Contrast mechanisms in magnetic resonance imaging

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1. General introduction

The first publications describing gel dosimetry used magnetic resonance imaging to detect changes in the proton longitudinal relaxation rate of a gel infused with ferrous ions and irradiated with ionizing radiation [1]. Later, different gel dosimeter systems were proposed that are based on the free-radical polymerization of monomers dispersed in a gel matrix [2]. In these polymer gels, changes in transverse relaxation rates were shown to be dependent on the absorbed dose. More recently, contrast in MR images based on the exchange of magnetization between polymer and water protons, following saturation of the polymer protons, has been exploited in polymer gel dosimeters [3]. In addition, variations in relaxation times in the rotating frame (T₁ρ) have been shown to produce contrast in MR images of irradiated polymer gel dosimeters. The signal and contrast in MR images may be manipulated to reflect a variety of these and other processes within an irradiated sample. An attempt is made here to provide an overview of the main different types of MRI contrast that may be used in gel dosimetry and, where possible, to relate this contrast to the nature of the chemical processes and structural changes that occur within the gels following the absorption of ionizing radiation.

2. Contrast in magnetic resonance imaging

2.1. Fundamentals of nuclear magnetic resonance

Magnetic resonance imaging usually relies on the detection of the nuclear magnetization of mobile water protons. Although a quantum mechanical description of nuclear spins is useful at times to illustrate how a net magnetization is generated in a sample, the macroscopic magnetization resulting from many nuclei may be treated as a classical quantity. When protons with spin = 1/2 are placed in a magnetic field, the Zeeman effect produces two different energy states (corresponding to spin “up” and spin “down”) whose energy separation is:

$$\Delta E = \gamma B_0$$

(1)
where $\gamma$ is the gyromagnetic ratio (a constant for protons $\gamma/2\pi = 42.6$ MHz) and $B_0$ is the strength of the external magnetic field. At room temperature, the magnetic interaction term is small so the relative population of the two spin states favors only slightly the lower-energy state (spin up)

$$\frac{N_\uparrow}{N_\downarrow} = \exp\left(\frac{\Delta E}{kT}\right)$$

(2)

where $N_\uparrow$ is the number of spins in the lower-energy state (spin up), $N_\downarrow$ is the number of spins in the higher-energy state (spin down), $k$ is Boltzmann’s constant and $T$ is the temperature of the sample. At room temperature, there is an excess of a very small fraction of spins in the lower-energy state (about 1 in $10^5$ or 6 at conventional fields) but the molar concentration of water protons is high so there is a detectable macroscopic magnetization $M$ which in equilibrium aligns with the applied field direction (i.e., the longitudinal direction). This magnetization may be detected when it is disturbed (by applying appropriate radiofrequency pulses) so that it has a component in a transverse plane. It will then precess (rotate) about the direction of the field at a characteristic frequency proportional to the field and by induction it will generate a voltage in a coil surrounding the sample. The characteristic or Larmor frequency is given by

$$\omega_0 = \gamma B_0$$

(3)

which is 42.6 MHz for protons at 1 Tesla field.

