Review of quantitative MRI principles for gel dosimetry

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Abstract. The radiation dose distribution absorbed by polymer gel dosimeters can be read out by several methods such as magnetic resonance imaging (MRI), optical CT, X-ray CT and ultrasound. MRI was the first method that was explored to read out polymer gel dosimeters. Although MRI was soon recognised as a promising technique, limited access to MRI scanners and the often (wrongly perceived) complexity in optimizing the imaging protocol has led to a search for other imaging modalities. In this paper we hope to unveil the mysticism of magnetic resonance imaging. Firstly, the basic principles of magnetic resonance image acquisition will be explained. Also, quantitative properties to describe the image quality are defined. Secondly, some sequences for quantitative T1 and T2 imaging will be analysed and specific issues concerning optimization and accuracy will be highlighted. Thirdly, we provide the reader with some easy guidelines and tools to investigate the accuracy of quantitative imaging sequences. It should also be noted that many of the parameters that describe the accuracy of the imaging technique also apply to other imaging modalities.

1. Introduction

In the early days of gel dosimetry, magnetic resonance imaging (MRI) was suggested as the method to read-out the gel dosimeters. The use of MRI as a non-destructive measurement method of a dosimeter gel was first proposed in 1984 by Gore \textit{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 \textit{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\textsuperscript{2+}) ions are converted to ferric (Fe\textsuperscript{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, agarose, sephadex and polyvinyl alcohol (PVA) were investigated. Chelating agents to reduce diffusion in Fricke gels, such as xylenol 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]. As explained elsewhere in these proceedings the spin-lattice relaxation rate (R1 = 1/T1) and the spin-spin relaxation rate (R2 = 1/T2) in Fricke gels is altered significantly upon irradiation. As R1 of an unirradiated Fricke gel dosimeter is small as compared to the R2 of an unirradiated Fricke gel dosimeter, the dynamic range of the Fricke gel dosimeter in relative terms is higher for R1 than R2. For this reason, R1 mapping is preferred to R2 mapping for Fricke gel dosimeters. Also R1 maps (at least in the early days) can be obtained with a shorter acquisition time than R2 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 agarose, which showed that the relaxation rates increased with absorbed dose [9]. Polymer gel dosimeters are based on the conversion of co-monomers to polymer aggregates upon irradiation. This reaction alters the mobility of surrounding water molecules which also results in a change in R1 and R2 [10]. The dose-response of R2 in gelatin based polymer gel dosimeters however is more pronounced than of R1. To explain the effect that the radiation-induced polymerization has on the R2 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 artefacts 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 artefacts 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.
2. Basic principles of magnetic resonance imaging

2.1. Basic components of an MR scanner and basic principle

In this paragraph, the basic components and principles behind MRI are explained very briefly for the reader that is completely unfamiliar with MRI. For a more comprehensive treatise of the basic principles of MRI, the reader is referred to more specialized literature [31-32]. There are also some interesting online textbook available [33-34].

The MR scanner is composed of three major components:

1. A strong magnet which is mostly a cryogenic magnet that produces a homogeneous strong main magnetic field. The magnetic field strength in clinical scanners ranges typically from 0.3 T to 7 T. The signal-to-noise ratio (SNR) increases with the magnetic field strength.

2. Magnetic field gradient coils that are able to produce a magnetic field which is also aligned in the same direction as the main magnetic field but which varies in field strength along a certain direction. Three gradient coil configurations produce magnetic field gradients in one of the three orthogonal directions (x, y, z). Typical magnetic field gradients in modern clinical scanners range in strength from 10 mT/m to 40 mT/m.

3. A radiofrequency (RF) coil (and corresponding electric circuitry) which is able to produce and/or receive an electromagnetic wave. There exist transmit and receive coils. Transmit coils produce an electromagnetic wave that excites the nuclei of the scanned subject while receive coils capture the signal produced by the precessing magnetic dipole moments (MDMs) of the excited nuclei. In many text books on nuclear magnetic resonance this is the place where the concept of ‘spin’ is introduced. The concept ‘spin’ is actually a quantum mechanical property. For the sake of simplicity, in this paper, we will keep to a classical mechanics (electromagnetic) approach. The reader is referred to other textbooks for a more comprehensive quantum mechanical explanation. It can be shown that the behaviour of the magnetic dipole moments in a classical mechanics approach is equivalent to the quantum expectation value of the spin magnetic moment in the quantum mechanical approach.

Apart from these three components, the MR scanner typically also contains shim coils in which a DC current can be applied in order to homogenize the static magnetic field. The scanner is also surrounded by a ‘cage of Faraday’ to eliminate interference of the electromagnetic waves with waves exterior to the scanner such as from radio-transmitters and other electronic instruments.

In the absence of a magnetic field, the MDMs will be aligned in random directions. When the patient is slid into the magnet of the MR scanner, the MDMs will precess around the direction of the main magnetic field. Due to magnetic dipole interactions with the surroundings, the spins will align with the main magnetic field. This process is called ‘spin-lattice’ or ‘T1 relaxation’ (figure 2a). In human tissue or

Figure 1. Major components of a clinical MRI scanner
polymer gels this occurs in a time span of typically 0.1 s to 3 s. In order to get a signal from the scanned subject, the MDMs are excited from their equilibrium state (figure 2c). The condition for excitation is that the frequency of the exciting RF wave \( f_{\text{RF}} \) has a frequency which corresponds to the Larmor frequency given by

\[
 f_{\text{RF}} = \frac{\gamma}{2\pi} B
\]

with \( \gamma \) the gyromagnetic ratio which is specific for the kind of nucleus (for hydrogen protons \( \gamma = 267.54 \text{ s}^{-1} \text{T}^{-1} \)) and \( B \) the magnetic field at the nucleus. The angle over which the MDM is flipped towards the plane transverse to the magnetic field (the transverse plane) is dependent on the length and intensity (amplitude) of the RF pulse. After excitation the MDMs will precess which results in a MR signal induced in a receive coil (figure 2d).

**Figure 2.** Basic principle of MR signal formation involving several steps: (a) When hydrogen protons are placed in a magnetic field \( (B_0) \), their magnetic dipole moments will start to precess. Due to (lossy) interactions with (magnetic fields of) surrounding nuclei and electrons (the lattice), the magnetic dipole moments will rapidly (0.1 s – 3 s) align with the main magnetic field (b). In this equilibrium state no signal is received. Subsequently, a transmit coil will send an RF pulse to the sample. If the RF pulse has the Larmor frequency, the nuclei will be excited and the magnetic dipole moments are brought out of equilibrium so that they will precess around the main magnetic field (c). This precession results in an electromagnetic wave that induces a current in the receive coil (d). This signal is then digitized and stored. The sequence of excitation and signal reception (c-d) can be repeated while different magnetic field gradients are applied to encode the MR signal spatially (e). After several encoded MR signals are recorded, a (2D/3D) Fourier transform is applied to reconstruct the MR image (f).
It should be noted that the MR signal decays with a time constant much faster than T1. This (T2*) decay is attributed to the presence of local magnetic field inhomogeneities within each voxel. These magnetic field inhomogeneities lead to phase dispersion in the precessing MDMs as the tiny variations in field strength result in slightly different Larmor frequencies and thus accumulating dephasing.

Sometimes the same coil is used for transmitting and receiving. To be able to extract spatial information from the received MR signal, the signal is encoded using magnetic field gradients. By applying a magnetic field gradient, the Larmor frequency is made space dependent (i.e. B in equation 1 becomes a function of spatial coordinates (and time) in other words B(x,y,z,t) ). The sequence of excitation and reception (figure 2c-d) is repeated with different phase encoding gradients. The recorded signals are digitized and stored in a matrix also called ‘k-space’ (figure 2e). Applying a fast (2D or 3D) Fourier transform (FFT) on k-space yields the MR image(s) (figure 2f).

2.2. Spatial encoding: building blocks

In an MR sequence three different spatial encoding steps can be recognized:

1. Slice selection: When a gradient is applied in combination with an RF excitation pulse, only one slab of MDMs will be excited in the scanned subject.
2. Phase encoding: When a gradient is applied after the MDMs have been excited but before signal reception, the MDMs will precess at a different frequency depending on their position in the gradient direction during the time this gradient is on. This leads to different phases in the phase encoding direction after a phase encoding gradient is applied.
3. Frequency encoding: Upon signal reception a frequency encoding gradient is switched on so that the MDMs will precess at different frequencies depending on their position in the gradient.

In conventional imaging sequences, the direction of the three encoding gradients is taken orthogonal. Spatial encoding can be easily explained by using an analogy in acoustics.

2.2.1. Slice selection

The principle of slice selection is illustrated in figure 3.

![Figure 3. Principle of slice selection illustrated in analogy with an acoustics experiment of resonating wine glasses (a) and in MRI (b).](image)
An analogy with acoustics is provided in figure 3a. Suppose three glasses are filled with different amounts of wine (Glass 1 is empty and glass 3 is filled). When an acoustic wave with a certain wavelength is created with a stem fork only the glass of which the mechanical resonance frequency corresponds to the frequency of the acoustic wave will vibrate. When the acoustic wave produced with the stem fork is abruptly stopped, the vibrating glass will still produce an acoustic wave with the same frequency.

