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# Proton spin-lattice relaxation of water molecules in ferrous–ferric/agarose gel system

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Proton spin-lattice relaxation time ($T_1$) of water in aqueous solutions of ferrous and ferric ions and in the corresponding agarose gel systems have been studied in the light of NMR relaxation theory. The theoretical analysis of $1/T_1$'s has revealed that, at the microscopic level, changes in the solvation states of paramagnetic ions in aqueous or gel environment are greater than difference in the paramagnetism between ferric and ferrous ions. The former change is the primary factor for the exhibition of radiation effect. At the phenomenological level, we have confirmed and demonstrated that: (1) Radiation effect is almost exclusively exhibited through changes in $1/T_1$ caused by the interactions between water proton and ferrous or ferric ions; and (2) fraction of conversion of ferrous to ferric ions induced by radiation is the ''true'' representation of the spatial distribution of radiation dose. © *1996 American Institute of Physics.* [S0021-9606(96)51133-5]

## I. INTRODUCTION

The Fricke dosimeter is one of the most commonly used chemical radiation dosimeters.[1] The method is based on conversion of ferrous to ferric ions caused by ionizing radiation. Gore *et al.*[2] showed that ferric ions produced in aqueous irradiated ferrous solution sufficiently influenced the $T_1$ relaxation time of the water proton to permit resolvable differences in their nuclear magnetic resonance signal. In radiation doses in the range 0–40 Gy, Appleby *et al.*[3] demonstrated that spatial distribution of radiation doses can be determined by using NMR imaging (MRI) method in aqueous agarose gels. Previous investigators[4,5] have attributed this capability, i.e., proportionality of proton relaxation times of water to radiation dose in ferrous–ferric/gel systems, to the greater paramagnetism of ferric than ferrous ions. This understanding can be examined in a more rigorous way by studying proton $T_1$ of water in ferrous–ferric/agarose gel systems as well as aqueous solutions containing ferrous or ferric ions in the light of NMR relaxation theory which is based on quantum and statistical mechanics.

In this work, we have experimentally determined proton $T_1$ of water in aqueous solutions of ferrous or ferric ions and the corresponding agarose gel systems. Proton $1/T_1$'s of water thus determined are analyzed in terms of NMR relaxation theory by focusing on what is the physicochemical reason for changes in the proton NMR relaxation behavior of water molecules caused by the conversion of ferrous to ferric ions in the above systems. Based on the results thus analyzed, we have studied effect of radiation on the above systems, paying particular attention to: (1) What is the radiation effect in terms of the fundamental quantities appeared in the phenomenological description of NMR (the Bloch equation[6,7]); and (2) How can the ''true'' radiation dose be expressed from these quantities? Finally, we have presented the true radiation dose distribution in the two-dimensional space by using MR images of the ferrous–ferric/agarose gel system (as a gelatenous tissue equivalent phantom) acquired before and after irradiation.

## II. EXPERIMENT

The original ferrous or ferric/gel system solution consisted of 1% (w/v) Seaplaque agarose (FMC Corp.), 0.4 mM ferrous or ferric ammonium sulfate, and 0.05 N sulfuric acid. The method of preparing and mixing the solution has already been described elsewhere.[7] In the present work, aqueous solutions of ferrous or ferric ions, plain gels, and ferrous or ferric/gel samples were prepared in small test tubes (10 mm o.d.) for $T_1$ determination and a glass container ($90\times 90 \times 110$ mm$^3$) for determination of radiation dose distribution by MR imaging. Quartz cuvettes ($10\times 10\times 40$ mm$^3$) were used for optical measurement.

We used a Technicare Teslacon II (0.6 T) MR imaging instrument instead of high-resolution NMR spectrometer: (1) In order to carry out simultaneous measurements of proton $T_1$ of water in several samples; and (2) in order to examine

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TABLE I. Comparison of apparent $T_1$ determined by the SVR method and true $T_1$ determined by the IR method in aqueous solutions containing various concentration of $CuSO_4$ at 20 °C.

| Method | $T_1$ (s) IR[a] | $T_1$ (s) SVR[b] | Ratio IR/SVR |
|---|---|---|---|
| Conc. (mM) | | | |
| 2.5 | 0.658 | 0.518 | 1.27 |
| 1.25 | 0.877 | 0.703 | 1.25 |
| 0.60 | 1.30 | 1.01 | 1.28 |
| | | Mean | 1.267 |

[a] $\ln[M_0-\langle M_Z(t)\rangle]=-t/T_1+\ln[2M_0]$ is used where $t=\mathrm{TI}-(xw_1+xw_2)/2$.
[b] $\ln[M_0-\langle M_Z(t)\rangle]=-t/T_1+\ln[M_0]$ is used where $t=\mathrm{TR}-xw_2/2-\mathrm{TE}$. Here, $xw_1$ and $xw_2$ denote widths of 180° and 90° rf pulses, respectively.

spatial distribution of radiation effect. The most orthodox method for measuring $T_1$ by MR imaging instrument with the currently available rf pulse sequences is the inversion recovery (IR) method with a long repetition time (TR). Our preliminary measurement of proton $T_1$ of water in plain agarose gel by means of the IR method gave 2.6 s (at 0.6 T) at 20 °C. In order to ascertain re-establishment of the $z$ component of the nuclear magnetization $[\langle M_z(t)\rangle]$ after a sequence of rf pulses is applied, one must practically set TR equals to at least 5 to 6 times $T_1$ in the IR method. This means that one must take at least TR=15 s for each IR experiment. Then, one scan will take more than 1 h with the number of phase encoding=128 and the number of NMR signal accumulations=2. Use of many different TI's (time between the first 180° and 90° rf pulses) is desirable in order to obtain reliable $T_1$ values. If eight different TI's are used, the total data acquisition with the same acquisition parameters as above will take more than 8 h.

