Penetration depth measurement of a 6 MeV electron beam in water by magnetic resonance imaging

B. E. Hammer,^{1,*} N. L. Christensen,^{2,†} M. J. Conroy,¹ W. J. King,¹ and N. Pogue²

¹*Center for Interdisciplinary Applications in Magnetic Resonance, Department of Radiology, University of Minnesota, Minneapolis, Minnesota 55455, USA*

²*Physics and Astronomy, Carleton College, Northfield, Minnesota 55057, USA*

(Received 17 February 2011; published 17 November 2011; publisher error corrected 21 November 2011)

We demonstrate magnetic resonance imaging (MRI) visualization of a 6 MeV electron beam in ferrous-doped water; a 25 mm penetration depth was measured. Time domain nuclear magnetic resonance was used to investigate the effect of generated free radicals on the free induction decay (FID) in nondoped water; no apparent effects to the FID were observed. We show that MRI visualization of charged particle beams used in medical applications will require exogenous agents to provide contrast enhancement.

DOI: 10.1103/PhysRevSTAB.14.114701

PACS numbers: 87.57.-s, 83.85.Fg, 87.56.-v

I. INTRODUCTION

Ionizing radiation such as x rays, γ rays, e^- beams, p^+ beams, etc. ionize the matter through which they pass. In aqueous systems, such as biological tissue, free radicals form during exposure to ionizing radiation. It is reasonable to expect that the nuclear magnetic resonance (NMR) relaxation properties of tissue alter in the presence of an ionizing radiation beam possessing a sufficiently high intensity and production of free radicals with relaxation times near the NMR Larmor frequency.

Visualization of a charged particle beam is possible by using T_1 , T_2 , and T_2^* weighted magnetic resonance imaging (MRI), in the presence of ferrous ions [1,2]. Irradiating matter in a magnetic field also increases the linear energy transfer due to spiraling of charged particles [3].

The use of NMR spectroscopy or imaging to measure the effect of ionizing radiation on biological and nonbiological systems is not new [2]. NMR imaging of T_1 distributions in irradiated ferrous (Fe^{2+}) sulfate doped gels show the dose distribution of radiation beams, typically x-ray beams, passing through these gels [4]. The principle behind the NMR dosimeter is identical to Fricke dosimetry [1,2]. Fricke dosimeters rely on the oxidation of Fe^{2+} to Fe^{3+} by free radicals as a consequence of radiation hydrolysis of water. The solution is maintained at low pH, i.e., 1.0, to keep Fe as a hexaquo complex. At more alkaline pH, the Fe nucleus associates with fewer water molecules, which changes the tumbling rate, and ultimately the relaxation rate of neighboring water molecules. The amount of Fe^{3+} generated as a consequence of irradiation

is historically determined by a spectrophotometer. Similarly, the NMR relaxation properties of water change when Fe^{2+} oxidizes to Fe^{3+} . Fe^{3+} is approximately twentyfold more effective in affecting the T_1 of water than Fe^{2+} [2]. Preparing Fe^{2+} gels that restrict the diffusion of water and ions yields a tool for visualizing 3D radiation dosimetry. Cross-linking gel polymers by radiation-induced polymerization is another method for 3D radiation dosimetry [5]. Both techniques are finding acceptance as a method to visualize and quantify the 3D radiation dose distribution for radiation treatment planning.

There are possible medical physics applications for imaging an ionizing radiation beam in matter [6]. Unfortunately, our initial NMR experiments with distilled deionized water exposed to a 6 MeV electron beam did not show evidence of changing the free induction decay (FID) amplitude or rate of decay. However, with Fe-doped water we demonstrate the ability to image the electron beam's penetration into matter. Presented here is an experimental demonstration of MRI visualizing an electron beam in matter, and measurement of the 25 mm penetration depth for a 6 MeV electron beam in ferrous-doped water.