Similarly in MRI (figure 3b), when a magnetic field gradient (slice selection gradient) is applied and a radiofrequency electromagnetic wave (RF pulse) is produced by a radiofrequency coil (antenna), only those MDMs of which the magnetic field and thus the Larmor frequency (equation 1) corresponds with the frequency of the electromagnetic wave will be excited. If the RF pulse has the correct pulse length and duration (energy), the MDMs can be flipped over an angle of 90 degrees in the transverse plane. As mentioned before, this will produce an alternating electromagnetic field (MR signal) which can be received using another (or the same) antenna. Thus the MR signal comes only from a slab of the scanned object.

2.2.2. Frequency encoding

The principle of frequency encoding is illustrated in figure 4.

![Figure 4. Principle of frequency encoding selection illustrated in analogy with an acoustics experiment of resonating wine glasses (a) and in MRI (b).](image)

As an analogy, again three wine glasses are considered (figure 4a). Suppose that initially the wine glasses are empty and that they are excited by an acoustic wave (having a frequency corresponding to the resonance frequency of an empty glass). The three glasses thus vibrate at the same frequency. Suppose now that while the wine glasses are still vibrating, they are filled to different levels of wine. As a result the vibration frequency will change. An observer will hear an acoustic wave composed of different frequencies. If this experiment would be repeated with different amounts of wine glasses (e.g. 6 empty, 2 half filled and 5 completely filled glasses) a well-practiced observer would be able to determine how many wine glasses of each filling level are present just by hearing the produced sound.

Similarly in MRI, when MDMs are precessing in the transverse plane after an excitation RF pulse, they will start to precess at different rates when a gradient is applied. The precession rate (frequency) for each MDM corresponds with its location in the magnetic field gradient as is described by the Larmor equation (equation 1). Performing a Fourier transform on the acquired electromagnetic MR signal will give a spectrum of which the frequencies correspond with unique spatial positions. The amplitude of the frequency components corresponds with the MDM density at that specific position.
2.2.3. Phase encoding

Phase encoding is very similar to frequency encoding. If a gradient is applied during a certain period of time and with a certain amplitude, the MDMs will gain a phase difference with respect to each other depending on the gradient strength, the duration of the gradient and their position in that gradient. If this procedure is repeated for different gradient strengths, the different frequency components (and thus the spatial position) can be extracted.

2.3. Spatial encoding: mathematical formalism

The total MR signal received by the receiver coil is the sum of all signals induced in the RF coil by the excited MDMs in the selected slice. The signal originating from one infinitesimal small voxel of MDMs has an amplitude and phase. The amplitude is determined by the concentration of MDMs within the voxel (the density), the attenuation due to relaxation and a scaling factor which is determined by the receptivity of the coil. The phase is determined by the history of the magnetic field at the location of the voxel and is caused by the precession of the MDMs at that location. Mathematically the magnetization in each voxel \( m_{xy} \) with coordinates \((x,y,z)\) at time \( t \) can be written as

\[
m_{xy}(x,y,z,t) = m_0 \cdot \rho'(x,y,z,t) \cdot e^{i\Gamma(x,y,z,t)} = m_x(x,y,z,t) + j \cdot m_y(x,y,z,t)
\]

The MR signal \( m_{xy}(x,y,z,t) \) in the voxel is thus a complex signal containing a real \( (m_x) \) and imaginary \( (m_y) \) part. The density \( \rho' \) is the density of MDMs also taking into account the relaxation. The phase \( \Gamma(x,y,z,t) \) acquired during a certain time period \( t \) in a magnetic field \( B(t) \) is

\[
\Gamma(x,y,z,t) = -\gamma \int \limits_{0}^{t} B(\tau) d\tau
\]

\[
= -\gamma \int \limits_{0}^{t} B_0(\tau) d\tau - \gamma \cdot x \int \limits_{0}^{t} G_x(\tau) d\tau - \gamma \cdot y \int \limits_{0}^{t} G_y(\tau) d\tau - \gamma \cdot z \int \limits_{0}^{t} G_z(\tau) d\tau
\]

The total received signal is the sum of all the precessing moments and will also be complex:

\[
M(t) = \iiint \limits_{\text{slice}} m_{xy}(x,y,z,t) \cdot dx \cdot dy \cdot dz = M_x(t) + j M_y(t)
\]

The complex MR signal can be detected using a quadrature detector.

Using the down-regulated MR signal (undone from the carrier frequency), the first term on the left side from equation 3 accounting for the free precession in the main magnetic field vanishes leaving only the gradient terms. If we assume that slice selection is performed the gradient induced phase dispersion occurs only in the x and y direction.
Figure 5. Spatial encoding in MRI. After slice selection, the slab of MDMs is further encoded by phase and frequency encoding gradients. The MR signal is the sum of all the signals produced by precessing MDMs in the excited slab.

Assuming slice selection in the z-direction, the MR signal can be written as:

\[ S(t) = S_0 \cdot \iiint_{\text{slice}} \rho(x, y, z = z_0) \cdot e^{-j(k_i(t)x + k_y(t)y)} \cdot dx \cdot dy \cdot dz \]  
(5)

with:

\[ k_i = \gamma \cdot \int_0^t G_i(\tau) \, d\tau \quad \quad i = x, y \]

Equation 5 has the shape of a Fourier transform. The inverse Fourier transform gives the ‘density’ of the protons in image space (i.e. the image).

\[ \rho(x, y, z = z_0) = C \cdot \iiint_{\text{slice}} S(k_x(t), k_y(t)) \cdot e^{j(k_x x + k_y y)} \cdot dk_x \cdot dk_y \]  
(6)
2.4. The spin-echo sequence

The spin-echo sequence, discovered by Erwin Hahn in 1950, is a basic MR sequences on which many of the current imaging sequences are based. The spin-echo sequence is drawn in figure 7. The first line shows the radiofrequency pulses while the second line shows the MR signal.

**Figure 7.** Spin-echo sequence and filling of the k-space matrix. The phase encoding is in the y-direction while the frequency encoding is in the x-direction. The letters A-E in k-space correspond with the events in the sequence indicated by A-E.
In the absence of imaging gradients, after excitation (90° pulse), a free induction decay (FID) signal is produced. The signal of the FID decays with a time constant $T_2^* (= 1/R_2^*)$. An important component in this decay process is related to phase dispersion by magnetic field inhomogeneities that originate from the applied static magnetic field at one hand and microscopic field inhomogeneities caused by the inhomogeneous microstructure at the other hand. After a time $TE/2$ (when the FID signal has decayed) a 180° pulse is applied. As we have seen previously this is achieved by an RF pulse with a double amplitude or duration. After a time $TE/2$ after the 180° pulse a spin-echo signal appears. After the 180° pulse the transverse component of the MDMs will be flipped in the opposite direction. The MDMs that were dephasing at a faster rate (due to local magnetic field homogeneities) before the 180° pulse will rephase at the same (faster) rate after the 180° pulse. The MDMs will be in phase after the same time as was given for the rephrasing (see also figure 8).

As explained in section 2.3, the k-space (figure 7, right) is filled by the digitized MR signal for different phase encoding steps. The filling of k-space can be easily understood by following the different steps (A-E) in figure 7. As discussed previously, the k-space has coordinates $(k_x, k_y)$ which correspond with the second integral expression in equation 5. Upon excitation of the MDMs, the longitudinal magnetization is flipped in the transverse plane, placing us in the centre of the k-space (A) with coordinates $(k_x, k_y) = (0, 0)$ (A). The (negative) phase gradient in B moves our pointer in the (negative) direction of $k_y$ (phase encoding direction). A positive gradient in the frequency encoding direction moves the pointer along path C to the right edge of k-space. The 180° RF pulse moves the pointer to a position which is point-mirrored with respect to the centre (D) at the left edge of k-space. Upon acquisition while a frequency encoding gradient is applied, one k-space line is recorded along E. This sequence is repeated after a time $TR$ (the repetition time) but with slightly different phase encoding gradients so that successive k-space lines (E) are recorded. The same logic can be followed to understand how k-space is filled with other sequences. This logic can also be extended to 3D imaging sequences.
3. Quantitative imaging sequences for measuring T1, T2 and MT

In principle, it is possible to use any kind of image in which the image contrast is monotonically related to the absorbed dose for dose mapping. Using calibration vials the image contrast can be related to the absorbed dose. Theoretically, it is possible to use a T1-weighted, T2-weighted or MT-weighted image. However, due to the inhomogeneity of the radiofrequency field, the image uniformity in these images is so poor that in practice a very bad accuracy is obtained. A far better performance in terms of accuracy is reached by using quantitative images such as T1-maps, T2-maps and MT-maps. In this section, different quantitative imaging sequences are discussed.

3.1. Quantitative R1 imaging sequences

3.1.1. The spin-echo sequence

The general shape of the spin-echo sequence is given in figure 8. The repetitive unit consists of an excitation RF pulse with flip angle $\alpha$ and a 180° refocusing pulse at TE/2. The repetition time (i.e. the time between two successive excitation RF pulses $\alpha$) is TR. In the example given below a Carr-Purcell approach is taken where both the excitation pulse $\alpha$ and the 180° refocusing pulse are given along the y-axis. In the literature on pulse sequence design, this is often written as $\alpha_y$-180$y$. Note that any other scheme (e.g. $\alpha_x$-180$y$) would give similar results.