In order to significantly shorten data acquisition time, we have used the usual single spin echo sequence[8,9] with variable TR's and a constant echo time (TE) (SVR method). Here, one scan must use a long TR in order to determine $\langle M_z(t=0)\rangle$ in thermal equilibrium. In the rest of the scans with variable TR's, TR's are much shorter than 5 to 6 times $T_1$. In these scans, RF pulses are applied before $\langle M_z(t)\rangle$ re-establishes thermal equilibrium and thus, they partially violate the physical principles of NMR experiments. Therefore, we must regard a time constant thus determined by the SVR method as ''apparent'' $T_1$. Now, we must establish a relationship between apparent $T_1$ thus obtained and true $T_1$ determined by the IR method. First, we have determined true $T_1$'s in aqueous solutions having various concentrations of $CuSO_4$ using the IR method with TR=8 s and nine different TI's. Secondly, we have also determined apparent $T_1$'s by the SVR method with 13 variable TR's for the same samples. All data were treated by the linear least squares analysis by using the Bloch equation. The results thus obtained are summarized in Table I.

The results indicate that true $T_1$ can be obtained by multiplying apparent $T_1$ by 1.267 with less than ±2.0% errors. Thus, we can correctly determine true $T_1$ values by the SVR method within 1 h. In the simultaneous $T_1$ measurements by the SVR method for aqueous solutions of ferrous or ferric ions as well as ferrous or ferric ions/gel systems, we have used the following data acquisition parameters: FOV=160 mm, slice thickness=5 mm, TE=30 ms, number of signal accumulations=2; number of phase encoding=128; and number of variable TR=13 including one long TR (6 s). It was experimentally confirmed that 6 s was sufficient to warrant re-establishment of thermal equilibrium in these systems when the SVR method is used.

A possible maximum value of radiation dose suitable for the above ferrous/gel systems was determined by the optical method. Optical density at 304 nm[7] was determined using a Beckman DU14 spectrophotometer as a function of the amount of radiation dose for ferrous/gel systems containing a fixed concentration (0.40 mM) of ferrous ions.

Diffusion of ferric ions produced in the irradiated ferrous/gel system has been reported[4,5] to have a significant effect on stability of the spatial distribution of radiation dose. We have usually initiated acquisition of MR imaging data immediately after irradiation and finished within 1 h, though we have also examined the stability of spatial distribution of radiation dose over a period of time longer than a few hours. First, a quartz cuvette was filled with the above gel solution and left to set for 2 h. The cuvette was then irradiated with 10 MeV x-rays by setting one half of the radiation field blocked so as to irradiate only one half of the cuvette. Measurements of optical density at 304 nm were initiated within 30 min after irradiation as a function of time by focusing on the nonirradiated section.

## III. RESULTS AND DISCUSSIONS

### A. Modeling of ferrous–ferric/agarose gel systems for water proton NMR relaxation phenomena

It is well known that the nuclear magnetic dipole–dipole interactions among protons are the predominant relaxation mechanism for liquid water protons.[10–12] The relaxation is caused by random motions of water molecules.[7,10] They are intramolecular relaxation by the rotational motions of water and intermolecular relaxations by the translational motions of molecules. In the case of an aqueous solution containing ferrous (system A) or ferric (system B) ion, there are also magnetic dipole–dipole interactions between protons of water and these paramagnetic ions. Here, it is a good approximation to assume that random motions of both water molecules and ions are much faster than the time scale of NMR and thus, only the average of the above relaxation processes can be observed. Then, $1/T_1$ for system A $[1/T_1(\mathrm{A})]$ may be expressed as

$$1/T_1(\mathrm{A})=1/T_1(\mathrm{H_2O–H_2O})+1/T_1(\mathrm{H_2O–Fe^{2+}}), \qquad (1)$$

where the first term on the right-hand side represents $1/T_1$ caused by nuclear magnetic dipole–dipole interactions among water protons and the second the interactions between water proton and ferrous ion. For system B, $Fe^{2+}$ in the second term of Eq. (1) must be replaced by $Fe^{3+}$.

In agarose gel systems, there are also intermolecular relaxations caused by interactions between water proton and proton of agarose molecules. Our proton $T_1$ and $T_2$ values of water in the plain gel system (system C) at 20 °C is 2.55 and 0.44 s, respectively. These can be compared with 3.2 s ($T_1=T_2$) in pure liquid water.[12,13] It is important to note that the $T_1$ value in the plain gel system is considerably shorter than that in liquid water and also $T_2$ is much shorter than $T_1$. This experimental fact means physically that water in the gel system is not in the extreme narrowing regime.[14] In other words, averaging of the dipole–dipole interactions by molecular motions of water is incomplete. This implies motion of molecules are restricted in the gel system much more than in liquid water. Since the amount of agarose is only 1%, it is apparent that water constitutes an actively participating component to form a gel system in which the physical state of water is different from that of liquid water. It is still a good approximation to assume that random motions of water molecules are much faster than the time scale of NMR and thus, one can experimentally observe only the average of the above relaxation processes. Then, experimentally measurable $1/T_1$ for water proton in system C may be expressed as

$$1/T_1(\mathrm{C})=1/T_1(\mathrm{H_2O{-}H_2O})+1/T_1(\mathrm{H_2O{-}agarose}), \tag{2}$$

where the second $1/T_1$ represents the interaction between water proton and proton of agarose.