II. EXPERIMENTAL METHODS

In this study the spatial distribution of a linear accelerator (LINAC) electron beam within an aqueous solution was quantified *in situ* by ^1H MRI. A 6 MeV electron beam was targeted into a 1 mM water-ferrous solution located at the center of a 1.5 Tesla MRI magnet. Images acquired at shorter echo times, e.g., 15 or 30 ms, with the same T_1 weighting had little contrast. Images acquired with longer echo times, e.g., 45 or 82 ms, with the same T_1 weighting, had high contrast. Based on these observations we acquired images that were heavily T_2 weighted to visualize the electron beam trajectory within an aqueous phantom. Oxidation of Fe^{2+} to Fe^{3+} by the ionizing radiation beam yields a sufficient change in water proton relaxation

*hammer@umn.edu

†nchriste@carleton.edu

Published by the American Physical Society under the terms of the *Creative Commons Attribution 3.0 License*. Further distribution of this work must maintain attribution to the author(s) and the published article's title, journal citation, and DOI.

properties to produce high contrast images of the beam path. The effect of the beam on the material was observed via MRI within a 15 to 30 second scan time per image. In addition, the time dependence and dynamics of solution convection due to electron beam interaction was monitored by MRI.

An industrial X-band (9.3 GHz) pulsed 6 MeV LINAC was used to produce the electron beam (AS E, Santa Clara, CA). This is an industrial version of the Schonberg intraoperative LINAC used for irradiating cancers during surgery. The modular design allows individual subsystems to operate far from a MRI magnet, thus minimizing the effects of the magnet's fringe field on accelerator components and vice versa.

The accelerator gun was located approximately 4 meters from the magnet center. The electron beam traveled down a 3 m drift tube (10^{-7} Torr) fitted with a 0.15 mm titanium end window to allow the electrons to exit with minimal attenuation, see Fig. 1. According to manufacturer specifications, the LINAC delivered 4 μ s pulses of 120 nC per pulse. Imaging experiments had 12 pulses delivered over three seconds. Output current was verified by calorimetric measurements of sample temperature over time. In 10 min, a 25 g water sample had a 9°C increase in temperature, which corresponds to 65 nC per pulse. Because of experimental constraints, the water sample was not under perfect thermal isolation, and thus the temperature rise was less than anticipated because of heat loss to the environment.

A. NMR FID measurement of irradiated water sample

The target tube for FID measurements was a 10 mm diameter $\times$ 50 mm long glass vial containing pure water or a Fricke solution. This was placed in a 30 mm inner diameter, eight leg, low-pass radio frequency (rf) bird cage coil, tuned to 63.87 MHz (1H Larmor frequency). Data acquisition on the MR spectrometer was triggered by LINAC pulses. FIDs were 16384 point records and sampled at 3 μ s/point, total acquisition time

49 ms. FIDs were also sampled at 0.3 μ s/point, total acquisition time 4.9 ms, to capture transient events. Triggering was varied and set to begin data acquisition prior and post LINAC pulse to detect electronic glitches in the FID from either LINAC electromagnetic interference or free radical effects on the FID. The FIDs had the same appearance with and without LINAC operation. Bulk spin lattice relaxation rate of 1 mM Fe^{2+} aqueous solution as a function of 6 MeV electron beam on time was measured by T_1 inversion recovery (T1IR) [7].

B. MRI of Fe-doped water samples exposed to an electron beam

The target phantom for MR imaging studies was a 25 mm diameter $\times$ 50 mm long glass vial containing a Fricke solution (1 mM ammonium iron(II) sulfate hexahydrate, 16 mM sulfuric acid, adjusted to pH = 1.5) [2] or a 2% agarose Fricke gel, and located within a 30 mm inner-diameter birdcage coil.