The signal in a spin-echo sequence is weighted by T1 (R1 = 1/T1) through the choice of the repetition time TR and by T2 (R2 = 1/T2) through the choice of TE. Thus by acquiring several spin-echo images recorded with different repetition times TR, the spin-lattice relaxation rate R1 can be
fitted. The signal of the spin-echo sequence acquired with an excitation pulse with flip angle \( \alpha \) in the steady state is given by

\[
S = S_{eq} \cdot \frac{1 - 2 \cdot \exp\left(-R1 \cdot \frac{TR}{2} - \frac{TE}{2}\right) + \exp(-R1 \cdot TR)}{1 + \cos \alpha \cdot \exp(-R1 \cdot TR)} \cdot \exp(-R2 \cdot TE) \cdot \sin \alpha
\]

(7)

with \( S_{eq} \) the equilibrium signal corresponding with full excitation and full signal recovery (i.e. the signal obtained when \( \alpha = 90^\circ \) and \( TR \to \infty \)).

In the special case that \( \alpha = 90^\circ \) (\( \cos \alpha = 0 \), \( \sin \alpha = 1 \)) equation 3 reduces to

\[
S = S_{eq} \cdot \left(1 - 2 \cdot \exp\left(-R1 \cdot \left(TR - \frac{TE}{2}\right)\right) + \exp(-R1 \cdot TR)\right) \cdot \exp(-R2 \cdot TE)
\]

(8)

The parameters \( R1 \) and \( R2 \) can be obtained from equations 3-5 can be fitted for various \( TR \) and \( TE \) using a \( \chi^2 \) minimization fitting such as a Levenberg-Marquardt algorithm. It is advisable to treat the flip angle \( \alpha \) as an unknown variable to account for imperfect excitation.

In the special case that the echo time \( TE \) is much smaller than the repetition time \( TR \) (and \( \alpha = 90^\circ \)), equation 4 can be further simplified to

\[
S = S_{eq} \cdot (1 - \exp(-R1 \cdot TR)) \cdot \exp(-R2 \cdot TE)
\]

(9)

This function can be used to fit only for the spin-lattice relaxation time \( R1 \).

In practice, several base images are recorded with differing repetition times (and echo times). The signal intensity in each pixel position of the set of base images is fitted against the functions 3, 4 or 5. The fitted parameters \( R1 \) and \( R2 \) for each pixel of the base images is plotted in a new image, respectively the parametric \( R1 \) and \( R2 \) map. A background filter on the base images is also often applied before fitting. This background filter makes that only those pixels with a value larger than a certain threshold value in the base images are taken into account for fitting. The pixels smaller than the threshold are considered as noise and are set to zero in the parametric maps.

3.1.2. The saturation recovery sequence (SRGE)

The shape of a saturation recovery sequence is given in figure 9. The saturation recovery sequence is a special case of the FLASH sequence (Fast Low Angle Shot) but with the flip angle of the excitation pulses equal to \( 90^\circ \). This way, all longitudinal magnetization that is rebuild during the repetition time \( TR \) is flipped in the transverse plane and gives way to signal.

The signal can thus be written as

\[
S = S_{eq} \cdot (1 - \exp(-R1 \cdot TR)) \cdot \exp(-R2' \cdot TE)
\]

(10)

Using the saturation recovery sequence, several base images are recorded with different repetition times \( TR \). The spin-lattice relaxation rate \( R1 \) can be obtained by fitting the signal intensity for
different TR on a pixel-by-pixel basis in the base images as described before. Spoiler gradients are applied after each gradient echo recording to remove phase coherence in the transverse magnetization.

Figure 9. RF pulse scheme and signal formation of a saturation recovery sequence with magnetization history of the longitudinal component ($M_z$) and the transverse component ($M_x$).

Spoiled gradient recalled echo imaging (SPGRE) in which the 90° pulses are replaced by $\alpha$-pulses can be found in a technique called DESPOT in which base images are recorded with various flip angles $\alpha$ [37].

3.1.3. The inversion recovery sequence (IRGE)

With the inversion recovery sequence (IRGE), a high T1-weighted contrast can be obtained.

Figure 10. Inversion recovery sequence with magnetization history of the longitudinal component ($M_z$) and the transverse component ($M_x$).
The first RF pulse in the IRGE sequence is a 180° inversion pulse. This inversion pulse, inverts the longitudinal magnetization (figure 10). The magnetization is restored during a time TI (the inversion time) by T1 relaxation. After a time TI, the magnetization is flipped in the transverse plane by a 90° RF pulse.

The z-component of the magnetization recovers exponentially according to:

\[ M_z = M_0 \cdot (1 - (1 - \cos \theta_{\text{inv}}) \cdot \exp(-R1 \cdot t) + \exp(-R1 \cdot TR)) \]  

with \( \theta_{\text{inv}} \) the flip angle of the inversion pulse (in figure 10, \( \theta_{\text{inv}} = 180° \)).

After the 90° pulse, the signal thus becomes (in the case that TE << TR):

\[ S = S_{eq} \cdot (1 - (1 - \cos \theta_{\text{inv}}) \cdot \exp(-R1 \cdot TI) + \exp(-R1 \cdot TR)) \cdot \exp(-R2' \cdot TE) \]  

Note that the signal in equation 11 can be negative. Amplitude images are strict positive. To improve fitting it may therefore be more appropriate to use the complex signal.

It should be mentioned that in reality there are no exact 90° and 180° slice selective pulses (figure 11). Instead the flip angle varies within the excited slice. The flip angle as a function of the distance perpendicular to the slice is called the slice profile. It should be mentioned that in all of the above equations a perfect slice is assumed. To account for the imperfect slice profile, the signal is a sum of the signals along the slice profile.

3.1.4. The Look-Locker sequence

A fast sequence to acquire an R1 map is the Look-Locker sequence [38] of which the RF sequence is shown in figure 12a. The Look-Locker sequence is similar to the IRGE sequence but the 90° RF pulse is replaced by a train of smaller \( \alpha \)-pulses. Each \( \alpha \)-pulse transfers some longitudinal magnetization into the transverse plane and gives way to a gradient echo by applying appropriate gradients. Also between each \( \alpha \)-pulse a small phase encoding gradient is applied so that each gradient echo results in a new k-space line. This means that for each inversion excitation part of k-space is sampled instead of only one k-space line in the case of the IRGE sequence. It can be shown that the relaxation weighting of the different k-space lines results in broadening of the point-spread-function (PSF) thus limiting the intrinsic resolution. The signal from the \( n^{th} \) readout pulse is given by

\[ S = S_{sc} (\tau, T1, \alpha, N) \cdot \left(1 - D(\tau, T1, \alpha, N) \cdot \exp(-R1' \cdot n \cdot \tau)\right) \]  

![Figure 11. Ideal and realistic slice profile corresponding with a 90° slice selective RF pulse.](image-url)
with $S_n(\tau, T_1, \alpha, N)$ a scaling factor and $D(\tau, T_1, \alpha, N)$ a dynamic range parameter. $\tau$ is the inter-readout-pulse interval and $N$ is the total number of echoes. $R1^*$ is the enhanced relaxation rate given by

$$R1^* = R1 - \frac{\ln(\cos \alpha)}{\tau}$$

(14)
To avoid severe artefacts as a result of the relaxation between the different k-space lines, a k-space ordering scheme is often proposed. In this scheme the central k-space lines (close to \( k_y = 0 \)) are from echoes recorded immediately after the first \( \alpha \)-pulse. A variant on the Look-Locker sequence is the TOMROP (T1 by multiple readout pulses) sequence (figure 12b). In this sequence the gradient echoes are grouped and interleaved with some recovery time to allow T1 relaxation to take place. Each group of gradient echoes is used in a separate T1 weighted image. The different T1-weighted images are then used to reconstruct an R1 map.

The Look-Locker sequence is particularly sensitive to RF pulse imperfections. Also changes in the flip angle distribution within the image (B1 field inhomogeneities) will affect the signal. A B1 inhomogeneity map can also be acquired when using equations 13-14. More complex analytical expressions for the signal may be derived. In addition more sophisticated numerical algorithms may be required to solve for the relaxation rate R1.

### 3.1.5. Steady-state free precession sequences (SSFP)

If a sequence of RF pulse excitations is given interleaved with a time TR, the signal will come in a steady state. In between two successive pulses the frequency encoding gradients can be placed in such a way that two echoes are obtained (figure 13). It can be shown that the signal amplitude of both echoes is given by [36]

\[
S_i = S_0 \tan\left(\frac{\alpha}{2}\right) \left[1 - \left(\frac{\exp(-R1 \cdot TR) - \cos \alpha \left(1 - \exp(-2 \cdot R2 \cdot TR)\right)}{\sqrt{p^2 - q^2}}\right)\right] \quad (15)
\]

and

\[
S_i = S_0 \tan\left(\frac{\alpha}{2}\right) \left[1 - \left(\frac{1 - \exp(-R1 \cdot TR) \cdot \cos \alpha \left(1 - \exp(-2 \cdot R2 \cdot TR)\right)}{\sqrt{p^2 - q^2}}\right)\right] \quad (16)
\]

with

\[
p = 1 - \exp(-R1 \cdot TR) \cdot \cos \alpha - \exp(-2 \cdot R2 \cdot TR) \cdot (\exp(-R1 \cdot TR) - \cos \alpha)
\]

\[
q = \exp(-R2 \cdot TR) \cdot (1 - \exp(-R1 \cdot TR))(1 + \cos \alpha) \quad (17)
\]

The signal for both echoes as a function of \( \alpha \) and TR is shown in figure 14a and b respectively.