With regard to the ferrous/agarose gel (system D) and ferric/agarose gel (system E), we suggest that the following model can be postulated based on the above experimental facts in NMR experiments. It is a good approximation to assume that NMR relaxation of water protons in these systems is caused by the magnetic dipole–dipole interactions (1) among water protons as well as (2) water proton and proton of agarose and (3) proton of water and paramagnetic cation. Mobility of water molecules in these systems is still high in terms of the time scale of NMR even though it is restricted more than liquid water. On the other hand, ferrous or ferric ion occupies certain sites for an extremely long period of time as compared to the time scale of molecular motion of water. The original concentration of ferrous ion is 0.40 mM vs 55.51 M of water in the ferrous/gel system. This means that there are about $1.388\times10^5$ water molecules (or $2.776\times10^5$ protons) per one ferrous cation. As for water molecule, therefore, the statistical chance of encountering cations is approximately $7.2\times10^{-6}$ times the water–water encounters. However, the magnitude of interaction is about $4.0\times10^6$ times greater than that of the water–water interaction. In this crude estimate, it is assumed that the magnitude is proportional to the squares of magnetogyric ratio of proton as well as of ferrous ion and the rest of variables such as distance and correlation time remains unchanged for both interactions (see below). In essence, the above model means that protons of water molecules relax by (1) encountering other water molecules and/or agarose molecules for most of the time (process A) and (2) occasionally encountering cations (process B). Thus, it is a good approximation to assume that both relaxation processes A and B occur independently without mutual interference. If ferrous–ferric/gel systems are regarded as pseudohomogeneous systems, it can safely be assumed that random motions of water molecules in gels are isotropic in three-dimensional space. Because of fast motions of water molecules as compared to the time scale of NMR, one can observe only the average of all these relaxation processes.

The above model leads to the following expression for experimentally measurable $1/T_1$ for water proton in the ferrous/agarose gel system $[1/T_1(\mathrm{D})]$:

$$1/T_1(\mathrm{D})=1/T_1(\mathrm{H_2O{-}H_2O})+1/T_1(\mathrm{H_2O{-}agarose}) + 1/T_1(\mathrm{H_2O{-}Fe^{2+}}), \tag{3}$$

where the third term denotes the magnetic dipole–dipole interaction between water proton and ferrous ion. The ferric/gel system has the same expression as Eq. (3) except $\mathrm{Fe^{2+}}$ in the third term on the right-hand side must be replaced by $\mathrm{Fe^{3+}}$.

### B. Proton NMR relaxation of water molecule caused by magnetic dipole–dipole interaction with paramagnetic ion in aqueous solutions of ferrous or ferric ion and in ferrous or ferric/agarose gel systems

According to the density matrix treatment of NMR relaxation phenomena, the spin-lattice relaxation of water proton caused by the magnetic dipole–dipole interaction with paramagnetic ion in aqueous environment can be expressed as[14]

$$d\langle I_z\rangle=(\langle I_z\rangle-I_0)/T_1, \tag{4}$$

where $\langle I_z\rangle$ is the $z$ component of magnetization of proton spin $I$, $I_0$ is the magnetization in a thermal equilibrium, and $T_1$ is the spin-lattice relaxation time by this mechanism. It should be noted that, since there is no polarization of electron spin in our experiments, Eq. (4) is an uncoupled equation.[14] Here, $1/T_1$ is given by

$$1/T_1=\gamma(^1\mathrm{H})^2\gamma(e^-)^2(\hbar^2)S(S+1)f(\omega_I,\omega_S,\tau), \tag{5}$$

where $S$ is electron spin quantum number of the paramagnetic ions (ferrous or ferric), $\gamma(i)$ is the magnetogyric ratio of spin $i$, $\hbar$ is Plank's constant divided by $2\pi$, $f(\omega_I,\omega_S,\tau)$ is relaxation function where $\omega_I$ and $\omega_S$ are Larmor frequencies of proton and electron, respectively, and $\tau$ is the correlation time.

A ferric ion in solution is surrounded by six water molecules which form a distorted octahedron. The ferric ion has five $3d$ electrons with no resultant orbital angular momentum and thus, the electronic state is $^6S_{5/2}$; i.e., spin quantum number ($S$) is 5/2. Therefore, the value of $g$ factor must theoretically be close to that of a free electron, i.e., 2.0023.[15–17] This is actually the case. The experimental value of $g$ factor determined by ESR is 2.004.[15] Since experimental values for both $g$ factor and the magnetic susceptibility are available for ferric ion, the following calculation was carried out. Magnetic susceptibilities are usually expressed in terms of the effective Bohr magneton number $\mu(\mathrm{eff})$. The experimental value of $\mu(\mathrm{eff})$ for ferric ion in solutions determined by susceptibility measurement is known to be 5.94.[18] The corresponding $g$ factor is expressed by $g=\mu(\mathrm{eff})/[S(S+1)]^{1/2}=5.94/2.958=2.008$. This value agrees very well with the $g$ factor directly determined by ESR. Thus, we can use either $\mu$(eff) or $g$ factor in further calculations. In Eq. (5), the quantity $[\gamma(e^-)\hbar]^2 S(S+1)$ represents the mean-square of the magnetic moment of the paramagnetic ion $(\langle\mu^2\rangle)$ and this formula is valid only for ions in an $S$ state in which there is no orbital magnetism.[17,21] Since $[\gamma(e^-)\hbar]^2 S(S+1)=(\langle\mu^2\rangle)=[\mu(\mathrm{eff})\times\beta]^2$ where $\beta$ is Bohr magneton ($0.927\times10^{-24}$ J/T), this quantity for ferric ion is: $(5.94\times\beta)^2=3.035\times10^{-45}$ (SI units).

A ferrous ion in solution is surrounded by a nearly regular octahedron of six water molecules. The ferrous ion has six $3d$ electrons and the state is $^5D_4$.[15,17] Therefore, the quantity $[\gamma(e^-)\hbar]^2 S(S+1)$ in Eq. (5) must be replaced by the quantity $\langle\mu^2\rangle$. Here, $\langle\mu^2\rangle$ is defined as $\Sigma_i p_i\langle\mu^2(i)\rangle$ where $\langle\mu^2(i)\rangle$ is the square of magnetic moment in the state $i$ and $p_i$ is the probability of ions in the state $i$.[14] Sum should be carried over all states. Since only a weak transition in ESR was observed at 20 K,[17,18] no sufficient data are available to evaluate $\langle\mu^2\rangle$ from this definition. Thus, $\mu$(eff) is the only source of information we can use for the calculation of $\langle\mu^2\rangle$. The $\mu$(eff) value for ferrous ion in solutions is reported to be 5.33[18] and thus, $\langle\mu^2\rangle=[\mu(\mathrm{eff})\times\beta]^2=2.443\times10^{-45}$ (SI units).

