this study, we used a combination of bisection, secant, and inverse quadratic interpolation methods, which is implemented in MATLAB as a function called “fzero.”

When the measured decay signals are carefully examined, we easily notice that the signal intensities at echo times much longer than $T2$ are not usually distinguishable from the measured background signal offset. If one uses those data, the parameter estimation is not accurate and the uncertainty

in the estimation becomes large. To remedy this problem, we proposed to use only the echo signals whose intensities are larger than a threshold M_λ . Here, the threshold is equal to the standard deviation of the Gaussian noise σ times a multiplier α (or $M_\lambda = \sigma \cdot \alpha$). Note that α is the SNR of a voxel with the signal intensity equal to the threshold value. To automatically determine the maximum number of echo signals useful for R_2 estimation, we calculated the average of three consecutive echo signal intensities starting at the first echo in the train of multiple echo signals. When the average signal intensity of the three signal intensities beyond the l th echo is equal to or smaller than the preset threshold M_λ , we set the number of the echoes used for the R_2 estimation to l . The R_2 estimation method utilizing this algorithm is called the variable echo-number technique, which is denoted as VAREC. Similar algorithms were used by other investigators under different names such as the truncation method.²⁰ Since the R_2 estimation method is applied to the echo signal intensity measured in a small voxel, the decaying echo signal intensities fluctuate more than the data taken over a large number of voxels. If only one echo signal is used to determine whether the signal intensity has reached the image magnitude background signal offset level, the selection of the last echo time may be erroneously shorter or longer than the true time. To preclude such an erroneous selection of the last echo signal, we used the average of three consecutive echo signal intensities.

Here we show that the time at which the echo signal intensity reaches the measured background signal offset level (denoted as t_∞) weakly depends on SNR of the scanned images. It is easy to find a relationship between SNR and t_∞ for a given T_2 by assuming a monoexponential decay of the echo signal intensity

$$\frac{t_\infty}{T_2} = \log \left(\sqrt{\frac{2}{\pi}} \text{SNR} \right). \quad (5)$$

Using this equation, one finds that t_∞/T_2 are 2.1, 3.2, 3.7, and 4.4 for SNR=10, 30, 50, and 100, respectively.

II.E. Data analysis and image processing

We used two programs depending on the tasks for analyses. The IMAGEJ program (National Institute of Health, Bethesda, MD) (<http://rsb.info.nih.org/ij/>)²¹ was used to measure the pixel values and to determine M_{BG} . We developed a GUI routine called ATOM²⁸ on the MATLAB platform (Version 2008b and higher) to process the DICOM data generated by a MRI scanner and to compute R_2 maps using the NLLS, VAREC, and MLE_R methods, eventually to obtain 3D dose distributions of irradiated polymer gel phantoms. It is noted that the median image filter was applied to all raw MR image data before an R_2 estimation algorithm was used in the ATOM program.

III. RESULTS

III.A. Echo signal analysis

We measured the mean signal intensities averaged over a small circular area (about 80 pixels) in 24 small vials shown in Fig. 1 for all 32 echo images. Figure 2 shows the decay curves as a function of echo time for 12 different doses. One can clearly see that the first echo signal is smaller than the second echo signal when the dose is smaller (or less than 4 Gy). The spurious signal intensity of the first echo stems from imperfect 180° RF pulses.²² For this reason we excluded the first echo signal from the R_2 estimation processes presented in this article. As the dose increases, the first echo signal becomes greater than the second echo signal. At the same time, the signals decay faster to the background signal offset level. In fact, the signal for 50 Gy reaches the background signal offset at the fifth echo (or 68 ms). Here it is worth mentioning that the echo signals obtained for every $1 \text{ mm} \times 1 \text{ mm} \times 2 \text{ mm}$ voxel in the MR data are much noisier than the data presented in Fig. 2. This makes the voxel-by-voxel parameter fitting more difficult and less precise.

As shown in Sec. III B, the SNR of the current MR scan was 32. Using Eq. (5), we obtained $t_\infty/T_2=3.2$. In fact, one can easily confirm from Fig. 2 that the signal intensity drops to the background signal offset (or the tail of the signal) at about $3 \times T_2$. For example, T_2 at 4 Gy is 82.6 ms. Figure 2 shows that the 4 Gy curve reaches the noise level at 250 ms, which corresponds to three times the T_2 length.