After recording images with various repetition times TR and flip angles \( \alpha \), R1 and R2 maps can be obtained by fitting the pixel intensities in the base images against equations 15-17.

If the repetition time TR is much greater than the spin-spin relaxation time T2 (i.e. TR >> T2), the signal amplitude becomes independent of R2.

\[
S_i = S_0 \cdot \sin \alpha \cdot \left(\frac{1 - \exp(-R1 \cdot TR)}{1 - \exp(-R1 \cdot TR) \cdot \cos \alpha}\right) \quad \text{TR >> T2} \quad (18)
\]

In the latter case, the flip angle can be varied to extract R1.
Under this condition, if we take two measurement with different flip angles of which the first is 90° and the second is α the R1 can be calculated from:

\[ R1 = \frac{1}{TR} \cdot \ln \left( \frac{S(\alpha) \cdot \cos \alpha}{S(\alpha) - S(90°) \cdot \sin \alpha} \right) \]  

\[ \text{TR} \gg \text{T2} \]  

(19)

A special case of SSFP is when the net gradient area is zero at any of the three gradient axes during one TR interval (between two successive RF excitations). This sequence is called balanced SSFP (figure 15b). In this case, only one echo is obtained.

**Figure 13.** Two variants of the steady-state free precession (SSFP) sequence. Depending on the phase of the flip angle sequence the sign of the SSFP signals are either all positive (a) or alternated in polarity every two echoes (b). The magnitude of the SSFP signal is the same in both cases.
Figure 14. Signal $S_I$ (a) and $S_{II}$ (b) in the SSFP sequence for various flip angles $\alpha$ and repetition times $TR$ for a sample with $R1 = 1 \text{ s}^{-1}$ and an $R2 = 10 \text{ s}^{-1}$.

The signal amplitude of the echo in balanced SSFP is given by [36]:

$$S = S_0 \cdot \sin \alpha \cdot \left( \frac{(1 - \exp(-R1 \cdot TR)) \cdot \exp(-R2 \cdot TE)}{1 - (\exp(-R1 \cdot TR) + \exp(-R2 \cdot TR)) \cdot \cos \alpha + \exp(-(R1 + R2) \cdot TR)} \right)$$

(20)

for no sign alternation between successive RF pulses (i.e. $\alpha_x - \alpha_x - \alpha_x - \ldots$) and

$$S = S_0 \cdot \sin \alpha \cdot \left( \frac{(1 - \exp(-R1 \cdot TR)) \cdot \exp(-R2 \cdot TE)}{1 - (\exp(-R1 \cdot TR) - \exp(-R2 \cdot TR)) \cdot \cos \alpha - \exp(-(R1 + R2) \cdot TR)} \right)$$

(21)

when sign alternation is used between successive RF pulses (i.e. $\alpha_x - \alpha_x - \alpha_x - \ldots$).

Figure 15. Non-balanced SSFP (a) yielding two echoes and balanced SSFP (b) yielding only one echo. The difference lies in the frequency encoding gradient which is completely refocused within one TR in the case of the balanced SSFP sequence.
3.1.6. Very fast acquisition sequences

Theoretically, very fast acquisition schemes such as echo-planar imaging (EPI), gradient and spin-echo acquisition (GRASE) and half-Fourier acquired single shot turbo spin-echo (HASTE) can be used in combination with a T1 magnetization preparation sequence. For T1 mapping, an inversion recovery preparation can be applied. Also the Look-Locker sequence can be used in which an EPI readout is performed for each $\alpha$-pulse. In this case, all the base images for a complete T1 map can be acquired within 3 s.

However, due to the very low bandwidth in the phase encoding direction, considerable image distortion can be produced in regions with off-resonance effects, such as field inhomogeneity, magnetic susceptibility variations, long time eddy currents and concomitant magnetic fields. Post-processing correction schemes have been proposed for EPI image distortions.

Because for gel dosimetry, high spatial accuracy is a prerequisite for the accuracy of the final dose maps, such very fast acquisition sequences may not be the best choice. Very fast acquisition may be used in combination with other k-space sampling schemes (such as spiral and projection acquisition). These sequences may perform much better in terms of spatial accuracy but care should be taken as with such acquisition schemes, artefacts will be smeared out over the entire image. This may compromise the dosimetric accuracy. Also the point-spread-function can be deteriorated significantly.

3.2. Quantitative R2 imaging sequences

3.2.1. The spin-echo sequence

The spin-echo has intrinsic T2 weighting. Changing the echo time, TE while keeping the repetition time, TR constant will result in a different T2 weighted spin-echo signal (figure 17). From two images recorded with different echo time an R2 map can be calculated. The R2 value in each pixel of the R2 map can thus be easily calculated from the corresponding pixel intensities in the different T2 weighted base images according to
\[ R_2 = \frac{1}{T_{E_2} - T_{E_1}} \ln \left( \frac{S(T_{E_1})}{S(T_{E_2})} \right) \]  

with \( T_{E_1} \) and \( T_{E_2} \) the echo times for both images and \( S(T_{E_1}) \) and \( S(T_{E_2}) \) the pixel intensity in corresponding pixels.

\[ S(T_{E_1}) = S_0 \cdot \exp(-R_2 \cdot T_{E_1}) \]

\[ S(T_{E_2}) = S_0 \cdot \exp(-R_2 \cdot T_{E_2}) \]

\[ \Rightarrow R_2 = \frac{1}{T_{E_2} - T_{E_1}} \ln \left( \frac{S(T_{E_1})}{S(T_{E_2})} \right) \]  

**Figure 17.** A spin-echo experiment repeated twice with two different echo times yields enough information to reconstruct an R2 map.

The advantage of the basic spin-echo sequence is that it is readily available on all scanners and that it is easy to understand and extract the R2 relaxation rate (equation 22).

Any displacement of both images with respect to each other (for example caused by eddy currents or motion of the object) can result in errors in the calculated R2 map. Although no object motion can be expected in the case of gel dosimeters, eddy current effects have been detected [39].

Another disadvantage of single spin-echo sequences concerns the acquisition time. If only a few images are recorded. There is a lot of dead time in the sequence (required for T1 recovery and T2 relaxation) but which is not been used for signal acquisition. This results in long measurement times to obtain sufficient signal-to-noise (thus dose resolution) in the dose maps or by other words a poor intrinsic precision (see further). It can be noted that multiple slices can be recorded in the time after the spin-echo and before the next (90°) excitation pulse (i.e. the time for T1 signal recovery). However for the longer echo time (figure 17b) this time period is significantly smaller.
3.2.2. Fast spin-echo sequence (turbo spin-echo sequence)

The acquisition for one slice can be accelerated by acquiring multiple echoes after each excitation pulse. Each echo is incrementally phase encoded for different phase lines in the k-space. The echo time in the calculation of the R2 map is replaced by an effective echo time. This effective echo time depends on the k-space phase ordering scheme. The number of echoes acquired within one repetition time in the fast spin-echo sequence is called the “turbo factor”. The problem with this acquisition scheme is that the different k-space lines have a different T2-weighting. This leads to a distortion of the point-spread-function (PSF) (see further) which compromises the intrinsic spatial resolution in the images []. With many echoes, this distortion of the PSF may become rather significant.

![Diagram of fast spin-echo sequence](image)

**Figure 18.** Fast spin-echo sequence yielding several echoes within one repetition time. All echoes within one repetition time have the same phase encoding. Each echo is stored in a separate k-space matrix. Finally, as many base images are obtained as there are echoes.

Different k-space line ordering schemes may help in minimizing the distortion of the PSF. In this case, the effective echo time is sometime difficult to determine. The fast spin-echo sequence is often regarded as a faster way to record R2 maps. However, when more than one slice is recorded, which is most often the case for 3D gel dosimetry, a multiple spin-echo sequence may be faster.
3.2.3. The multiple spin-echo sequence

In the multiple spin-echo sequence a train of 180° RF pulses is applied. In contrast to the fast spin-echo sequence, the spin-echo signals have the same phase encoding and are stored in separate k-space images which after FFT result in different T2-weighted base images.

![Diagram of the multiple spin-echo sequence](image)

**Figure 19.** Multiple spin-echo sequence yielding several echoes within one repetition time. All echoes within one repetition time have the same phase encoding. Each echo is stored in a separate k-space matrix. Finally, as many base images are obtained as there are echoes.