Hence, the ratio of $\langle\mu^2\rangle(\mathrm{Fe}^{3+})$ vs $\langle\mu^2\rangle(\mathrm{Fe}^{2+})$ in aqueous solutions is 1.24. This is the theoretical ratio of $1/T_1$ ($H_2O$–$Fe^{3+}$) vs $1/T_1$ ($H_2O$–$Fe^{2+}$) when spin-lattice relaxation processes of water protons are solely governed by the difference in paramagnetism of ferrous and ferric ions.[20] This value should be compared with the experimental values which are obtained as follows.

Experimental values of $1/T_1$ for water proton in aqueous solutions of ferrous and ferric ions (0.40 mM) (systems A and B) are determined to be 0.611 and 5.76 ($s^{-1}$), respectively. Then, $1/T_1$ ($H_2O$–ion) for $Fe^{2+}$ and $Fe^{3+}$ ions in water (systems A and B) are evaluated to be 0.299 and 5.45 $s^{-1}$, respectively by using Eq. (1) where $1/T_1(H_2O\text{–}H_2O)$ is taken to be 0.313.[12,13] We have determined $1/T_1$ ($H_2O$–$H_2O$, agarose) from the plain gel (system C) to be 0.390 $s^{-1}$. $1/T_1$ (D) in the ferrous/gel system (system D) and $1/T_1$ (E) in the ferric/gel system (system E) are determined to be 0.712 and 2.85 $s^{-1}$, respectively. By combining these results with Eqs. (2) and (3), $1/T_1$ ($H_2O$–$Fe^{2+}$) and $1/T_1$ ($H_2O$–$Fe^{3+}$) in systems D and E are easily evaluated to be 0.322 and 2.46 $s^{-1}$, respectively. Thus, the experimental ratio of $1/T_1$ ($H_2O$–$Fe^{3+}$) vs $1/T_1$ ($H_2O$–$Fe^{2+}$) in the aqueous environment is 5.45/0.299=18.2. The corresponding ratio in agarose gels is 2.46/0.322=7.64. These two experimental values are much greater than the ratio solely arising from the difference in paramagnetism between ferric and ferrous ions.

TABLE II. Some properties of solvated ions in water (Ref. 23) $v_0$ partial molal volume; $G_0$: partial molal Gibbs free energy; $H_0$: partial molal enthalpy; $S_0$: partial molal entropy; rhi: radius of hydrated ion; $vh_0$: molar hydrated ionic volume.

| Ion | $v_0$ $(m^3)\times10^{-6}$/mol. | $G_0$ kJ/mol. | $H_0$ kJ/mol. | $S_0$ J/K mol. | rhi pm. | $vh_0$ $(m^3)\times10^{-6}$ |
|---|---|---|---|---|---|---|
| $NH_4^+$ | 17.86 | | −771.2 | 17.70 | 159 | |
| $Fe^{2+}$ | −29.7 | −2761.9 | −2810.4 | −162.8 | | |
| $Fe^{3+}$ | −43.7 | −5632.0 | −5712.0 | −268.0 | 457 | |
| $SO_4^{2-}$ | 13.98 | | | | 364 | 214 |

It is apparent that the above discrepancy between the theoretical and experimental ratio of $1/T_1(H_2O\text{–}Fe^{3+})$ vs $1/T_1$ ($H_2O$–$Fe^{2+}$) must arise from the difference in relaxation functions $f(\omega_I,\omega_S,\tau)$ for both ions. Here, $f(\omega_I,\omega_S,\tau)$ represents both dynamic and static nature of interactions between water and ion. With regard to aqueous solution of ions, we may assume that rapid motions of both water molecules and ions are occurring in an isotropically random fashion while preserving the nearby configuration of water molecules around an ion. Thus, $f(\omega_I,\omega_S,\tau)$ for $1/T_1$ ($H_2O$–$Fe^{2+}$ or $Fe^{3+}$) may be taken from Torrey's theory for spin-lattice relaxation caused by translational diffusion.[22] By adopting his theory to ferrous and ferric aqueous solutions, $1/T_1$ ($H_2O$–ion) may be written as

$$1/T_1(H_2O\text{–ion})=(4/5)\,\gamma(^1\mathrm{H})^2\langle\mu^2\rangle[n\tau/(a_0)^3]\times[1+12\langle a_0^2\rangle/5\langle r^2\rangle], \tag{6}$$

where $a_0$ is mathematically the lower limit of radial integration and physically interpreted as approximately the closest possible distance of approach of proton and paramagnetic ion, $\langle r^2\rangle$ is the mean squared flight distance, $\tau$ is the mean time between flights, and $n$ is the number density of paramagnetic ions.

Assuming $a_0^2=\langle r^2\rangle$ for either ferrous or ferric ions, with the identical concentration of ions (0.4 mM), a ratio of the quantity, $(\tau/a_0^3)$, for ferric vs ferrous ion can be evaluated from Eq. (6). The value is calculated to be 14.7 (=18.2/1.24). Since the quantity is a product of the static ($a_0$) and dynamic ($\tau$) factors, it represents a physical state of the hydrated ion. In order to evaluate the dynamic factor $\tau$, we need a value for $a_0$ from sources other than NMR. Solvation of either ferrous or ferric ions in water have been well studied by various means. Some of the macroscopic (thermodynamic) data for these ions in water are quoted from Ref. 23 as shown in Table II. Now, $\tau$ for ferric ion can be estimated from Eq. (6) by setting $a_0(\mathrm{Fe}^{3+})$ equal to radius of hydrated ion for $Fe^{3+}$ $[\mathrm{rhi}(\mathrm{Fe}^{3+})]=4.57\times10^{-10}$ m (Table II). We find $\tau(\mathrm{Fe}^{3+})=1.17\times10^{-10}$ s.