2.2. RF pulses and spin echoes

Radio-frequency (RF) pulses contain an oscillating magnetic field orthogonal to the main applied field which is applied to the sample for a short time. The frequency of the pulse is normally tuned to the Larmor frequency of the water protons (Equation 3). This is the “on resonance” condition, or the “R” in “MRI”. RF pulses can stimulate spin transitions between the two spin states. From a classical point of view, an RF pulse tips the magnetization vector away from its equilibrium orientation along the longitudinal axis, towards the transverse plane. The intensity and length of a so-called 90° pulse are such that the magnetization vector is tipped to lie in the transverse plane. For simplicity, let us assume this is done instantaneously. Immediately after the RF pulse, the nuclear spins have the same phase i.e. the same projection into the transverse plane. However, spin-spin interactions between protons and the presence of magnetic field inhomogeneities will result in a loss of coherence and therefore a decrease of the net magnetization vector magnitude. The signal decays more rapidly as the range of Larmor frequencies experienced by the nuclei in the sample increases. The relaxation time constant for this decay is called $T_2^*$ (see Figure 1). The dephasing due to field inhomogeneities can be reversed by the application of a 180° RF pulse applied along a direction in the transverse plane. Essentially each 180° pulse reverses the direction of the time axis along which the phases of the nuclei evolve, so that a spin echo will be formed at a time $T_E$ following the 90°. A train of 180° pulses will generate a train of echoes. The influence of static interactions such as those due to inhomogeneities in the main magnetic field are largely removed in spin echoes. The time between subsequent 180° pulses will be the same time separating the echoes and is called the echo spacing (ES). The magnitude of the signal at each echo time is used to calculate the spin-spin relaxation time constant $T_2$, which represents all those dynamic processes that are not completely reversed by the 180° pulses. Two or more echoes
must be used to calculate $T_2$ in polymer gel dosimetry, and there are some trade-offs to be made in the use of more or fewer echoes. The pulse sequence represented schematically in Fig. 1 is referred to as the Carr-Purcell-Meiboom-Gill (CPMG) sequence.

![Figure 1. Schematic representation of a CPMG pulse sequence. The initial 90° generates transverse magnetization that decays rapidly due to field inhomogeneities and spin-spin interactions. The relaxation time constant for this decay is $T_2^*$. Application of 180° pulses rephases the dephasing due to field inhomogeneities and gives rise to spin echoes. The relaxation time constant $T_2$ is calculated from the monoexponential echo amplitude decay](image)

Phenomenologically, the decay of transverse magnetization ($M_{xy}$) as a function of time ($t$) may often be represented by a monoexponential decay:

$$M_{xy} = M_{0}e^{-t/T_2}$$  (4)

Typically, a number of spin echo images acquired with a given echo spacing ES are used to generate a $T_2$ map (or more commonly, a map of $R_2 = 1/T_2$) where each pixel value is the $T_2$ (or $R_2$) value obtained by a fitting routine. It has been reported that the precision of the $T_2$ estimate is dependent on the ES [4] for a given number of echoes and on the number of echoes for a fixed minimum ES [5].

2.3. Spin-spin relaxation in polymer gel dosimeters

The main processes that affect spin-spin relaxation rates are briefly described. A more complete description of this topic can be found in the original text by Abragam [6] and multiple references on exchange processes published subsequently.

2.3.1. Dipolar relaxation. A nuclear spin that has been excited by an RF pulse does not spontaneously recover to its ground state very rapidly, but instead relies on interactions with the surrounding medium which accelerate this recovery. Relaxation in liquids is dominated by the effects of fluctuating magnetic fields experienced by the nuclear spins, which are modulated by thermal motion of the molecules [7]. Each nuclear spin generates a dipolar field through space that may be experienced by neighboring nuclei. The intensity of this dipolar field at any location fluctuates in time due to the
molecular random motions. The correlation time that characterizes the time scale of these fluctuations is short in free liquids such as water but may be longer in other environments. In gel dosimeters, the mobile monomers present in the gel before irradiation are small and do not affect relaxation of the water very strongly. Within the period of a Larmor precession, the molecular fields fluctuate many times and essentially average to a low net value (= motional narrowing). After irradiation the polymer that forms has a relatively high molecular weight and may be “immobilized”. Water molecules in the vicinity of the polymer may undergo a transient binding or restricted mobility during which their motions are not isotropically averaged or in which they experience slowly fluctuating magnetic fields from protons in the polymer, which will lead to a loss of transverse coherence. The transverse relaxation times of the polymer protons are generally short compared to that of water protons, since these protons all experience the slowly varying magnetic fields of their neighbors in the polymer.