III.B. Evaluation of R_2 estimation methods

The VAREC method with $\alpha=2$ was used to estimate the T_2 values of two test phantoms with known T_2 values. The measured T_2 values were 81.3 ± 0.1 and 232.6 ± 0.5 ms for the bottle phantom and the clear phantom, respectively. Those values are smaller by 18.7% and 13.9% than the expected values of those phantoms. For comparison, it is noted that the T_2 value obtained by the MLE_R method was

FIG. 2. Echo signal intensity as a function of echo time for calibration vials which received various absorbed doses.

81.0 ± 0.1 ms for the bottle phantom. The measured T_2 values were smaller than expected values because of the effects of imperfect 180° RF pulses. Such underestimation of T_2 was commonly observed with the CPMG pulse sequence used for this study.^{23,24}

For the BANG polymer gel study, the image magnitude background signal offset M_{BG} was calculated as a mean of the pixel values in a $4 \text{ cm} \times 4 \text{ cm}$ square area with 1573 pixels outside the polymer gel phantoms but inside the field-of-view. All 480 image slices ($32 \text{ echoes} \times 15 \text{ slices}$) were used for this calculation. M_{BG} and its related standard deviation was 70.5 ± 30.9 . From Eq. (1), the standard deviation of the true Gaussian noise (σ) is estimated to be 56.2. The maximum SNR of this scan was 32. Although SNR can be improved by increasing NEX, this option is not practical due to longer scanning time. Note, for example, that the current scan with NEX=1 took 30 min for imaging 15 slices.

Figure 3(a) shows R_2 values as a function of dose for the NLLS, VAREC with $\alpha=2$, and MLE_R methods. The error bars indicate three times the measured standard deviation of the MLE_R data (i.e., 99% confidence level). The result of NLLS that used 31 echo signals (excluding the first echo signal) shows anomalous R_2 values for the dose above 10 Gy, at which the R_2 value abruptly dropped to the zero-dose level. The VAREC method lead to R_2 values in agreement with those of the MLE_R method within the measurement uncertainty. Figure 3(b) shows the same data as Fig. 3(a) except it presents the data for doses below 12 Gy. It is noteworthy that the R_2 values of VAREC and MLE_R agreed with each other within the measured standard deviations of less than $\pm 4\%$ for doses smaller than 10 Gy. For doses larger than 10 Gy, the uncertainty increased to a value greater than 5% and the response was highly nonlinear for doses larger than 20 Gy. Hence, the use of this type of polymer gel is discouraged for measurements of such large doses.

Figure 4 shows the dependence of estimated R_2 values on the threshold M_Δ (or the multiplier α) for VAREC solutions. The solution with $\alpha=0$ (not included in Fig. 4), which is equivalent to the NLLS solution, exhibited the same anomalous behavior as that of NLLS shown in Fig. 3. The same problem persists with even $\alpha=1$ (or $M_\Delta=\sigma$) as seen in Fig. 4. As α increased, the R_2 values increased for a given dose. Because a smaller number of the echo signals in the tail region of the decay curves were used for a larger threshold, the estimated slope (or the R_2) tended to increase with increasing α . Note also that the solutions erroneously resulted in zero R_2 values at 50 and at 20 Gy and higher for $\alpha=3$ and 5, respectively.

Table I shows the standard deviations of the measured R_2 values for various thresholds with the VAREC method. One can see that the uncertainties of the measured R_2 values are larger for small threshold cases ($\alpha=0, 1$, and 1.253) and for a large threshold case ($\alpha=5$) than those with $\alpha=2$. Furthermore, the method with larger thresholds could not find a solution for higher doses (i.e., 50 Gy for $\alpha=3$ and above 15 Gy for $\alpha=5$). Hence, there is a range of the threshold value which is optimum in terms of the uncertainty of the esti-

(a)

(b)

FIG. 3. (a) R_2 vs dose for NLLS, VAREC ($\alpha=2$), and MLE_R methods. The uncertainties (three times the measured standard deviation or 99% confidence level) of the MLE_R data are also indicated. (b) A replot of (a) for a smaller dose range (or <12 Gy).

ated R_2 value and the capability of finding a solution for a wide range of dose. With $\alpha=2$, the uncertainty of R_2 was less than 3% for doses up to 6 Gy. For higher doses the uncertainty increased, reaching 12% at 40 Gy. Based on the observations made in Fig. 4 and Table I, therefore, we recommend the α value between 2 and 3 for practical applications.