Since $\mathrm{rhi}(\mathrm{Fe}^{2+})$ is not known, we must estimate rhi in order to calculate $\tau$. Here, we pay attention to the ratios of various thermodynamic quantities. For example, both partial molal Gibbs free energy and enthalpy are negative and the values for ferric ion is more than twice of that for ferrous ion. The partial molal entropy also has the same trend as above. The ratios of the same quantities for ferric vs ferrous ions are as follows. For partial molal volume ($v_0$), absolute partial molar ionic volume ($va_0$), partial molal Gibbs free energy ($G_0$), partial molal enthalpy ($H_0$), and partial molal entropy ($S_0$), the values are 1.47, 1.70, 2.04, 2.03, and 1.65, respectively. The mean value of these is 1.78. These ratios imply that ferric ions are more favorably bound by water molecules than are ferrous ions. Then, the reciprocal of

$[\mathrm{rhi}(\mathrm{Fe}^{3+})/\mathrm{rhi}(\mathrm{Fe}^{2+})]^3$ must have the same trend as above. Assuming $\mathrm{rhi}(\mathrm{Fe}^{2+})=\mathrm{rhi}(\mathrm{Fe}^{3+})\times 1.78$, we find $\tau(\mathrm{Fe}^{2+})=4.34\times 10^{-11}$ s with Eq. (6). These $\tau$ values may be interpreted as such meaning water molecules bound in a hydration environment of ferric ion are staying for a period of time longer than that for ferrous ion by nearly a factor of 3. It should be mentioned that our $\tau$ values are considerably longer than those used in Refs. 2 and 19. These authors did not evaluate $\tau$ values from their experiments for ferrous–ferric/agarose gel systems.

Since our model for the ferrous–ferric/gel systems implies that relaxation of water protons will occur when translationally diffusing water molecules are close to an ion, Eq. (6) may also be applicable to estimate a ratio of the quantity $(\tau/a_0^3)$ for both ions in gels. The ratio for ferric vs ferrous ion is 6.16 $(=7.64/1.24)$ as compared to 14.7 in aqueous environment just obtained above. Although the relative magnitude between two ions in gel systems is less than that in aqueous solutions, changes in ion's hydration state make a more important contribution than the difference in paramagnetism to $1/T_1$. Separation of the above two factors, $\tau$ and $a_0$ is not feasible because, $a_0$'s in gel environments are not known and thus, it is not possible to investigate how and to what extent cations are bound in agarose gels.

### C. Application to exhibition of dose distribution in MR images

We showed that agarose gel doped with ferrous ammonium sulfate supports a chain reaction for the conversion of ferrous to ferric ions when irradiated with x-ray or electron beams.[24] The *G* value[25] of ferric production was found to be around 100 compared with only about 16 for the well known Fricke dosimeter. The high *G* value found in the gel system makes radiation dose studies possible with doses normally used in clinical practice.

#### 1. Stability of irradiated ferrous/gel system

Our previous studies indicate that spatial distributions of radiation doses determined by proton MR imaging method remain unchanged over several hours after the irradiation[7,25] though, other investigators pointed out this is the origin of blurring MR images.[3,4] Hence, the stability of the ferrous–ferric/gel system was reexamined by measuring optical density along a quartz cuvette containing a ferrous–ferric/gel system as a function of distance and time. A small but distinct change in optical density was observed at one hour and two hours after irradiation. A part of the increase in optical density within this time span arises from a slow oxidation reaction of ferrous to ferric ions. But there is no apparent difference between measurements taken at 2, 3, and 4 h after irradiation. A small but recognizable change in the irradiated section became observable after 5 h. This emphasizes that accurate imaging of the dose distribution should be carried out as soon as possible after irradiation. Therefore, all MR imaging data acquisitions used for calculations in this paper were initiated immediately after irradiation and completed within 1 h.

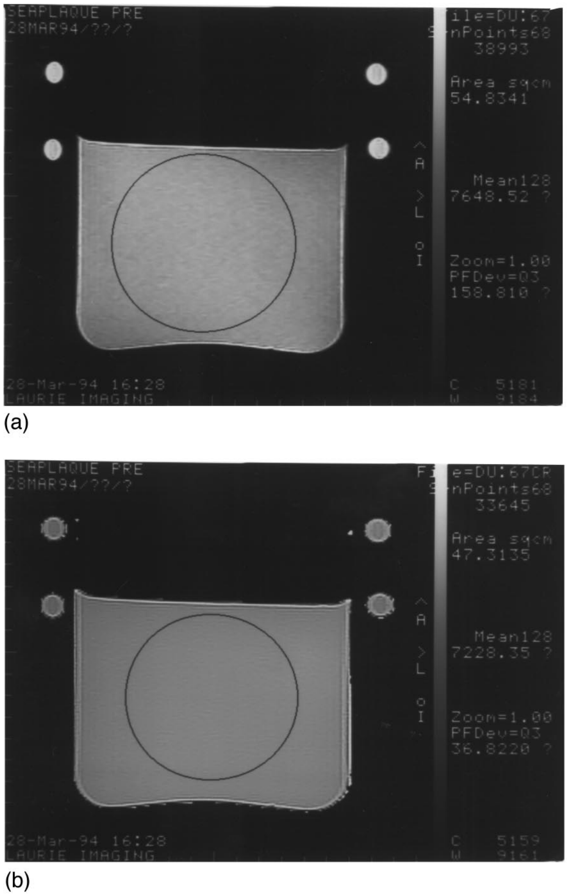

FIG. 1. Original and ''corrected'' MR images of the nonirradiated ferrous/gel system (D): (a) original, (b) ''corrected.''