2.3.2. Chemical exchange. Protons in a water molecule can be rapidly exchanged with protons in other water molecules or with other labile protons, to a degree that may depend on the pH. Examples of rapidly exchanging protons include the protons in NH$_2$ and OH groups, as opposed to CH$_3$ and CH$_2$ groups (see Fig. 2). Almost all monomers used to date in polymer gel dosimeters bear rapidly exchanging protons. The presence of exchangeable protons can affect transverse relaxation in two ways. First, if the protons in these groups undergo rapid relaxation (e.g. because of the effects of neighbors or inability to average dipolar fields), they provide a “relaxation sink” for magnetization within the entire sample. Chemical exchange enables the bulk water to sample this efficient relaxation process. Second, if the protons in these groups experience a different net magnetic field (i.e. are chemically shifted in resonance frequency relative to water) then the exchange process introduces another source of loss of transverse magnetization even when the relaxation within the group is not efficient. The rate of proton exchange between water molecules and the polymer depends on the local pH, and this has been demonstrated to affect $T_2$ in the context of polymer gel dosimetry [8]. In addition, some specific chemical moieties with high proton exchange rate constants e.g. hydroxyl and amino groups, have been shown to promote relaxation efficiently [9] compared to others e.g. carboxyl groups. When appropriate substitutions of groups can be made, it has been possible to demonstrate the importance of some specific relaxation phenomena in gels, such as the superiority of acrylic acid over acrylamide or the contributions of cross-linking agents to gel responses.

Whether chemical exchange or dipolar relaxation is the dominant mechanism depends on the conditions, but both processes may be important in gels. Various models may be developed that incorporate the different pools of protons in various environments, and some success has been achieved in explaining the main features of gel properties by assuming fast exchange between these pools [10,11]. Such models do not necessarily require the precise mechanisms of relaxation to be identified [12].
Figure 2. Schematic ball and stick representation of a polymer backbone in interaction with water molecules. It is noted that water protons can readily exchange with protons from NH groups but have a very slow exchange rate with protons on CH$_2$ groups.

2.4. Longitudinal relaxation in Fricke gel dosimeters

The water proton magnetization can be tipped into the transverse plane by supplying energy to the spin system with an RF pulse. Magnetic dipolar interactions between water protons and with other local magnetic fields such as those produced by unpaired electrons gradually restores the original orientation of the magnetization vector along the main magnetic field. This process of energy exchange is accelerated when paramagnetic atoms which contain unpaired electrons that generate strong dipolar fields are present in the system. Fricke gel dosimeters are based on this effect. After irradiation, ferrous ions (Fe$^{2+}$) that react with water free radicals are oxidized to ferric ions (Fe$^{3+}$) [13]. Both species are paramagnetic and can drastically reduce the relaxation time constants of water when present even in small concentrations, but they differ in their effects on water relaxation so that there is a change in overall relaxation times when one converts to the other. Equation 5 shows the longitudinal relaxivity induced by paramagnetic ions in aqueous solution, as developed by Solomon [14] and Bloembergen and Morgan [15]:

$$
\frac{1}{T_{1m}} = \frac{2}{15} \frac{S(S+1)g^2 \beta^2 g_N^2 \beta^2_N}{h^2 r^6} \left( \frac{3 \tau_c}{1 + \omega_I^2 \tau_c^2} + \frac{7 \tau_c}{1 + \omega_S^2 \tau_c^2} \right) + \frac{2}{3} \frac{S(S+1)}{h^2} \frac{a^2}{1 + \omega_I^2 \tau_c^2} \left( \frac{\tau_c}{1 + \omega_S^2 \tau_c^2} \right)
$$

The relaxation time constant $T_{1m}$ of the protons in the coordination shell of the metal ion is seen to depend on the electron spin ($S$), the electronic and proton g factors ($g$ and $g_N$, respectively), the Bohr magneton ($\beta$), the nuclear magneton ($\beta_N$), the hyperfine coupling constant ($a$), the ion-nucleus distance ($r$), and the Larmor frequencies for the proton and electron spins ($\omega_I$ and $\omega_S$, respectively). The correlation times $\tau_c$ and $\tau_e$ are characteristic of the rate of change of the interactions between the metal ion and neighboring protons. Of particular significance here is that the electronic correlation time $\tau_e$
for the ferric and the ferrous ions are markedly different and their abilities to promote spin relaxation
differ considerably. This effect is responsible for the decrease of $T_1$ obtained experimentally in a gel
containing ferrous ions and irradiated with ionizing radiation [1].