A two-dimensional distribution of the number of echoes N used by the VAREC solution with $\alpha=2$ is displayed in Fig. 5, which clearly shows that the optimum number of echo signals strongly depends on the dose (or R_2). In low dose re-

FIG. 4. Dose vs estimated R_2 . The R_2 values are shown for various threshold values used with VAREC. The multiplier α was set to 1.0, 1.253, 1.5, 2, 3, and 5.

regions, 31 echo signals were used, whereas in high dose regions, in particular, in the 45 Gy region at the center of the 200 ml phantom where two photon beams intersected, only four echo signals were needed. The last column in Table I also presents the number of echo signals used for various doses when $\alpha=2$. Previously, De Deene *et al.*⁵ concluded that the optimum range of spin echoes sampled for R_2 estimation is about 1.2 times T_2 when the multipoint method with multiple spin echoes is used. Our results show that, for example, in the area where R_2 was 15 s^{-1} or $T_2=66 \text{ ms}$ (i.e., for dose of 6 Gy), the number of echoes used for the R_2 estimation was 10 (see Table I). This indicates that the range of the sampled echo signals was 149.6 ms. Hence, the VAREC method tends to sample the echo signals for longer

FIG. 5. The spatial distribution of the number of echoes N used for R_2 estimation using the VAREC method with $\alpha=2$. The phantom arrangement is presented in Fig. 1.

time intervals than the De Deene *et al.* result. A reason for this difference stems from the selection of the threshold value. We used $\alpha=2$ (or $\text{SNR}=2$), whereas De Deene *et al.* used SNR of 3 for their analysis.

IV. DISCUSSION

The direct maximization of the maximum likelihood estimator given by Eq. (2), the MLE_R method, is accurate and feasible. However, our experiences indicated that the computation time for this method was too long to be practical mainly due to the time-consuming evaluations of the Bessel function. The computing time on a PC (1.86GHz Pentium-M processor) was 6 h for processing single 256×256 pixel image shown in Fig. 5, whereas the VAREC method took only 90 s. With the VAREC technique, we can avoid using the

TABLE I. The measured standard deviations of R_2 for VAREC with various threshold values. The multiplier α was set to 0, 1, 1.253, 1.5, 2, 3, and 5. The last column shows the number of echo signals N used for the R_2 estimation by the VAREC solution with $\alpha=2.0$.

Dose (Gy)	Multiplier α used to determine the threshold M_α							N^a
	0.0	1.0	1.253	1.5	2.0	3.0	5.0	
0	0.8	0.9	0.8	0.9	0.8	0.9	0.8	31
1	1.2	1.2	1.1	1.2	1.1	1.1	1.4	31
2	1.2	1.2	1.2	1.2	1.3	1.2	1.2	26
4	2.5	2.5	3.1	2.4	2.3	2.1	2.3	16
6	3.6	3.8	5.3	3.1	2.9	2.7	3.1	10
8	5.9	6.8	7.0	4.3	3.3	3.6	3.8	8
10	9.0	10.4	9.9	4.3	4.1	4.0	5.4	7
15	35.4	32.4	13.2	7.9	6.9	6.8	^b	5
20	12.1	13.3	23.5	8.0	6.5	5.5	^b	4
30	9.2	9.2	28.3	9.4	7.5	6.0	^b	4
40	7.9	31.8	26.2	9.1	12.0	7.4	^b	4
50	18.2	42.1	33.4	10.9	9.3	^b	^b	3

^a N is the number of echo signals used for the R_2 estimation by the VAREC solution for $\alpha=2.0$.

^bThe solution resulted in zero R_2 value.

very computationally expensive MLE_R method and can obtain an equally accurate solution for doses lower than 10 Gy with the BANG3 type polymer gel.