MRI experiments were performed in a 1.5 T whole body magnet where the electron beam trajectory was collinear with the magnetic field. Multislice spin echo MRI data were obtained prior, during and after LINAC operation with no apparent electronic interference between the two systems. Each line of k space was obtained in 1170 ms for longitudinal (imaging plane along magnet B_0 and electron beam axis) images and 366 ms for transverse (imaging plane normal to B_0 and electron beam travel) images. Field of view was 40 mm, image matrix 128 (frequency encode) $\times$ 32 pixels (phase encode), slice thickness = 5 mm, spin echo time (T_E) = 45 ms, repetition time (T_R) = 814 ms, acquisition time per image = 26 s. The longitudinal MRI images used a matrix 128 (frequency encode) pixels $\times$ 17 (phase encode) pixels, slice thickness = 5 mm, T_E = 86 ms, T_R = 1300 ms, acquisition time per image = 22 s. The magnetic field had the effect of keeping the electron beam spread small (less than 5 mm in diameter, as measured by scintillation fibers and photographic film placed in the beam line).

C. NMR relaxation measurement of stable free radicals

The effect of stable free radicals on water proton T_1 and T_2 relaxation was measured in the 1.5 T MRI system. Table I shows the effect of free radical concentration on water proton T_1 and T_2 . Inversion recovery [7] and CPMG methods [8] were used to measure T_1 and T_2 , respectively.

FIG. 1. A 6 MeV electron beam was sent down a 3 m drift tube to the center of a 1.5 T MRI magnet. The electron beam exited the drift tube through a 0.15 mm titanium end window and impacted upon a glass vial containing a 1 mM Fe^{2+} pH = 1.5 aqueous solution.

TABLE I. H_2O T_1 and T_2 as a function of 4-hydroxyl-TEMPO concentration at 1.5 T.

TEMPO	0.0 mM	0.5 mM	1.0 mM	5.0 mM	10.0 mM	20.0 mM
T_2	2640 ms	1780 ms	1630 ms	570 ms	310 ms	150 ms
T_1	2800 ms	2330 ms	2000 ms	716 ms	412 ms	224 ms

III. RESULTS

A. Free radical generation by ionizing radiation

Bombarding liquid water with ionizing radiation yields e_{aq}^- , H and OH radicals as the major reactive species. It is e_{aq}^- that will be the primary agent affecting relaxation of solvent protons. When a high-energy electron thermalizes in water, a solvation cage of water molecules orients around the electron, thus resulting in a hydrated electron. The chemical yield of e_{aq}^- is 2.7 per 100 eV [9]. The physical properties of e_{aq}^- have the potential of altering the water proton relaxation time. The chemical lifetime of e_{aq}^- is about 100 μ s in liquid water [10].

B. Generation of e_{aq}^-

To gauge the sensitivity of detecting the effect of a charged energy beam on water relaxation times, we measured T_1 and T_2 of a 4-hydroxyl TEMPO (2,2,6,6-tetramethyl-piperidin-1-oxyl), a stable free radical, as a function of concentration (Table I). 4-hydroxyl TEMPO serves as a model of free radical effects on water relaxation. Roughly 10 mM of free radical is necessary to measure T_2^* FID changes. At the beam current used, the e_{aq}^- concentration resulting from the electron beam is not sufficient to alter bulk T_1 and T_2 of pure water; no effect on the FID T_2^* was noted for pure water. The LINAC deposits 120 nC of electrons per 4 μ s pulse. The pulsing frequency (4 Hz) is slower than the hydrated electron lifetime (100 μ s to 230 μ s) and thus we are limited to the

effect of one pulse on the FID T_2^* . In 0.49 cm³ (= 5 mm diameter $\times$ 25 mm high tube) the e_{aq}^- concentration is 0.4 mM (= 120×10^{-9} C $\times$ 6×10^6 eV / (37 eV/ip $\times$ 1.6×10^{-19} C/electron $\times$ 4.9×10^{-4} L $\times$ 6.02×10^{23} electrons/mole). As expected, a free radical concentration of this magnitude had a negligible effect on the T_1 and T_2 of water.