#### 2. Comparison of original and corrected image

In order to correctly determine dose distributions in the two- or three-dimensional space in terms of pixel value, it is extremely important to correct the nonuniformity steming from factors other than the effect of radiation. Figure 1(a) shows the original image of a nonirradiated gel (system D) obtained by the SVR method with TR=6.0 s. Since Fig. 1(a) is the image in which all water proton spins completely reestablish a thermal equilibrium, the image should be featureless and plain. This is actually not the case. The image become brighter toward top. The image shown in Fig. 1(b) was generated according to the correction procedure described in Appendix A. The brightness of corrected image shown as Fig. 1(b) certainly is very uniform. One quantitative measure for the evaluation of correction process can be demonstrated as the difference in the ratios of standard deviation of pixel values vs the mean pixel value of a large ROI taken inside of gel. This ratio for the original image is $151.145/7644.83=1.977\times 10^{-2}$ as compared to the corrected one $43.506/7228.84=6.018\times 10^{-3}$. The latter value is less than one third of the former.

#### 3. Effect of radiation—macroscopic view

We have obtained the $1/T_1$, $M_0$, cc and sd images for a ferrous/gel system before (system D) and after (system F) irradiation by following the procedure given in Appendix B. Figures 2(a), 2(b), and 2(c) are the spatial distributions of $1/T_1$, water content (or proton number density) and cc values in system D. Figures 3(a), 3(b), and 3(c) are the corresponding images obtained from system F. The cc values for all pixels in both gel systems are found to be always greater than 0.99. [The mean pixel value over 8341 pixels in the image shown in Fig. 2(c) is 3446.97. The corresponding true cc value is obtained by multiplying by the rescaling factor ($2.8782\times10^{-4}$) to be ($3446.97\times2.8782\times10^{-4}$)$=0.9921$. The corresponding value for the image shown in Fig. 3(c) is $3476.82\times2.8535\times10^{-4}=0.9921$.] These indicate that: (1) Proton NMR relaxations in the gel systems are well represented by the Bloch equation; and (2) the quality of experimental MRI data obtained here are very high and reliable as demonstrated by both Figs. 2(c) and 3(c). The quality is quantitatively expressed by the ratio of standard deviation of pixel values vs the mean pixel values of a large ROI taken inside of gels. They are $7.98354/3446.97=2.316\times10^{-3}$ [see Fig. 2(c)] and $5.94731/3476.82=1.7106\times10^{-3}$ [see Fig. 3(c)] for Systems D and F, respectively.

A comparison of Fig. 2(a) with 3(a) and 2(b) with 3(b) reveals clearly that radiation effect is exclusively attributable to changes occurred in $1/T_1$ values since the $M_0$ image after radiation [Fig. 3(b)] does not exhibit a particular radiation effect anywhere in gel. This is clearly revealed by a constant line profile of $M_0$ along the direction of irradiation. A line profile of $1/T_1$ shows a rapid increase with increasing distance from the irradiation source. After reaching a maximum at 25 mm measured from the surface of gel, it gradually decreases.

When a ferrous/gel (D) system is irradiated, a part of ferrous ions is converted to ferric ions[1,2,7,19,25] displaying the radiation effect and it becomes System F. If $\alpha$ is defined as a fraction of this conversion, experimentally measurable $1/T_1$ in the system F [$1/T_1$(F)] can be expressed as Eq. (7),

$$\begin{aligned}1/T_1(\mathrm{F}) = {} & (1/T_1)(\mathrm{H_2O–H_2O,\ agarose}) \\ & +\alpha(1/T_1)(\mathrm{H_2O-Fe^{3+}})+(1-\alpha) \\ & \times(1/T_1)(\mathrm{H_2O–Fe^{2+}}).\end{aligned} \tag{7}$$

Here, the first term represents a combined expression for the sum of the first and second terms in Eq. (2). Since the conversion factor $\alpha$ represents radiation effect, $\alpha$ can be expressed by Eq. (8a) by rewriting Eq. (7) for the factor $\alpha$,

$$\begin{aligned}\alpha = {} & [(1/T_1)(\mathrm{F})-(1/T_1)(\mathrm{H_2O–H_2O,\ agarose}) \\ & -(1/T_1)(\mathrm{H_2O–Fe^{2+}})]/[(1/T_1)(\mathrm{H_2O–Fe^{3+}}) \\ & -(1/T_1)(\mathrm{H_2O–Fe^{2+}})].\end{aligned} \tag{8a}$$

We have experimentally confirmed that there is no radiation effect on $1/T_1$ in both plain gel (C) and ferric/gel (E) systems and therefore, Eq. (8a) can be simplified to Eq. (8b) with the aid of Eq. (3),

$$\alpha=[(1/T_1)(\mathrm{F})-(1/T_1)(\mathrm{D})]/[(1/T_1)(\mathrm{E})-(1/T_1)(\mathrm{D})]. \tag{8b}$$