Parameter estimation is more precise when more data points are used for parameter fitting.^{5,8,25} Straightforward ways to increase the number of echoes are either to shorten the echo-time spacing or to increase SNR. These are, however, not easy to accomplish because of limitations in both the MRI hardware and scanning time. One way to utilize as many echo signals as possible, hence, is to adjust the radiation response of the polymer gel for the intended dose range so that the R_2 value is less than a certain small value, e.g., 10 s^{-1} . From this point of view, some of newer polymer gels, for example, VIPAR (Ref. 26) and PAGAT,²⁷ are ideal for measuring high doses. An alternative is to develop a method for more accurate estimation of large R_2 values (or short T_2) by rigorously considering the effect of signal noise. Some more advanced techniques were presented in a recent article.¹²

V. CONCLUSIONS

MRI users of polymer gel dosimetry must remember that a careless application of a parameter fitting method for R_2 estimation might lead to erroneous results because of improper consideration of the background noise in the estimation. Specially, if the expected T_2 value is much shorter than the longest echo time used in a multispin echo protocol, the estimation often results in a large error. To remedy this problem, the echo signals at the background signal offset level should be excluded from the R_2 estimation. The number of echoes useful for accurate estimation of R_2 depends on the expected R_2 value. Based on the current results, we recommend the VAREC technique with two to three times the standard deviation of the Gaussian noise as the threshold (or $\alpha = 2$ to 3) to determine the maximum number of echoes specific to each image voxel. The proposed method is simple and robust for the R_2 estimation with short computing time.

ACKNOWLEDGMENTS

Some of the results in the current article were previously presented at the AAPM Annual Meeting (Anaheim, CA) in July 2009. One of authors (Y.W.) was previously supported by a Minnesota Medical Foundation grant, which was awarded to the preliminary study and the work was performed with Dr. Bruce Hammer at the Center for Innovative Applications of Magnetic Resonance of University of Minnesota. The Center for Magnetic Resonance Research (CMRR) was funded by NIH grants (Grant Nos. P30 NS057091 and P41 RR008079). The authors, in particular, the second author (H.K.), also would like to acknowledge the staff at the 3T MRI facility of Nagoya University for help.

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¹C. Baldock, Y. De Deene, S. Doran, G. Ibbott, A. Jirasek, M. Lepage, K. B. McAuley, M. Oldham, and L. J. Schreiner, "Polymer gel dosimetry," *Phys. Med. Biol.* **55**, R1–R63 (2010).

²M. J. Maryanski, R. J. Schulz, G. S. Ibbott, J. C. Gatenby, J. Xie, D.

Horton, and J. C. Gore, "Magnetic resonance imaging of radiation dose distributions using a polymer-gel dosimeter," *Phys. Med. Biol.* **39**, 1437–1455 (1994).

³M. Lepage, K. McMahon, G. J. Galloway, Y. De Deene, S. A. Back, and C. Baldock, "Magnetization transfer imaging for polymer gel dosimetry," *Phys. Med. Biol.* **47**, 1881–1890 (2002).

⁴H. M. Whitney, D. F. Gochberg, and J. C. Gore, "Magnetization transfer proportion: A simplified measure of dose response for polymer gel dosimetry," *Phys. Med. Biol.* **53**, 7107–7124 (2008).

⁵Y. De Deene, R. Van de Walle, E. Achten, and C. Dewagter, "Mathematical analysis and experimental investigation of noise in quantitative magnetic resonance imaging applied in polymer gel dosimetry," *Signal Process.* **70**, 85–101 (1998).

⁶I. C. Baustert, M. Oldham, T. A. Smith, C. Hayes, S. Webb, and M. O. Leach, "Optimized MR imaging for polyacrylamide gel dosimetry," *Phys. Med. Biol.* **45**, 847–858 (2000).

⁷R. A. Crescenti, S. G. Scheib, U. Schneider, and S. Gianolini, "Introducing gel dosimetry in a clinical environment: Customization of polymer gel composition and magnetic resonance imaging parameters used for 3D dose verifications in radiosurgery and intensity modulated radiotherapy," *Med. Phys.* **34**, 1286–1297 (2007).

⁸Y. De Deene and C. Baldock, "Optimization of multiple spin-echo sequences for 3D polymer gel dosimetry," *Phys. Med. Biol.* **47**, 3117–3141 (2002).

⁹C. Baldock, M. Lepage, S. A. Back, P. J. Murry, P. M. Jayasekera, D. Porter, and T. Kron, "Dose resolution in radiotherapy polymer gel dosimetry: Effect of echo spacing in MRI pulse sequence," *Phys. Med. Biol.* **46**, 449–460 (2001).

¹⁰M. Lepage, P. M. Jayasekera, S. A. Back, and C. Baldock, "Dose resolution optimization of polymer gel dosimeters using different monomers," *Phys. Med. Biol.* **46**, 2665–2680 (2001).