2.5. **Magnetization transfer imaging for polymer gel dosimetry**

The contrast in MR images can be made sensitive to the rate and degree of exchange of magnetization
between water protons and other species of protons that have different resonance frequencies or which
respond to RF pulses that are off resonance for the water protons. One approach to manipulating this
exchange process is to prepare the magnetization of the system by using a train of RF pulses whose
frequency and frequency range are chosen to selectively affect the polymer protons. The linewidth of
water protons is narrow (i.e., in the order of Hz) whereas the linewidth of polymer protons may be
broad (see Fig. 3) and may respond to RF pulses over a much wider range of frequencies. Thus, by
using RF pulses with a frequency different from the water protons frequency, it is possible to saturate
the magnetization of the polymer protons while affecting minimally the magnetization of water
protons.

If the two proton populations exchange magnetization (either via dipolar interactions or by
physically swapping protons, usually called chemical exchange), then the net magnetization of water
decreases as a function of the polymer concentration. Figure 4 shows the results of this approach
when applied to a polymer gel dosimeter [3]. As is the case for $T_2$ relaxation, the rates of
magnetization transfer may be influenced by pH when chemical exchange contributes to the process.

![Figure 3](image-url)

**Figure 3.** Schematic representation of a magnetization transfer experiment. RF
pulses applied off-resonance can saturate protons from the polymer whose linewidth
is large compared to the water protons. Saturation is then transferred to the water
molecules via either chemical exchange or dipolar relaxation. A decrease in water
intensity can then be detected by a standard spin echo sequence.
Figure 4. Magnetization transfer (MT) imaging experiment on a polymer gel dosimeter composed of 2-hydroxyethylacrylate (HEA), N,N’-methylene-bisacrylamide (BIS), gelatin and water. Images can be acquired with ($M_z$) or without ($M_0$) magnetization preparation by saturation RF pulses with a 600 Hz frequency offset. a) Irradiation dose (in Gy) absorbed by the gels and b) corresponding $M_z/M_0$ image. Mean intensities and standard deviations extracted from b) are shown in c).

2.6. Relaxation in the rotating frame

Magnetization tipped in the transverse plane can be locked in that plane by the application of a long RF pulse oriented along the magnetization vector direction and rotating at the Larmor frequency around the permanent field direction. Relaxation of the magnetization in that plane during the RF pulse provides a contrast that is different from $T_1$ and $T_2$ effects and provides information on slow molecular motions within a sample. A detailed theory for a system containing a liquid and a solid, such as polymer gel dosimeters, is not available. However, general principles can be deduced from equations 6, where the major trend for $T_1$, $T_2$ [16,17] and $T_{1p}$ [17] in liquids is expressed in terms of the spectral density, or the amount of energy available in the local magnetic fields in the system, at the Larmor frequency $\omega_0$, and the strength of the locking field $B_1$. 
For motions that are much faster than $\gamma B_1$, as in typical in liquids, $T_{1p}$ will behave in a similar fashion as $T_2$. However, in a solid with very slow motion ($\gamma B_1 \approx \omega_0$), $T_{1p}$ is expected to approach $T_1$.

### 3. Conclusion

A number of different MRI contrast mechanisms can be exploited for gel dosimetry. There is potential for exploiting each of these contrast mechanisms for the three-dimensional mapping of dose distributions using MRI. While the current review did not deal with the specifics of pulse sequences, imaging artefacts and imaging time, continuing research in these areas is likely to provide additional tools to bring gel dosimetry closer to a routine clinical application. The measurement of each NMR parameter often involves errors and artifacts, and each approach may have advantages compared to others for specific conditions and equipment. The further understanding of the detailed molecular mechanisms responsible for contrast in MRI will help guide the development of improved dosimeters.

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