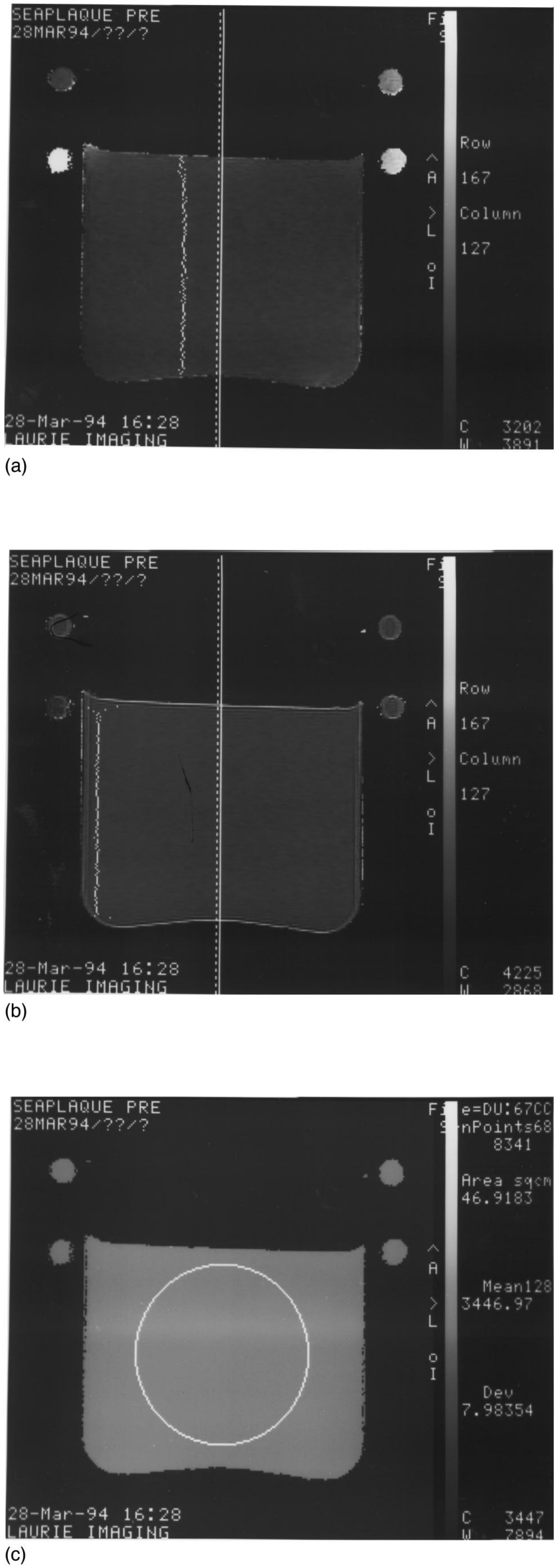

FIG. 2. Spatial distribution of $1/T_1$, $M_0$, and cc in the nonirradiated ferrous/gel system (D): (a) $1/T_1$, (b) $M_0$, (c) cc.

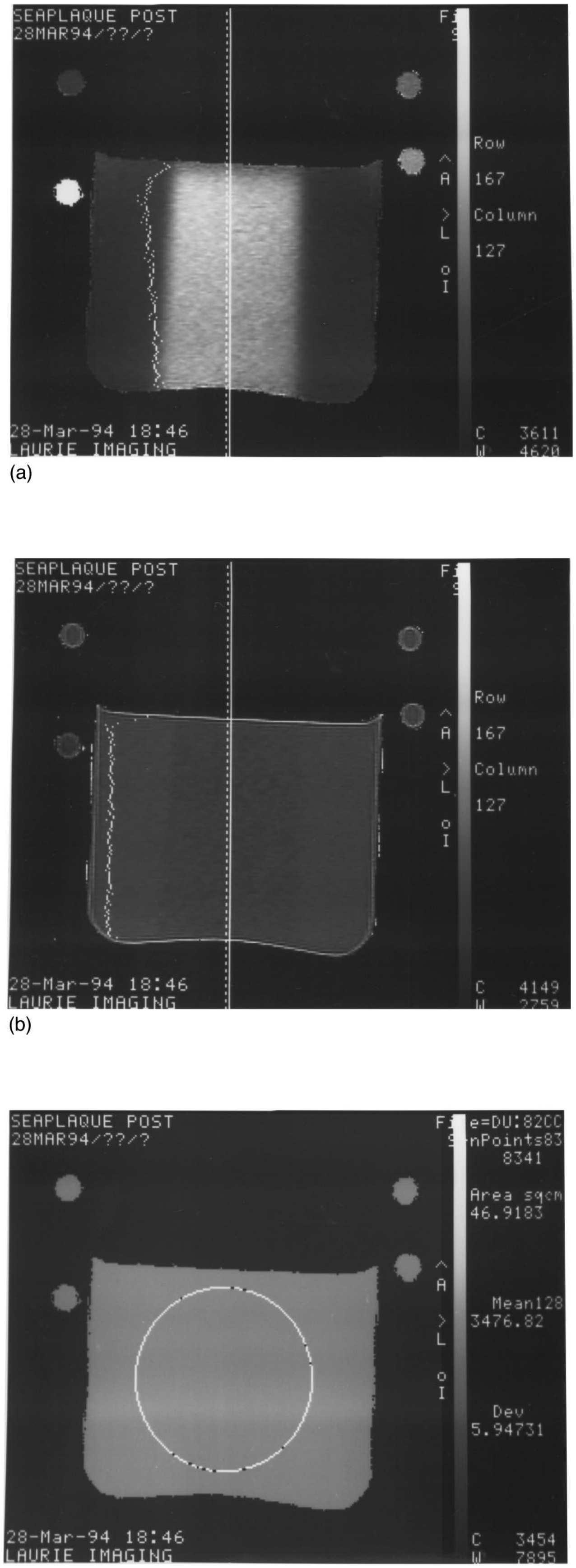

FIG. 3. Spatial distribution of $1/T_1$, $M_0$, and cc in the irradiated ferrous/gel system (F) where 45-deg wedge field of electron beam is used: (a) $1/T_1$, (b) $M_0$, (c) cc.

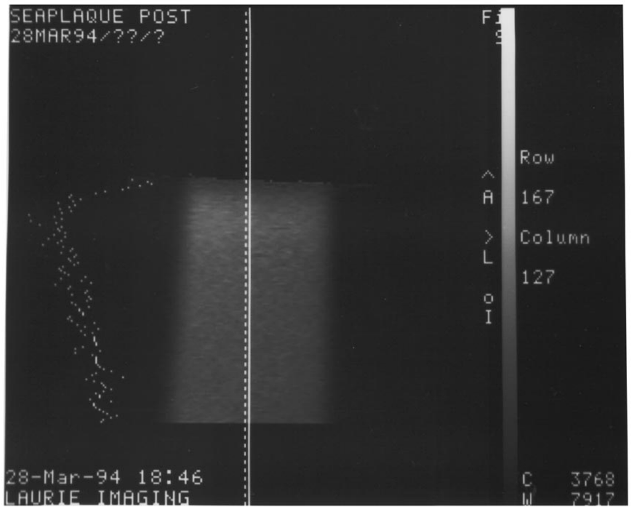

FIG. 4. Distribution of the conversion factor $\alpha$ in the two-dimensional space evaluated from $1/T_1$ shown in Figs. 2 and 3.