¹¹P. A. Hardy and A. H. Andersen, "Calculating T_2 in images from a phased array receiver," *Magn. Reson. Med.* **61**, 962–969 (2009).

¹²J. G. Raya, O. Dietrich, A. Hornig, J. Weber, M. F. Reiser, and C. Glaser, " T_2 measurement in articular cartilage: Impact of the fitting method on accuracy and precision at low SNR," *Magn. Reson. Med.* **63**, 181–193 (2010).

¹³J. M. Bonny, M. Zanca, J. Y. Boire, and A. Veyre, " T_2 maximum likelihood estimation from multiple spin-echo magnitude images," *Magn. Reson. Med.* **36**, 287–293 (1996).

¹⁴J. R. Roebuck, S. J. Haker, D. Mitsouras, F. J. Rybicki, C. M. Tempany, and R. V. Mulkern, "Carr-Purcell-Meiboom-Gill imaging of prostate cancer: Quantitative T_2 values for cancer discrimination," *Magn. Reson. Imaging* **27**, 497–502 (2009).

¹⁵Y. Murakami, T. Nakashima, Y. Watanabe, T. Akimitsu, K. Matsuura, M. Kenjo, Y. Kaneyasu, K. Wadasaki, Y. Hirokawa, and K. Ito, "Evaluation of the basic properties of the BANGkit gel dosimeter," *Phys. Med. Biol.* **52**, 2301–2311 (2007).

¹⁶R. M. Henkelman, "Measurement of signal intensities in the presence of noise in MR images," *Med. Phys.* **12**, 232–233 (1985).

¹⁷H. Gudbjartsson and S. Patz, "The Rician distribution of noisy MRI data," *Magn. Reson. Med.* **34**, 910–914 (1995).

¹⁸J. Sijbers, A. J. den Dekker, P. Scheunders, and D. Van Dyck, "Maximum-likelihood estimation of Rician distribution parameters," *IEEE Trans. Med. Imaging* **17**, 357–361 (1998).

¹⁹C. D. Constantinides, E. Atalar, and E. R. McVeigh, "Signal-to-noise measurements in magnitude images from NMR phased arrays," *Magn. Reson. Med.* **38**, 852–857 (1997).

²⁰T. He, P. D. Gatehouse, P. Kirk, R. H. Mohiaddin, D. J. Pennell, and D. N. Firmin, "Myocardial T_2 measurement in iron-overloaded thalassemia: An ex vivo study to investigate optimal methods of quantification," *Magn. Reson. Med.* **60**, 350–356 (2008).

²¹M. D. Abramoff, P. J. Magelhaes, and S. J. Ram, "Image processing with ImageJ," *Biophotonics Int.* **11**, 36–42 (2004).

²²C. F. Maier, S. G. Tan, H. Hariharan, and H. G. Potter, " T_2 quantitation of articular cartilage at 1.5 T," *J. Magn. Reson. Imaging* **17**, 358–364 (2003).

²³M. E. Masterson, R. McGary, K. Schmitt, and J. A. Koutcher, "Accuracy and reproducibility of image derived relaxation times on a clinical 1.5 T magnetic resonance scanner," *Med. Phys.* **16**, 225–233 (1989).

²⁴C. Thomsen, K. E. Jensen, M. Jensen, E. R. Olsen, and O. Henriksen, "MR pulse sequences for selective relaxation time measurements: A phantom study," *Magn. Reson. Imaging* **8**, 43–50 (1990).

- ²⁵P. R. Bevington and D. K. Robinson, *Data Reduction and Error Analysis for the Physical Sciences*, 2nd ed. (McGraw-Hill, New York, 1992).
- ²⁶E. Pantelis, C. Antypas, L. Petrokokkinos, P. Karaiskos, P. Papagiannis, M. Kozicki, E. Georgiou, L. Sakelliou, and I. Seimenis, "Dosimetric characterization of CyberKnife radiosurgical photon beams using polymer gels," *Med. Phys.* **35**, 2312–2320 (2008).
- ²⁷T. A. Pourfallah, M. Allahverdi, N. R. Alam, M. R. Ay, and M. H. Zahmatkesh, "Differential dose volume histograms of Gamma knife in the presence of inhomogeneities using MRI-polymer gel dosimetry and MC simulation," *Med. Phys.* **36**, 3002–3012 (2009).
- ²⁸See supplementary material at E-MPHYA6-38-046102 for MATLAB source files of the ATOM program.