A 2% agarose gel doped with 1 mM Fe²⁺ exhibited a faint response to a 6 MeV 120 μ C electron beam. This was surprising because the G value (ion pairs/100 eV) in gel is reported to be greater than doped water [11]. This discrepancy may be due to agarose properties, dissolved O₂, or high density of free radicals, leading to recombination prior to reacting with the gel matrix. A 1 mM Fe²⁺ aqueous solution exposed to the same conditions showed a strong response to the electron beam.

Figures 2 and 3 show it is possible to obtain an image of the spatial distribution of radiation in a liquid Fricke solution by MRI. The location of the electron beam striking the solution is clearly apparent when comparing Figs. 2(a) and 2(b). In Fig. 3 the depth of penetration of the electron beam is visualized.

Figure 4 displays transverse images of the e-beam passing through the vial. The e-beam trajectory is normal to the eight imaging planes, with slice thicknesses of 5 mm. Note the e-beam effectively stops prior to the imaging plane 35 mm from e-beam entry into the vial.

A line plot through the longitudinal MR image of the cylindrical vial, Fig. 5, shows a penetration depth of

FIG. 2. Time sequence of transverse MRI images showing effect of a 6 MeV electron beam on MRI contrast through a 25 mm diameter vial of 1 mM Fe²⁺. Electron beam trajectory is normal to imaging plane. Electron pulse duration was 16 μ s. Multislice MRI parameters = 3 of 8 is shown (20 mm from where beam entered vial), image matrix 128 $\times$ 32 pixels, slice thickness = 5 mm, T_E = 45 ms, T_R = 814 ms, acquisition time per image = 26 s. (a) Prior to e-beam impact; (b) 65 s post e-beam impact; (c) 195 s post e-beam impact; (d) 455 s post e-beam impact; (e) 663 s post e-beam impact; (f) 793 s post e-beam impact.

FIG. 3. Time sequence of longitudinal (along magnets field and electron beam axis) MRI images showing effect of a 6 MeV electron beam on MRI contrast through a 25 mm diameter vial of 1 mM Fe²⁺. Electron beam trajectory is parallel to the imaging plane. The slice is along the vial midline. Electron pulse duration was 16 μ s. Multislice MRI parameters: slice = 4 of 8 shown (along central axis of vial), image matrix 128 $\times$ 17 pixels, slice thickness = 5 mm, T_E = 86 ms, T_R = 1300 ms, acquisition time per image = 22 s. (a) Prior to e-beam impact; (b) 33 s post e-beam impact; (c) 187 s post e-beam impact; (d) 319 s post e-beam impact; (e) 451 s post e-beam impact; (f) 627 s post e-beam impact.

FIG. 4. Transverse images of an e-beam passing through a 25 mm diameter vial of 1 mM Fe^{2+} . The e-beam trajectory is normal to the eight imaging planes. Note the e-beam effectively stops prior to the imaging plane 35 mm from e-beam entry into the vial. The horizontal artifact in midplane is due to residual transverse magnetization from previous spin excitations. The intensity for all imaging planes, except that in the bottleneck (56 mm) are roughly equivalent for preirradiation. The rf homogeneity/sensitivity in the bottleneck is less than for the other imaging planes because that imaging plane is near the end of the rf coil. Images where the e-beam is present show a darker background, presumably from a shorter T_2 . Beam pulse duration was 16 μs . Multislice MRI parameters: 8 slices, image matrix 128×32 pixels, slice thickness = 5 mm, $T_E = 45$ ms, $T_R = 814$ ms, acquisition time per image = 26 s.

approximately 25 mm for the electron beam. This is consistent with what is observed in Figs. 3 and 4. It is known that high-energy electron beams have a relatively long and smooth decrease in the percentage depth dose distribution; see, for example, the 10 MeV results in [12], or for higher energies in [13]. The MRI observed range of 25 mm is less than the maximum electron range of 29 mm reported in Table 8.2 of [13]. There are a few possible explanations why the shapes of these curves are different. For example,

FIG. 5. Line plot through MR image of cylindrical vial of 1 mM Fe^{2+} aqueous solution after passage of a 6 MeV electron beam; the penetration depth of 25 mm for the electron beam is apparent. Note there is a background level of 160 (arbitrary units) from the Fricke solution.