A Levenberg-Marquardt $\chi^2$-minimization algorithm can be used to fit the R2 value from the base images. Also with the multiple spin-echo sequence, multiple slices can be recorded interleaved. In that case, after each echo train a new slice is excited (with a 90° RF pulse) within the same repetition time. It is shown that the number of echoes (or the echo time spacing) can be optimized with respect to dose precision for a certain number of slices [40]. The number of echoes in imaging sequences provided by the manufacturer is often restricted. In that case, the echo time spacing between the echoes can be optimized [41]. It is shown that heating of the phantom may be induced by the large number of 180° refocusing pulses. To compensate for temperature related imaging artefacts, a central k-space ordering scheme is preferred [42]. Also, it is shown that the interplay of stimulated echoes and varying eddy currents induced may induce imaging artefacts. To prevent these effects, a gradient train can be applied to bring the eddy currents in a steady state before the onset of the sequence [39]. Although the concept of fitting an R2 map from the different base images compensates theoretically for B1-field inhomogeneities, the R2 map may still be susceptible to secondary effects caused by the interplay of stimulated echoes and the B1 field inhomogeneities. Several strategies for compensating the remaining inhomogeneities in the R2 maps have been proposed [43, 44].
3.2.4. Single-shot free precession sequences

As demonstrated in section 3.1.5 the SSFP signal is weighted with both R1 and R2. With a repetition time TR much smaller than T1 and a flip angle $\alpha = 90^\circ$ the ratio of the two signals in the non-balanced SSFP sequence becomes

$$\frac{S_u}{S_f} = \exp\left(-2 \cdot R2 \cdot (TR - \Delta)\right)$$

with $\Delta$ the time between the second echo and the next 90° excitation pulse.

3.3. Quantitative magnetization transfer imaging sequences

Polymer gel dosimeters contain both synthetic and bio-polymers which create a macromolecular proton pool. These protons give rise to a broadened spectral peak (as a result of their short T2). Upon polymerisation, the proton pool increases which results in a larger fraction of the broad spectral component. This makes it possible to image polymer gel dosimeters using magnetization transfer (MT) based contrast [45].

Using an off-resonance RF pulse (figure 20), part of the macromolecular proton magnetization can be saturated (‘demagnetized’). Due to magnetization transfer between the macromolecular proton pool and the liquid proton pool the loss of magnetization of the macromolecular proton pool will be reflected in a decrease in magnetization of the liquid proton pool. As a result, an MR signal decrease will be observed. For a quantitative interpretation of magnetization transfer between the different proton pools, the reader is referred to more specialized literature [46-48]

![Figure 20](image.png)

**Figure 20.** Principle of magnetization transfer. Short T2 (long R2) proton pools (such as from (bio)polymers and lipids) result in broadened spectral peaks. If an off-resonance RF pulse is applied, a fraction of these protons will be demagnetized. Due to the transfer of magnetization from the ‘liquid’ proton pool to the demagnetized protons the signal from the liquid proton pool will be decreased.
In the case of low-density foam gel dosimeters, R2 mapping is no longer possible due to the signal loss caused by diffusion weighting in the microscopic background magnetic field gradients that originate from susceptibility differences between the gas bubbles and the gel fraction [49]. It has been shown that quantitative magnetization transfer imaging at the other hand is well suited for these lung equivalent gel dosimeters [50].

### 3.3.1. MT prepared sequence

A pulsed MT prepared spin-echo sequence is shown in figure 21. The sequence consists of a magnetization preparation part and a readout part. The magnetization preparation consists of a series of off-resonance MT saturation pulses. The number \(N_{\text{sat}}\), frequency offset \(f_{\text{off}}\) and intensity of the MT saturation pulses can be varied by the user. In theory, a single MT pulse with a long duration and significant amplitude can be used. This is recognized as the initial continuous wave MT sequence. Most scanners however, do not allow such long RF pulses because of RF energy restrictions (patient safety limits and coil protection). The readout part can be any basic imaging sequence scheme such as spin-echo, fast spin-echo, gradient echo or EPI. A quantitative MT ratio image can be obtained by acquiring images with different MT saturation pulse intensities. Also the offset frequency can be varied.

![Figure 21. Magnetization transfer imaging sequence with MT magnetization preparation consisting of a number \(N_{\text{sat}}\) of off-resonance MT saturation pulses, spoiler gradients and a spin-echo readout sequence. The number, intensity and frequency offset of the MT saturation pulses can be varied.](image)

The observed magnetization in the MT experiment is \(M_{\text{SAT}}\). The observed relative signal decrease is called the magnetization transfer ratio MTR and is defined as

\[
MTR = \frac{M_0 - M_{\text{SAT}}}{M_0}
\]
with $M_0$ as the equilibrium magnetization, which is obtained by scanning without MT saturation pulses. The MTR consists of two contributions: $M_{\text{dir}}$, the direct effect contribution which is due to the saturation of the water proton pool, and $M_{\text{MT}}$, the true magnetization transfer contribution due to magnetization transfer between the water proton pool and the polymer proton pool.

$$MTR = \frac{M_{\text{dir}}}{M_0} + \frac{M_{\text{MT}}}{M_0}$$  \hspace{1cm} (25)

The direct effect $M_{\text{dir}}$ is experimentally determined from the signal intensity in a water sample $M_{\text{H}_2\text{O}}$. As a result, the true magnetization transfer ratio, $MT=M_{\text{MT}}/M_0$ is given by

$$MT = \frac{M_{\text{MT}}}{M_0} = MTR - \frac{M_{\text{dir}}}{M_0} = \frac{M_{\text{H}_2\text{O}} - M_{\text{SAT}}}{M_0}$$  \hspace{1cm} (26)

An MT offset frequency dispersion plot can be obtained by recording the signal intensity as a function of the MT saturation pulse frequency offset (figure 22b). An optimum offset frequency can be determined from this plot.

![Figure 22](image_url)

**Figure 22.** The observed relative signal decrease MTR is due to both direct saturation of the water protons $M_{\text{dir}}$ and to magnetization transfer between the water proton pool and the polymer proton pool $M_{\text{MT}}$ (a). A spectral MT measurement of a low-density methacrylic acid polymer gel foam (b). The red dots represent the MT difference between a sample irradiated to 20 Gy and an unirradiated sample.

The correlation between the number of MT saturation pulses and the MT weighting can be analytically derived [51].

### 3.3.2. Pulsed magnetization transfer steady state imaging

As for R1 and R2 mapping, also for MT imaging, a steady state sequence can be used [52]. A schematic drawing of the pulsed MT steady state sequence is shown in figure 23. The pulse sequence consists of three distinct elements: An off-resonance MT saturation pulse (with duration $\Delta$, frequency offset $f_{\text{off}}$ and amplitude $\theta$) succeeded by a spoiler gradient, a small RF pulse with flip angle $\alpha$ which produces transverse magnetization for the liquid pool but has negligible effect on the semisolid pool, and finally a repetition time TR, which incorporates spatial encoding (gradients not shown in figure 23) and evolution of image contrast.
The pulsed magnetization transfer steady state imaging sequence consisting of MT pulses with spoiler gradient (with total time duration $T$) and a small flip angle excitation (flip angle $\alpha$).

Image contrast is determined by five parameters: the MT pulse amplitude $\theta$ and duration $\Delta$, the MT pulse offset frequency $f_{\text{off}}$ and the spoiled gradient echo parameters $\alpha$ and $T$. The correlation between the true magnetization transfer ratio, MT, and the two pool model can be described by a numerical model [53].

A different steady state sequence has been proposed by Gochberg et al [54] in which a train of RF pulses is used that selectively invert the magnetization of the free water protons while the macromolecular proton pool is minimally disturbed.

### 3.3.3. Stimulated echo preparation sequence

In describing the magnetization transfer experiment, a two compartmental model (figure 24) consisting of both a liquid (A) and a macromolecular proton pool (B) can be considered. This model is similar to a pharmacokinetic dilution model. If in pool A the protons are labelled (filled circles), magnetisation transfer (described by the exchange rates $k_{AB}$ and $k_{BA}$) causes redistribution of the labelled protons. Also R1 relaxation takes place in both pools decreasing the labelled protons ($R_{1A}$ and $R_{1B}$). The process can be modelled by differential equations describing the change in magnetization in both pools:

$$\frac{dM_A(t)}{dt} = -M_A(t) \cdot (R_{1A} + k_{AB}) + M_B(t) \cdot k_{BA}$$

$$\frac{dM_B(t)}{dt} = -M_B(t) \cdot (R_{1B} + k_{BA}) + M_A(t) \cdot k_{AB}$$

(27)

where $M_A(t)$ and $M_B(t)$ refer to the free and bound pool magnetization of the labelled spins, respectively. In the stimulated echo preparation sequence (figure 25a), labelling of the protons in the liquid proton pool (A) is performed by a spin preparation consisting of a 90° RF pulse followed by a
modulation gradient and a second 90° RF pulse that flips the prepared transverse magnetization back in the longitudinal direction. The spins in the bound proton pool are not affected by this preparation because the transverse magnetization will vanish during a typical pulse separation time of a few milliseconds due to the short T2 decay of the bound protons. Solving the differential equation 27 with the boundary condition $M_B(t=0) = 0$, yields a bi-exponential decay of the magnetization in the free proton pool.

\[
M_A(t) = M_0 \cdot (C_1 \cdot \exp(-\lambda_1 \cdot t) + C_2 \cdot \exp(-\lambda_2 \cdot t))
\]  

(28)

$\lambda_1$ is a “fast” rate responsible for the quick approach to a steady state between both pools while $\lambda_2$ is a “slow” rate is roughly comparable to R1. The time t in equation 28 is the time after the sin preparation (i.e. time after the second 90° RF pulse). The different coefficients can be fitted from a biexponential fit to a stimulated echo dataset obtained with different mixing times. From these coefficients the fraction of bound proton pool at total proton pool can be derived.