Equation (8b) is a more convenient expression than Eq. (8a) because, once $1/T_1$ has been determined for system E (in which the concentration of ferric ions is prepared to be equal to that of ferrous ions in system D), $\alpha$ can be experimentally determined only by the $1/T_1$ quantities [on the right-hand side of Eq. (8b)] for the ferrous/gel system before (system D) and after irradiation (system F). It should be emphasized that $\alpha$ is the quantity which represents ''true'' radiation effect.

By using Eq. (8b), we have generated an image of the conversion factor $\alpha$ as shown in Fig. 4. Here, a single pixel represents the mean values of $\alpha$ within a volume of $(0.625 \times 0.625 \times 5)\ \mathrm{mm}^3$. A dose profile along the direction of radiation shown in Fig. 4 indicates that a maximum dose occurs at 25 mm measured from the surface of gel. The shape of the line profile is almost identical to that obtained by treatment planning computer.[19,26]

## IV. CONCLUSION

The theoretical analysis of proton spin-lattice relaxation time of water in aqueous solutions of ferrous and ferric ions as well as in the corresponding agarose gel systems has revealed that, at the microscopic level, proton $1/T_1$ of water is affected by changes in the solvation states of paramagnetic ions much more than the differences in paramagnetism between ferric and ferrous ions. Thus, the former change is the primary factor for the exhibition of radiation effect. At the phenomenological level, we have confirmed that radiation effect is almost exclusively exhibited through changes in $1/T_1$ caused by the interactions between water proton and ferrous or ferric ion. We have shown that the fraction of conversion ($\alpha$) of ferrous to ferric ions induced by radiation is the ''true'' representation of the spatial distribution of radiation dose.[27]

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## APPENDIX A: GENERATION OF IMAGES CORRECTED FOR ''IMPERFECTION'' OF MR IMAGING SYSTEM

MR images of a homogeneous object (phantom) should theoretically be plain and featureless, i.e., pixel values must be identical everywhere within some experimental error range. However, it is well known that pixel values within a homogeneous phantom actually depend on the spatial position of the pixels. If pixel values along a particular direction across a two-dimensional image of homogeneous phantom are examined, they usually exhibit a considerable variation and certain trend beyond the noise level. This nonuniformity of pixel values arises from various factors. Chief among them are: (1) Nonuniform three-dimensional (3D) sensitivity profile of the rf coil transmits/receives; (2) eddy current effects; and (3) homogeneity of constant magnetic field (produced by main magnet and shim coils) over an object and its stability over both short and long terms. For simplicity, we call the above factors together ''imperfections'' of a MR imaging system.

We have developed a method to correct this problem as briefly described below. Since all pixel values determined in a homogeneous phantom system must logically be identical, uniformity can be obtained, in principle, by multiplying the original values by the corresponding reciprocal of the original pixel values. A (256×256) array of the reciprocal of all original pixel values obtained in a homogeneous phantom system constitutes a ''correction'' table. Because agarose gel systems can be regarded as pseudo-homogeneous and the same experimental arrangements were used for all data acquisition, it is a good approximation to assume that nonuniformity of pixels which is caused by the above ''imperfections'' found in ferrous/agarose gel systems (nonirradiated systems) (system D) remains unchanged in ferrous–ferric/gel systems (irradiated system) (system F) as well. Thus, we can obtain images ''corrected'' for the above nonuniformity by simply multiplying pixel values of any original gel images by the ''correction'' table which was generated from system D.

Since the reciprocal of the original pixel values for random noise will give unrealistically very large correction factors, any pixel values below the r.m.s. of noise values must be set to zero and the r.m.s. value was subtracted from other pixel values before taking their reciprocals. The r.m.s. of noise was calculated by setting an appropriate threshold value for the noise level which can be judged properly from a histogram of all pixel values.

## APPENDIX B: GENERATION OF IMAGES WHERE PIXEL VALUES REPRESENT SINGLE QUANTITY OF PHYSICAL SIGNIFICANCE

If the Bloch equation is valid for water protons in gel systems, we can predict time-dependent behaviors of the nuclear magnetization once $1/T_1$ or $1/T_2$ and $M_0$ are determined. We have obtained $1/T_1$ (slope) and $M_0$ (intercept) together with linear correlation coefficient (cc) and standard deviation (sd) by applying the linear least squares treatment to data acquired by the SVR method. Thus, if this treatment is applied to all pixels (maximum 256×256 pixels) by performing calculations, pixel by pixel, it results in generating images where pixel values represent only one physical or mathematical quantity. They are $1/T_1$, $M_0$, cc, and sd images. In obtaining a $M_0$ image, we have calibrated water content per unit volume (or proton number density per unit volume) in gel with respect to that in a very diluted aqueous solution of $CuSO_4$. The mean pixel value of $M_0$ in the latter is taken as $10^4$ and then, pixel values in gel are normalized with respect to this value. From the meaning of cc and sd in the linear least squares analysis, smoothness over the entire region in the cc and sd images implies a good quality of experimental data.

We have first corrected a series of the original images obtained by the SVR method by applying the above correction method and thus generated images corrected for ''imperfection'' of MR imaging system. Then, we have obtained $1/T_1$, $M_0$, cc, and sd images for gel systems.[27]

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is a contribution from the orbital magnetism. Because of this error in the treatment (Refs. 2 and 19), their theoretical values for the ratio of $1/T_1$ ($Fe^{3+}$) vs $1/T_1$ ($Fe^{2+}$) are not valid.

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[27] It should be mentioned that widely used so-called ''$T_1$ weighted'' and ''$T_2$ weighted'' image represent $\langle M_a(t)\rangle$ values (in arbitrary units) modified by: (1) $T_1$ effect; (2) $T_2$ effect; and (3) uncalibrated $M_0$ with respect to an external reference. In many cases, the third factor has never re-established a thermal equilibrium within a MRI scan. Therefore, it is not appropriate to use the above images in the pursuit of determining $1/T_1$, $1/T_2$, and $M_0$ and then quantitative determination of radiation dose.