the electron beam passes through approximately 1 to 2 mm of glass before reaching the Fricke solution which accounts for the slightly reduced range in the Fricke solution. In addition, the data is a result of an MR image where it is necessary for the electrons to interact with Fricke solution and perhaps not enough electrons are available near the end of their range to produce enough ferric ions to affect image contrast. It should be emphasized, however, that our modality depends on electron interactions with the Fe^{2+} solution, and subsequent MR imaging; it is not surprising that distributions that we measure could have a slightly different form than those measurements made by other techniques. The tail of the distribution seen in Fig. 5, past 25 mm, is due to bremsstrahlung [13], and background from the MR image. Another experiment was run with a 50 mm block of plastic between the vial and the beam line exit to produce bremsstrahlung x rays; the MR images did not show evidence of *localized* contrast changes. The background signal in our image originates from water. An MR image of water, or ferrous-doped water, must have a signal or else it would not be possible to visualize condensed matter. It is well known that changes in image intensity, or contrast, arise from a spatial variation of T_1 or T_2 within a solution being investigated. MR experiments manipulate spins by rf pulses at the Larmor frequency. The effect of these rf pulses on the spin system can result in an image of greater or less intensity than the base image, i.e., background. In this experiment it was necessary to have a sufficient number of electrons interacting with the Fricke solution to produce a contrast above this background. A limitation faced in this experiment could be that there

was insufficient contrast above the water background signal to enable observation of the tail-end electron distribution.

For the first 60 s after e-beam irradiation, a hyperintense signal appears and rises from the center of the vial to the top, presumably due to thermal convection. In Fig. 2(c), the cloud starts to drop vertically and then travels up the vial wall [Figs. 2(d) and 2(f)] from the bottom to the top via its momentum. If pure thermal convection is dominant, the cloud is expected to move along the container walls from top to bottom. This is possibly due to precipitation of Fe^{3+} . While it is outside the scope and content of the present

VIDEO 1. A movie showing the T_1 weighted 1.5 T MR image of a 1 mM Fe^{2+} solution irradiated by a $16 \mu\text{s}$ 6 MeV electron beam. This movie displays the transverse MR images of the vial viewed out to 800 s after e-beam irradiation.

VIDEO 2. A movie showing the T_1 weighted 1.5 T MR image of a 1 mM Fe^{2+} solution irradiated by a $16 \mu\text{s}$ 6 MeV electron beam. This movie displays the longitudinal MR images of the vial viewed out to 800 s after e-beam irradiation.

FIG. 6. Bulk spin lattice relaxation rate of 1 mM Fe^{2+} aqueous solution as a function of 6 MeV electron beam on time.

paper, images of the time-dependent contrast variation can be viewed out to 800 s after e-beam irradiation; collages of images and movies can be viewed on this journal's Supplemental Material page [14]. See, for example, the movies showing the time-dependent contrast variation from transverse, Video 1, and longitudinal, Video 2, perspectives.

While we believe we can use information like that contained in Figs. 3–5 to report delivered dose as a function of depth, more accurate calibration studies are necessary. Attempting to spatially map T_1 and equating it to local dose is not straightforward in this dynamic system. T_1 and T_2 simultaneously modulate image intensity in a time-dependent manner. However, one can make a bulk measurement of radiation dose versus T_1 relaxation rate. In Fig. 6 bulk T_1 was measured as a function of beam of time. The sample tube diameter (10 mm) was comparable to the electron beam diameter and the length was 25 mm. Calculations based on the beam current yielded a dose of 6.7×10^4 cGy/pulse. For a $4 \mu\text{s}$ pulse we observed a relaxation rate, $1/T_1$, of 3.6 s^{-1} .