![Figure 25](image)

Figure 25. Stimulated echo preparation sequence for labelling spins.

A modified version of the stimulated echo sequence requiring only two measurements to extract the pool fractions is shown in figure 25b. This sequence is run twice: Once with a 180° RF pulse during the mixing time (time between the second and third 90° RF pulse) and once without the 180° RF pulse [55]. With a non-selective 180° RF pulse (1 ms) placed in the centre of the mixing period which changes the sign of the phase of the free-pool spins only, an imbalance is achieved. After the 180° RF pulse, the originally labelled spins in pool B will be diluted by the spins in pool A, which have opposite phase. Conversely, the spins in pool A, with opposite phase, will be diluted by the originally labelled spins from pool B. The pool fraction can be determined from both measurements.
4. How to evaluate the performance of the imaging sequence?

4.1. Accuracy and imaging artefacts

Whatever imaging technique is applied to map a dose-effective contrast (R1, R2, MT, optical absorbance, X-ray absorbance, ultrasound attenuation, dielectric constant, etc.) there are two essential criteria that should be accomplished in the imaging technique: First of all, the images should be accurate both in space as in dose (i.e. not contain systematic errors) and secondly, the stochastic deviations on each voxel should be as low as possible within a reasonable measurement time and for a certain image resolution. An interesting parameter to evaluate the stochastic deviations is the minimum detectable dose difference, defined as the dose resolution [56].

The target figure of accuracy that is aimed in gel dosimetry for high-precision radiotherapy is about 2–3% of the maximum dose in regions of homogeneous dose and a spatial error of less than about 2 mm in regions of high-dose gradients. However, in a conventional MR scanner, several imaging artefacts 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 artefacts have resulted in different compensation strategies.

In treating imaging artefacts, we will mainly focus on T1 and T2 measurements but many of the artefacts that occur in these measurements may also appear in images obtained with other MR sequences. The spatial accuracy of the dose maps is affected by geometrical distortions. Eddy currents, main magnetic field inhomogeneities and gradient inhomogeneities cause machine related geometrical distortions, while susceptibility variations and chemical shift variations in the imaging volume cause object related geometrical distortions. Also dose inaccuracies can be machine related such as those caused by eddy currents, stimulated echoes, inhomogeneities in the B1-field and standing radiofrequency (B1) waves or they can be object related such as temperature drift and molecular self-diffusion. Table 1 gives an overview of the most important MRI artefacts that may compromise the reliability of gel dosimetry.

Table 1. Overview of important artifacts that may occur in MRI gel dosimetry classified by two criteria. The abbreviation as most often used in the literature is also given.
4.1.1. Image non-uniformities

**Manifestation**
A parametric MR image of a uniform sample may demonstrate areas of non-uniform signal intensity. For gel dosimetry purposes, non-uniformities result in areas of over- and under-dosages if not corrected for.

**Causes**
Image non-uniformities will mainly occur in images recorded with a surface coil acting as a transmitter. A realistic transmitting RF coil produces a non-uniform RF field also called B1-field. Some imaging sequences are more sensitive to B1-field inhomogeneities than others.

In T1 imaging (for Fricke gel dosimetry), severe non-uniformities were found when a spin-echo sequence was used with different repetition times (TR) [57]. These non-uniformities are attributed to a non-uniform B1 field in combination with inherent differences in T1 relaxation for different relaxation times. These non-uniformities were found to be considerably less pronounced when an inversion recovery sequence was used with different inversion times (TI).

In T2 imaging for monomer/polymer gel dosimetry using a multi-echo sequence in combination with a circularly polarized (CP) transmit/receive head coil, the R2 map was found to be uniform over an area of 120 cm in the centre of the coil, while the R2 values (apparent dose values) decreased considerably near the edges of the coil [43] (figure 26d). Using a body coil, the B1-field is far more uniform (figure 26a) resulting in a much more uniform R2 map (figure 26c). However, measuring R2 using the body coil both as transmitter and receiver is at the cost of signal-to-noise (SNR).

![Figure 26](image)

**Figure 26.** B1 field map (effective flip angle) acquired with a body coil (a) and with a transmit/receive head coil (d). R2 images of a blank non-irradiated polymer gel dosimeter acquired with the body coil and head coil are shown in (c) and (f) showing the effect of the inhomogeneous B1-field for the head coil. The field-of-view (FOV) is 320 x 320 mm². Corresponding longitudinal profiles through the center are also shown (b and e). The plot in figure (g) gives the relation between the change in R2 and the flip angle for a nominal flip angle of 90°.

The plot of change in R2 versus effective flip angle provided in figure 26g is dependent on the rf pulses used in the multiple spin-echo sequence. This relation can be theoretically derived using numerical simulations and can be experimentally derived by acquiring the signal of a homogeneous (blank) phantom in the centre of the coil for different excitation and refocusing flip angles [43].
There are several sources of non-uniformities in spin-echo images. These sources include B1-field inhomogeneity, RF standing waves, skin effect at high field strengths, crosstalk between multiple slices, mistuning of the head coil, eddy currents and static field inhomogeneities [58]. Most of these non-uniformities scale with the image intensity in the base images. As a result, the artefacts are cancelled out after fitting the quantitative MR parameter (T1, T2 or MT). However, some of these artefacts may not vanish completely in the parametric images if some other sequence specific mechanisms interfere. In clinical MR-scanners, the non-uniformities in the T1 and T2 images are mainly caused by B1 field inhomogeneities. It is well known that the B1 field generated by a radio-frequency coil is not completely homogeneous. B1 field inhomogeneities are attributed to RF amplifier distortions [59], digitization of the RF pulse [60], RF coil geometry [61-63] and penetration in the scanned object [64,65].

In the quantitative T1 spin-echo experiment, the incomplete excitation in some parts of the phantom due to B1-field inhomogeneity makes that the restoration of the longitudinal component of the magnetization is different for different repetition times. It is clearly seen that the inhomogeneous signal intensity pattern varies over the different T1 weighted base images [57]. Also in our T2 studies, the non-uniformities are mainly caused by an inhomogeneous B1-field in combination with stimulated echoes. As a result of the inhomogeneous B1-field, the flip angle of the nuclear magnetic moments after an excitation or a refocusing pulse will not be equal throughout the scanned volume. Thus the history of spin magnetization during a multiple spin-echo sequence will depend on the position of the nuclear moments in the slice and therefore the deviation in the R2 value will depend on the position [42]. Computer simulations solving the Bloch equations for the multi-echo sequence predict the correlation of the measured R2 with the local B1 field. The simulations are completely in accordance with the experimental findings. By mapping the B1 field it is now possible to predict how the R2 deviations will vary with slice position [42].

Another source of non-uniformities is an inhomogeneous temperature drift of the gel phantom during scanning. Due to RF power absorbed by the gel, a temperature rise in the order of 1-3 °C is not uncommon. As the outer boundaries of the phantom are surrounded by air (mostly in flow), temperature differences in the phantom will build up [43]. As the T2 of the dosimeter gel is temperature dependent, dose errors in the order of 3% to 10% (relative to the maximum dose) can be expected.

Figure 27. Temperature images recorded with the proton resonance frequency method at several time points during a multi-echo sequence. The interval between two successive maps is approx. 4 hours. The sequence was stopped after the recording of image IV. The scale is in degrees Celsius.

Compensation strategies

It has already been mentioned that T1 images can be obtained by an alternative spin inversion recovery sequence [57] if the uniformity in the T1 images exceeds 2-3% with the spin-echo sequence. The B1 field can be measured by several ways and can be used to correct the R1 and R2 images. However, in that case, also the influence of the B1 field upon the R1 and R2 image has to be known. An analytical expression cannot be derived easily in the case of a multiple spin-echo sequence because...
of the rapid (exponential) increase in magnetization pathways after a few imperfect RF pulses. Computer simulations solving the Bloch equations may help in deriving this correlation. A more practical, but theoretically less founded method is to measure the R2 distribution in a homogeneous phantom (for example, the gel phantom before irradiation) and using this image-set as a template to correct the resulting R2 images. It is obvious that these post-processing corrections are founded on the fact that the position of the phantom can be determined accurately. In applying this strategy, quality control of the reproducibility of the non-uniformities and the dependency of the non-uniformities on phantom shape should be performed on a regular basis. A more direct way of minimizing B1-field related non-uniformities is by using the body coil as a transmitter at the cost of a lower signal-to-noise ratio. Some scanners are equipped with receive-only coils that can be used in combination with the body coil acting as transmitter. This results in a more homogeneous B1-field while still preserving a good signal-to-noise ratio. The temperature drift related non-uniformities can be disposed of by centric k-space filling [42].

As non-uniformities may lead to severe dose errors and are very likely to occur to some extend in three dimensional scanning of the gel phantom, it is of ultimate importance that the uniformity of the parametric images is measured in advance and that scanning is performed using adequate compensation strategies to keep the non-uniformity level below acceptable levels.

4.1.2. Image distortions

**Manifestation**
The geometrical shape of the phantom is deformed in the dose maps (parametric images). These deformations may have an effect on the global image or may occur only locally in part of an image, especially around inclusions of other structures in the phantom. Some structures of the phantom may be displaced with respect to others. Important to note is that displacements and scaling of the whole phantom may occur both in the image plane as out of the image plane.

**Causes**
Low magnetic field scanners may suffer more from machine related image distortions than cryogenic magnets. The inclusion of other structures such as air cavities and low-density materials may result in object related distortions in the vicinity of these structures. Slice displacements may occur in scanners with non-active shielded gradients.

Spatial encoding of the recorded MR-signal is based upon the correlation of magnetic field strength and the frequency of the rf pulses, described by the Larmor equation (equation 1). By switching linear magnetic field gradients in three orthogonal directions during the MR-sequence, an encoding in three orthogonal directions is obtained. The magnetic field gradients, produced by gradient coils, may deviate from the assumed linearity to some extent. Furthermore, the main magnetic field, B0, is not completely homogeneous. This results in a deformation of the recorded image. Similar encoding errors may occur during phase encoding and slice selection.

To measure the magnitude of deformations from non-linear gradients and main magnetic field inhomogeneities several phantoms have been proposed [66-68]. In observing in-plane distortions a pin-cushion phantom is often used. To account for errors in the construction of the phantom, the phantom is first scanned by use of CT. By overlaying the images indicating the positions of the tubes of the MR images on the CT images a distortion map can be derived. Apart from these static deviations in the magnetic field and gradients, the magnetic field may also deviate from the theoretical expected shape due to time-varying magnetic field components. These time-dependent magnetic field deviations are caused by “eddy currents”. The eddy currents are induced through switching of the imaging gradients giving way to an electromotive force that acts on the cryostat and metal casings. Several techniques to measure and analyze eddy currents in clinical scanners have been described [39, 69-76]. The eddy current induced magnetic field is mostly described by a first order approximation.
composed of a global offset of the main magnetic field, $\Delta B_0(t)$ and a change in the magnetic field gradients, $\Delta g_i(t)$ ($i = x, y, z$) [69]. The eddy current related spatial encoding errors are mainly due to eddy current fields that are present during frequency encoding and slice selection. Depending on the moment in the sequence that eddy currents are present, they will cause slice shifts or slice tilting in different directions. To measure slice displacements, a pyramidal phantom can be used [39]. A special designed quality control phantom consisting of a perspex plate with holes drilled in special directions and filled with gel can also visualize slice warping (see further).

To extend gel dosimetry to phantoms that include air cavities (for example to investigate effects of electronic disequilibrium), materials with different electron densities are inserted in the gel phantom. These materials very often have a different magnetic susceptibility. This will result in susceptibility related distortions in the base images and in the final parametric images. The distortion is inversely proportional to the receiver bandwidth. Also the inclusion of materials with a different chemical composition (organic liquids, fats) in the gel may result in a (chemical) shift of these objects in the frequency encoding direction.

An example of a susceptibility related artefact is shown in figure 28a. This example was obtained by coincidence: In order to save some measurement time, two gel phantoms were placed in the scanner at the same time. The magnetic field and the frequency encoding direction are oriented upward in the images. It can be clearly seen that the phantoms are distorted near the interface between the phantoms. When the phantoms are oriented perpendicular to the magnetic field, the artefact disappears. Also changing the frequency and phase encoding direction will make the distortion disappear. Another example of susceptibility artefacts caused by a guiding catheter of a brachy source can be found elsewhere [77]. In this example the magnetic field distortion is shown as imaged and calculated numerically.

**Figure 28.** Two cylindrical gel phantoms scanned in different directions illustrate susceptibility related deformations at the interface between both recipients. The circular lines are drawn on the image to show the actual boundary of the phantoms.

Compensation strategies

External (fiducial) markers on the phantom are often used to allow image fusion with computer planning or other dosimetry techniques. These external markers may give a first indication of deformations or slice displacements. A scaling error of the phantom can also be detected by use of image fusion/matching software.

To measure machine related distortions, use can be made of a dedicated quality control phantom (as discussed further). A distortion map can be derived and used as a correction matrix for the dose map as has been done for MR-guided stereotactic neurosurgery [68].

Object related geometrical distortions may be compensated by first measuring or simulating the local magnetic field distortions caused by susceptibility differences and chemical shift artefacts. These magnetic field maps can then be used to construct a correction template which can be used to correct the parametric images [78]. Another method to correct for local magnetic field distortions is by a technique called ‘view-angle-tilting’ [79]. This method has the advantage that no post-processing is needed but has the disadvantage that the point-spread function is broadened which may lead to an erroneous interpretation of the spatial resolution. Important to emphasize is that the artefacts act on a
pixel-related scale instead of a geometrical scale. Increasing the resolution will decrease the artefact on a geometrical scale. Another important parameter is the receiver bandwidth. The distortions are inversely proportional to the receiver bandwidth. However, increasing the bandwidth will decrease the signal-to-noise ratio.

4.1.3. Dose errors

Manifestation
Dose errors cannot be observed directly by inspection of the parametric images or dose maps but may be discovered by comparison of the gel measured dose values against those measured with other dosimetry techniques. In some cases, the dose response may be dependent on the scanning orientation and other sequence parameters such as the field-of-view (FOV). The whole dose response can be higher or lower with a constant offset or the dose sensitivity can be altered.

Causes
With the use of a multiple spin-echo sequence, the dose-response curve can be dependent upon scanning orientation and image parameters (field-of-view). These effects may be more pronounced in scanners with non-active shielded gradients and in applications where high gradient strengths and short echo times are used. It is well known that the R2 values of the gel are temperature dependent [10, 19]. A temperature increase during scanning may result in a dose-underestimation. If the gels are not thermally equilibrated before scanning, temperature changes may cause severe dose errors. The chance for dose errors to occur is higher if scanning of the calibration tubes is performed in different circumstances and imaging parameters than the gel phantom.

The effect of eddy currents on image deformation has already been discussed in previous paragraph. The magnetic fields induced by eddy currents experience a certain decay time. The succession of many imaging gradients in a multi-echo sequence may lead to a continuous increase of magnetic field during the start of the sequence. From measurements of eddy current created by gradient trains containing different numbers of gradients, it is found that saturation in the eddy current induced magnetic field offset is obtained after 10 gradients [39]. Through computer simulations (solving the Bloch equation numerically) it is proven that the continuous change in the eddy current induced magnetic field offset during the first 10 echoes leads to a deterioration of the slice profiles which results in a change of the measured T2-decay curve. As the eddy currents (and especially the magnetic field offset) are dependent on the imaging direction, the disturbance of the excitation history of stimulated echoes is different and therefore also the measured T2 values.

Partial volume effects may also lead to a misinterpretation of the dose in each pixel. It has been shown that partial volume effects can cause severe dose discrepancies in pixels adjacent to a point source as occurring in a brachytherapy experiment [77]. Also outer-volume effects may result in dose errors. In-plane outer volume effects are related to the point spread function while in the slice selective direction outer volume effects may be expected from imperfect slice profiles. In multi-slice imaging care has to be taken in excitation of the slices. Even if excitation of the different slices is performed interleaved, cross-talk between slices may lead to inter-slice variations.

Compensation strategies

The addition of a gradient train may bring the eddy currents in a steady state regime. It is shown experimentally and through computer simulations that by this preparation gradient train, the slice profiles are shifted in the slice-encoding direction but that the shape of the slice profiles is preserved. It is advisable for other scanners to measure the eddy current fields for different numbers of gradients in order to determine the required number of gradients to bring the eddy currents in a steady state regime.
Another source of dose errors is related to a temperature drift in the phantom during scanning. Although precautions are made in letting the gel phantom equilibrate at the room temperature of the scanner, a temperature increase may still occur during scanning by absorption of the RF energy of the excitation and refocusing pulses. In figure 29, the temperature in the gel phantom during a long scanning experiment is shown. Note that a temperature increase is present during T2 scanning but not during temperature mapping (FLASH-sequence) illustrating the high-energy transmittance during the multiple spin-echo sequence. The sequence can be made significantly less sensitive to temperature drift by using a centric k-space ordering scheme instead of a standard linear k-space ordering scheme [42]. Partial volume effects can be minimized by using special designed slice-selective RF pulses and by increasing the time between excitation of adjacent slices.

Some websites that provide lists of other imaging artefacts that may occur in clinical imaging applications are provided in the references [60-62].

4.2. Precision and acquisition time

The overall dosimetric precision is governed by variations in the several operations that take place in the dosimetry experiment. The first step in a gel dosimetry experiment is weighing the chemicals. Stochastic variations in the weighting will result in variations in the measured dose-related value (R2, MT, OD) as the dose-response is determined by the chemical composition. It is found that other manufacturing conditions may also have an influence on the dose-response such as the temperature during fabrication. Stochastic variations in the controlled temperature will therefore also lead to variations in the measured dose-related value. Also during irradiation there are different sources of stochastic variable contributions that determine the overall dosimetric precision such as variations in the dose delivery, variations in the temperature during irradiation and stochastic variations in the positioning of the calibration phantoms. Any form of scanning the gel dosimeter will introduce thermal detector noise. The noise contribution is determined by some scan parameters. Often, the scan parameters can be optimized in order to achieve an optimal figure of precision.