IV. CONCLUSION

The goal of this research is to explore the physics and technology that will lead to dynamic targeting of radiation beams through real-time MR images. While this is admittedly a specific example, this experiment does show that a LINAC, delivering an electron beam to a target, can effectively and efficiently operate in an MR environment. The spatial extent of the radiation can be imaged and quantified by MRI in three dimensions. In this experiment it was demonstrated that the electron depth in water can be visualized and measured by MRI in a Fricke-doped

solution. However, the MRI-Fricke method shows some variance with the electron depth dose curve as measured by other methods [13].

Future applications may include encapsulating a Fricke solution within micron-sized biocompatible polymeric capsules. More efficient contrast agents can be developed for imaging ionizing radiation beams, similar to the use of Fricke dosimetry in this experiment. With respect to medical applications, our results show that one will almost certainly need a contrast agent to image ionizing radiation beams.

In addition to the possibility of imaging electron beams, this technique should be applicable to imaging proton beams [15]; the technique could even be applicable with the generation of proton beams from new nonaccelerator based methods [16,17]. The combination of radiotherapy methods and MRI techniques may provide for more effective treatment of patients. A portable MR system, based on a permanent magnet, can provide 3D images of dose distribution within biological samples doped with Fe^{2+} as a means of dose verification [18]. It could also be useful to apply the imaging techniques described in this paper to measure the penetration depth of pencil beams of light ions in various samples and materials [19].

ACKNOWLEDGMENTS

This work was supported by NIH Grant No. 5R21 RR13375-02, the University of Minnesota Biomedical Engineering Institute, and Carleton College.

[1] H. Fricke and S. Morse, *Philos. Mag.* **7**, 129 (1929).

[2] J. C. Gore and Y. S. Kang, *Phys. Med. Biol.* **29**, 1189 (1984).

- [3] B. E. Hammer and N. L. Christensen, *IEEE Trans. Nucl. Sci.* **42**, 1371 (1995).
- [4] L. E. Olsson, S. Petersson, L. Ahlgren, and S. Mattsson, *Phys. Med. Biol.* **34**, 43 (1989).
- [5] M. J. Maryanski, G. S. Ibbott, P. Eastman, R. J. Schulz, and J. C. Gore, *Med. Phys.* **23**, 699 (1996).
- [6] B. E. Hammer *et al.*, in Proceedings of the ISMRM 12th Annual Meeting, Kyoto, Japan, 2004, Abstract No. 972 [<http://cds.ismrm.org/ismrm-2004/Files/Program04.pdf>].
- [7] H. Gunther, *NMR Spectroscopy: An Introduction* (John Wiley and Sons, Chichester, 1980).
- [8] S. Meiboom and D. Gill, *Rev. Sci. Instrum.* **29**, 688 (1958).
- [9] E. J. Hart and M. Anbar, *The Hydrated Electron* (John Wiley and Sons, New York, 1970), p. 40.
- [10] A. S. Jeevarajan and R. W. Fessenden, *J. Phys. Chem.* **93**, 3511 (1989).
- [11] G. Gambarini, S. Arrigoni, M. C. Cantone, N. Molho, L. Facchielli, and A. E. Sichirollo, *Phys. Med. Biol.* **39**, 703 (1994).
- [12] A. Brahme, G. Hultén, and H. Svensson, *Phys. Med. Biol.* **20**, 39 (1975).
- [13] W. Strydom, W. Parker, and M. Olivares, in *Radiation Oncology Physics: A Handbook for Teachers and Students*, edited by E. B. Podgorsak (International Atomic Energy Agency, Vienna, 2005), p. 273.
- [14] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/PhysRevSTAB.14.114701> for images and movies of the 25 mm diameter vial of 1 mM Fe^{2+} out to 870 past e-beam irradiation.
- [15] M. Hata *et al.*, *Cancer* **104**, 794 (2005).
- [16] T. Toncian *et al.*, *Science* **312**, 410 (2006).
- [17] J. Fuchs *et al.*, *Nature Phys.* **2**, 48 (2006).
- [18] <http://www.aspect-mr.com/>.
- [19] J. Kempe and A. Brahme, *Phys. Rev. ST Accel. Beams* **13**, 104702 (2010).