The concept of dose-resolution was introduced to evaluate the intrinsic dosimetric precision in terms of dose sensitivity and scanning signal-to-noise [56]. The dose resolution, written as $D_{res}$, is defined as
the minimal detectable dose difference within a given level of confidence, $p$. The dose resolution is related to the standard deviation on dose $\sigma_D$ by the equation

$$D_{\Delta p} = k_p \cdot \sqrt{2} \cdot \sigma_D$$

(29)

For a 95% confidence level the dose resolution becomes $D_{\Delta p}^{95\%} = 2.77 \cdot \sigma_D$.

In most radiation dosimetry experiments, gel dosimeters are used in a relative manner in the sense that the dosimeter is exposed to the same treatment as the patient but with a different total radiation dose. The total dose delivered to the dosimeter is scaled to cover the active dose range of the dosimeter. In this context, it is preferable to use the concept of dose resolution relative to the operating dose range, here defined as relative dose resolution:

$$D_{\Delta p}^\% = \frac{D_{\Delta p}}{(D_{\max} - D_{\min})} = \sqrt{2} \cdot k_p \cdot \left(\frac{\sigma_D}{D_{\max} - D_{\min}}\right)$$

(30)

If the dose maps are derived from quantitative NMR-$\Psi$ maps, it can be shown that the relative dose resolution ($D_{\Delta \Psi}^\%$) is equal to the relative $\Psi$ resolution ($\Psi_{\Delta \Psi}^\%$) which is defined in a similar way:

$$D_{\Delta \Psi}^\% = \sqrt{2} \cdot k_p \cdot \left(\frac{\sigma_{\Psi}}{\Psi_{\max} - \Psi_{\min}}\right) = \Psi_{\Delta \Psi}^\%$$

(31)

with $\Psi$ either R1, R2, MT or any other contrast. This also applies to non-MRI contrasts.

It should be emphasized that dose-resolution as defined here does not include stochastic variations in chemical concentrations, in dose delivery or in the calibration procedure. For that reason, dose-resolution can be considered as an intrinsic lower limit of dosimetric precision. It is a misconception that the dose-resolution would be a parameter that is only related to the type of gel dosimeter. In some publications, the concept of dose resolution has been misused as the criteria to compare different types of gel dosimeters. This is misleading as these studies report on dose resolutions obtained with suboptimal scanning parameters. A completely different outcome would be obtained when different scanning parameters would be used. The concept of dose resolution however is very practical to optimize the intrinsic NMR sequence in terms of intrinsic precision [40,41]. In optimizing the NMR sequence, it is also important to take into account the number of slices that are required for the 3D dosimetry application as the optimization may also depend on the number of slices.

A dose-$\Psi$ curve is used to calibrate the $\Psi$ map [41] (again with $\Psi$ either R1, R2, MT or any other contrast). The uncertainty on the dose value $\sigma_D$ extracted from a linear dose-$\Psi$ plot with equation $\Psi = \Psi_0 + \alpha \cdot D$ is given by

$$\sigma_D^\prime = \frac{\sigma_\epsilon}{\alpha} \cdot \sqrt{\frac{(D_i - D)^2}{N_{\text{cal}}} + \frac{1}{N_{\text{cal}}}}$$

(32)

with $\sigma_\epsilon$ the standard deviation on the property $\Psi$ in the calibration points [41]. This value is derived from the standard deviation in a region of interest of the calibration vials $\sigma_{\text{ROI}}$. If $N_{\text{ROI}}$ is the number of points in the region of interest (ROI), the standard deviation on the calibration point is given by

$$\sigma_\epsilon = \frac{\sigma_{\text{ROI}}}{\sqrt{N_{\text{ROI}}}}.$$
\( D' \) is the estimated dose, \( \overline{D} \) is the mean dose of all dose values in the calibration plot (i.e. \( \overline{D} = \frac{1}{N_{\text{cal}}} \sum_{i=1}^{N_{\text{cal}}} D_i \) with \( D_i \) the dose in the \( i^{th} \) calibration point and \( N_{\text{cal}} \) the number of calibration points.

In order to make an equitable comparison between different imaging modalities, a figure of intrinsic precision on dose readout (\( IP_D \)) can be defined which is independent of spatial resolution and measurement time. The concept of intrinsic precision on dose readout (\( IP_D \)) can be used to compare the precision obtained with different imaging modalities such as MRI, optical CT and X-ray CT.

\[
IP_D = \frac{1}{D'_{\text{meas}} \cdot \Delta V \cdot t_{\text{meas}}} \cdot \Delta \cdot \sqrt{t_{\text{meas}}}
\]  
(33)

with \( \Delta V \) the real imaging voxel size and \( t_{\text{meas}} \) the measurement time. In comparing different imaging modalities it is also important to compare the \( IP_D \) for the same scanning volume. A large \( IP_D \) is the most optimal.

5. How to optimize my MRI readout protocol?

Here we provide some guidelines for optimizing your MRI readout protocol. Many of the elements mentioned here, also apply to other imaging modalities.

1. **Choose the contrast mechanism and imaging sequence that is suitable for your gel system.**  
   Any gel system may have a different dose sensitivity with respect to different MR properties (such as \( R1, R2 \) and MT). For stable gel dosimeters, the choice of contrast mechanism and imaging sequence depends on the optimum intrinsic precision on dose readout that can be obtained. It should be mentioned that at a first glimpse a particular contrast and sequence may appear to have a better dose sensitivity, however it should be emphasized that also the measurement time, spatial resolution and total imaging volume should be taken into account when evaluating the overall precision on readout (equation 33).
   
   In some cases however, fast scanning is required to avoid deterioration of the measured dose distribution by instability of the gel system (such as in the case of diffusion of contrast carrying chemicals). In these cases, the accuracy requirement overrules the search for maximum precision.

2. **Evaluate the imaging sequence on quality control phantoms of which the MR properties \( R1, R2, MT \) are comparable to the gel dosimeter that you plan to use.**  
   A thorough investigation of all the possible imaging artefacts (table 1) may be a tedious job. However, by scanning a blank gel phantom (an unirradiated phantom) the homogeneity in the dose maps can be investigated. The blank phantom should be scanned with the same scanning parameters and RF coil as in the normal gel dosimetry protocol. Also post-processing should be performed in the same manner. Alternatively, a liquid filled phantom can be used, but care should be taken with convection currents of the liquid that may occur in the phantom.
These currents may lead to additional motion artifacts that may be interpreted as non-uniformities. By subdividing the image in square regions of 7-by-7 pixels a distinction can be made between the stochastic and structural deviations. The stochastic deviation (noise) is obtained by calculating the average of the standard deviations in all square regions within the phantom. The structural deviation is obtained by calculating the standard deviation of the mean intensity values of all square regions.

Other parameters of interest are the slice profile, the actual spatial resolution, image deformations and slice warping. To investigate these properties, use can be made of a dedicated quality control phantom (figure 31).

![Figure 31. A multi-purpose quality control phantom of which eight image slices through the phantom provide a check of respectively (from left to right and top to bottom): image resolution (A), slice profile (C), signal-to-noise ratio (E), slice warp (G), ghost artifacts (B), pincushion distortion (D), quadrature errors (F) and susceptibility and chemical shift artifacts (H). With the drawing of the different sections, some images as obtained at an Expert 1T Siemens scanner (Ghent University hospital) are provided. For a more comprehensive description of the phantom see ref. 83.](image)

3. **Optimize your sequence in terms of dose precision**

Imaging parameters (TE, TR, α, etc.) can be optimized with respect to the dose precision. The relative dose resolution can be derived theoretically by analytical or by numerical means through a Monte Carlo random generation of signal noise in the base signal. Theoretical derivations for the optimization of echo time spacing and number of echoes for R2 measurements can be found in the literature [40,41]. Similar derivations can be made for other imaging sequences. Alternatively, the dose resolution can be determined experimentally for different imaging parameters.
4. *Optimize the calibration procedure*

   Enough calibration points should be taken. Both the number of calibration points and the dose precision of the calibration points determine the precision of the calibration (equation 32). The accuracy of the calibration procedure should be investigated by validation of the gel measured dose map of a known dose distribution. To minimize effects of chemical instability and temperature variations it is advisable to scan calibration vials together with the volumetric gel dosimeter phantom.

5. *Validate your sequence on a well defined test case of which dose profiles can be compared against some “gold standard”.*

   This is an important step that is often neglected. By comparing dose profiles obtained with a golden standard against the gel measured dose profiles, an idea on the overall accuracy is obtained. It should be noted however that through this procedure not only the scanning protocol is validated, but also the fabrication and irradiation of the gel dosimeter (figure 32). Any error that occurs in the latter procedures may appear as a deviation between the gel measured dose distribution and the dose measured by the golden standard.

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**Figure 32.** Gel dosimetry is performed in different stages. Errors can occur at each of the stages, leading to a decrease in the overall precision and accuracy. The scanning accuracy and precision can be determined by scanning a phantom with a predefined distribution of MR contrast (R1, R2, MT) several times.
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